DRAFT
TOXICOLOGICAL PROFILE FOR POLYBROMINATED BIPHENYLS AND POLYBROMINATED DIPHENYL ETHERS

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

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UPDATE STATEMENT

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. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

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Background Information

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 prepare 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 October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated 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); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Julie Louise Gerberding, M.D., M.P.H.
Administrator
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Disease Registry

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

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0057
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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@AOEC.ORG • Web Page: http://www.aoec.org/.

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: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. 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.

2. 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.

3. 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

Peer reviewers for the second draft (pre-public comments) of the toxicological profile on polybrominated biphenyls and polybrominated diphenyl ethers are as follows:

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These experts collectively have knowledge of PBBs and PBDEs' 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 polybrominated biphenyls (PBBs) and polybrominated dephenyl ethers (PBDEs) 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. PBBs have been found in at least 9 of the 1,613 current or former NPL sites. PBDEs have not been identified in any of the 1,613 current or former NPL sites. However, the total number of NPL sites evaluated for these substances is not known. As more sites are evaluated, the sites at which PBBs are found may increase. This information is important because exposure to PBBs 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 PBBs or PBDEs, 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 PBBs AND PBDEs?

PBBs and PBDEs are chemicals that are added to plastics used in a variety of consumer products, such as computer monitors, televisions, textiles, and plastic foams, to make them difficult to burn. Because they are mixed into plastics rather than binding to them, they are able to leave the plastic and find their way into the environment. Commercial production of PBBs and PBDEs began in the 1970s. Manufacture of PBBs was discontinued in the United States in

1976, while production of PBDEs has continued to the present. Concern regarding PBBs is mainly related to exposures resulting from an agriculture contamination episode that occurred in Michigan over a 10-month period of 1973–1974. Concern for the health effects of PBDEs has increased in recent years because these chemicals are found widely in the environment at concentrations that keep increasing.

PBBs and PBDEs are similar but not identical compounds, and comprise two distinct groups of synthetic organic chemicals. There are no known natural sources of these compounds in the environment. PBBs and PBDEs are solids and are colorless to off-white. Some PBDEs are volatile and may exist as a vapor in air. Both PBBs and PBDEs enter the environment as mixtures containing a variety of individual brominated biphenyl (for PBBs) or brominated diphenyl ether (for PBDEs) components, known as congeners. Some commercial PBB mixtures are known in the United States by their industrial trade name, Firemaster, while commercial PBDE mixtures are known by their industrial trade names, Bromkal, Tardex, and Saytex. While PBBs are no longer used in North America because of the agriculture contamination episode that occurred in Michigan in 1973–1974, PBDEs are still produced and widely used. More information on the physical properties and uses of PBBs and PBDEs can be found in Chapters 4 and 5.

1.2 WHAT HAPPENS TO PBBs AND PBDEs WHEN THEY ENTER THE ENVIRONMENT?

In the past, PBBs entered the air, water, and soil during their manufacture and use. In addition, in lower Michigan in 1973, animal feed was accidentally mixed with 500–1,000 pounds of PBBs. This contamination of the feed/food chain resulted in the contamination of millions of farm animals and humans living in Michigan at this time. PBBs entered the environment during the disposal of animal feed and animal products that were contaminated during the agriculture contamination episode. PBBs entered the environment when PBB-containing wastes generated during their manufacture and use were disposed in waste sites. Small quantities of PBBs also entered the environment from accidental spills during transport. PBBs are no longer manufactured in North America, but very small amounts of PBBs may be released into the

environment from poorly maintained hazardous waste sites and improper incineration of plastics that contain PBBs.

PBDEs enter air, water, and soil during their manufacture and use in consumer products. When solid PBDEs are suspended in air, they can be present as particles. They eventually return to land or water by settling and washing out by snow and rainwater. Chemical reactions with sunlight may reduce the levels of PBDEs in air. However, it is not yet possible to say how long PBDEs remain in the air. PBDEs do not dissolve easily in water and therefore, high levels of PBDEs are not found in water. The small amounts of PBDEs that do occur in water stick to particles and eventually settle at the bottom. Sediments at the bottom of bodies of water, such as lakes and rivers, generally act as reservoirs for PBDEs, and PBDEs can remain there for years. Some PBDEs in water may build up in fish. In general, the breakdown of PBDEs in soil is very slow, so they may remain in soil for several years. PBDEs bind strongly to soil and do not usually spread deep into soil with rainwater.

More information about what happens to PBBs and PBDEs in the environment can be found in Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO PBBs AND PBDEs?

PBBs are no longer produced or used in the United States. Thus, the general population exposure to PBBs will only be from past releases. For people residing in the lower peninsula of Michigan, especially near PBB contaminated areas, exposure to PBBs may still be occurring today. However, environmental levels have decreased since the 1970s and current exposure, if any, will be at low levels. For other regions of the United States, the levels of exposure will either be very low or none.

Measured data in air, water, soil, and food, as well as body burden data (blood, urine, breast milk, and body fat), indicate that the overwhelming majority of people within the state of Michigan who were exposed to PBBs received very low levels of PBBs. The body levels due to exposure were slightly higher for people living in the lower peninsula of Michigan and highest

among farm populations living on contaminated dairy farms. Consumption of contaminated meat and dairy products caused the higher levels of PBBs in the body. Monitoring of the workplace environment and body burden of workers indicated that those in PBB industries were exposed to higher levels of PBBs than the general population. These workers were exposed to PBBs by breathing contaminated workplace air and by skin contact with PBBs. Occupational exposure also could have occurred from the incineration of materials containing PBBs. Exposure in workplaces is no longer likely because PBBs are no longer manufactured. People who live near hazardous waste sites that contain PBBs may be exposed primarily by breathing air that contains PBBs.

PBDEs are still produced and used in the United States. PBDEs are found throughout the environment and are measured at low levels in air, sediments, animals, and food. Body burden data (blood, breast milk, and body fat) indicate that most people are exposed to low levels of PBDEs. People are exposed to PBDEs by breathing air and eating food that contain PBDEs. In the United States, the concentration of PBDEs in outdoor air ranges from 2 to 77 trillionths of a gram per cubic meter (or pg/m^3), which indicates low levels of exposure to the general population. Indoor air concentrations of PBDEs in lecture halls, computerized indoor environments, and rooms with other electronic devices, such as televisions, also have low levels of PBDEs. Workers involved in the production and manufacture of PBDE-containing products are exposed to higher concentrations of PBDEs. Occupational exposure can also occur in confined workplaces where plastic and foam products are recycled, and computers are repaired. People who live near hazardous waste sites may be exposed to PBDEs by breathing contaminated air.

More information about exposure to PBBs and PBDEs can be found in Chapter 6.

1.4 HOW CAN PBBs AND PBDEs ENTER AND LEAVE MY BODY?

If you breathe air that contains PBBs or PBDEs, or swallow food, water, or soil contaminated with PBBs or PBDEs, they can enter your body through your lungs and stomach and pass into the bloodstream. It is not known how much of the PBBs and PBDEs will pass into the blood from the lungs, although most will probably pass into the blood from the stomach and intestines. Also, if you touch soil containing PBBs or PBDEs, which could happen at a hazardous waste site, it is possible that some of the PBBs and PBDEs could pass through your skin into the bloodstream. However, it is not known how fast PBBs and PBDEs enter the blood from the lungs, stomach, or skin. The most important current source of PBBs is not known because PBBs are no longer produced and used in North America, and are rarely found in air and drinking water away from production plants and contaminated sites. The main source of exposure to PBDEs may be the diet, particularly foods with high fat content such as fatty fish. PBDEs have been detected in air samples, indicating that the general population can also be exposed by inhalation. Once PBBs and PBDEs are in your body, they can change into breakdown products called metabolites, some of which might be harmful. Some metabolites and some unchanged PBBs and PBDEs may leave your body, mainly in the feces and in very small amounts in the urine, within a few days. Other unchanged PBBs and PBDEs may stay in your body for many years. PBBs and PBDEs are stored mainly in your body fat, tend to concentrate in breast milk fat, and can enter the bodies of children through breast feeding. PBBs and PBDEs also can enter the bodies of unborn babies through the placenta. More information on how PBBs and PBDEs can enter and leave your body can be found in Chapter 3.

1.5 HOW CAN PBBs AND PBDEs AFFECT MY HEALTH?

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.

Much of what is known about the health effects of PBBs in people comes from studies of ingestion in Michigan in the early-to-mid 1970s, where feed for farm animals was accidentally contaminated with a fire retardant containing PBBs. People were exposed to PBBs for several months when they ate meat, milk, and eggs from the contaminated animals. After news of the contamination episode became widespread, many Michigan residents complained of various health problems, including nausea, abdominal pain, loss of appetite, joint pain, fatigue, and weakness. However, it could not be clearly established that any of the problems were caused by eating the food contaminated with PBBs. PBBs also did not cause any definite changes in the livers or immune systems of the Michigan residents. However, some people who ate the contaminated food developed skin disorders, such as acne and hair loss. It is likely that PBBs caused the skin problems because other chemicals similar to PBBs also cause these effects. Workers who were exposed to PBBs for a few days to months by breathing and skin contact also developed acne, although not all persons exposed to PBBs developed acne. Nothing is known about the health of people who are exposed to low levels of PBBs for long periods by eating, breathing, or skin contact.

Laboratory animals fed PBBs had body weight loss, skin disorders, and nervous system effects, and their livers, kidneys, thyroid glands, and immune systems were seriously injured. Some animals fed high amounts died. PBBs also caused birth defects in animals, but it is not known for sure whether PBBs make males or females infertile. Most of the effects in animals occurred after they ate large amounts of PBBs for short periods or smaller amounts for several weeks or months. In a lifetime study in rats and mice treated orally with PBBs at doses higher than those expected from environmental exposure, body weight loss and effects on the livers, kidneys, and thyroid glands were observed. A few studies tested animals exposed to PBBs by skin contact. These animals had injuries to the liver and skin. Only one study tested animals exposed to PBBs by breathing, and no health effects were observed.

It is not definitely known if PBBs caused or will cause cancer in people who ate food contaminated with PBBs. Rats developed cancer in their livers after eating a large amount of a PBB mixture only once. The offspring of exposed rats also developed cancer in their livers after eating a large amount of the same PBB mixture only once. Liver cancer also developed in rats and mice that ate smaller amounts of the PBB mixture for several months. Mice that had skin contact with a small amount of a PBB mixture for several months did not develop skin cancer. There are no cancer studies in animals that breathed PBBs. Based on the cancer in animals, the National Toxicology Program (NTP) of the Department of Health and Human Services (DHHS) determined that PBBs may reasonably be anticipated to be carcinogens. Similarly, the International Agency for Research on Cancer (IARC) has determined that PBBs are possibly carcinogenic to humans. The EPA has not classified the carcinogenicity of PBBs.

The health effects of PBDEs are not as well studied as for PBBs and practically all of the information is from studies in laboratory animals. No definite information in known on effects of PBDEs in people. Rats and mice that ate food containing moderate amounts of PBDEs for short periods of time had mainly thyroid effects, and those that ate smaller amounts over several weeks or months developed effects in the liver as well as in the thyroid. Preliminary findings from short-term animal studies suggest that PBDEs might cause reduced immune system function and neurobehavioral alterations. Behavioral changes were observed in young animals and might be related to effects on the thyroid, because development of the nervous system is dependent on thyroid hormones. More studies are needed to determine if PBDEs can impair reproduction, but PBDEs are not known to cause birth defects. Animals that were exposed to PBDEs by skin contact showed signs of dermal irritation only when the skin was previously scratched.

It is unclear if PBDEs can cause cancer in people, although liver tumors developed in rats and mice that ate decabromodiphenyl ether throughout their lives. Decabromodiphenyl ether is one type of PBDEs; other kinds of PBDEs have not yet been tested for cancer. Based on the evidence for cancer in animals, decabromodiphenyl ether is classified as a possible human carcinogen by EPA. Neither DHHS nor IARC have classified the carcinogenicity of any PBDEs.

It is not known whether the effects found in animals exposed to PBBs and PBDEs would also occur in people exposed in the same way. The amounts of PBBs and PBDEs that caused health effects in animals are much greater than levels of PBBs and PBDEs normally found in the environment or as yet found in people. Long-term exposure to these chemicals has a greater potential to cause health effects than short-term exposure to low levels because of their tendency to build up in your body over many years. More information on how PBBs and PBDEs can affect your health can be found in Chapter 3.

1.6 HOW CAN PBBs AND PBDEs 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 PBBs and PBDEs in generally the same way as are adults, mainly by eating contaminated food. Because of their smaller weight, children's intake of PBBs and PBDEs per kilogram of body weight may be greater than that of adults. The most likely way that infants will be exposed is from breast milk that contains PBBs and PBDEs, although fetuses in the womb are also exposed. Children who live near hazardous waste sites might accidentally eat some PBBs or PBDEs 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. It is also possible that children could be exposed to PBDEs following transport of the chemical on clothing from the parent's workplace to the home (PBBs are no longer being produced).

Some information on health effects of PBBs in children is available from studies of the Michigan contamination episode. Symptoms of ill health were not associated with increased exposure to PBBs and general neurological examinations did not show any abnormalities. More detailed studies of physical and neuropsychological development showed no effects that were clearly related to PBBs among Michigan children exposed during the episode. Neurobehavioral alterations have been found in animals that were exposed to PBBs in the womb and by nursing. Animal studies also found that exposure to PBBs during pregnancy and/or lactation caused

changes in thyroid hormone levels in the newborn animals and, at high doses, increases in prenatal death and structural birth defects. Thyroid and neurobehavioral alterations also occurred in newborn babies of animals that were exposed to PBDEs during pregnancy and lactation, further indicating that these are possible effects of concern in children exposed to PBBs or PBDEs.

As indicated above, children can be exposed to PBBs and PBDEs both prenatally and from breast milk. PBBs and PBDEs are stored in the mother's body and can be released during pregnancy, cross the placenta, and enter fetal tissues. Because PBBs and PBDEs dissolve readily in fat, they can accumulate in breast milk fat and be transferred to babies and young children. PBBs and PBDEs have been found in breast milk; however, in most cases, the benefits of breast-feeding outweigh any risks from exposure in mother's milk. You should consult your health care provider if you have any concerns about PBBs or PBDEs and breast feeding. Because the nervous system and thyroid are still developing in the fetus and child, the effects of PBBs and PBDEs on these target systems might be more profound after exposure during the prenatal and neonatal periods, which could make fetuses and children more susceptible to PBBs and PBDEs than adults.

More information regarding children's health and exposure to PBBs and PBDEs can be found in Chapter 3 (Section 3.7).

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PBBs AND PBDEs?

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

Since PBBs are no longer produced or used, the risk of exposure to these compounds is limited. PBDEs are currently in widespread production and use. You and your children may by exposed to PBBs and PBDEs by eating fish or wildlife caught from contaminated locations. Children who live near hazardous waste sites should be discouraged from playing in the dirt near these sites because they could contain PBBs or PBDEs. Children should also be discouraged from eating the dirt, and careful handwashing practices should be followed.

As mentioned in Section 1.3, workplace exposure to PBDEs can occur during their production and the manufacture of PBDE-containing plastic products. Workers involved in recycling plastic products, computer repair in confined workplaces can also be occupationally exposed to PBDEs. If you are exposed to PBDEs while at work, it may be possible to carry them home on your clothes or body. Your occupational health and safety officer at work can tell you whether the products you work with may contain PBDEs and are likely to be carried home. 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 PBBs AND PBDEs?

There are tests to determine whether PBBs and PBDEs 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 PBBs and PBDEs in people exposed to them in the environment and at work. If your PBB and PBDE levels are higher than the normal levels, this will show that you have been exposed to high levels of the chemicals. However, these measurements cannot

determine the exact amount or type of PBBs or PBDEs that you have been exposed to, or how long you have been exposed. Although these tests can indicate whether you have been exposed to PBBs and PBDEs 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 PBBs and PBDEs. Results of such tests should be reviewed and carefully interpreted by physicians with a background in environmental and occupational medicine. Although exposures to PBBs have been of greatest concern in Michigan as explained in Section 1.3, nearly everyone has been exposed to PBDEs because they are found throughout the environment, and the general population is therefore more likely to have detectable amounts of PBDEs in their blood, fat, and breast milk. Recent studies have shown that PBDE levels in the general population continue to rise, whereas levels of PBBs have declined since the 1970s. More information on tests used to determine whether you have been exposed to PBBs or PBDEs 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 also 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 PBBs include the following:

There are no federal guidelines or recommendations for protecting human health from exposure to PBBs.

EPA requires that companies that transport, store, or dispose of *p*-bromodiphenyl ether (a particular PBDE compound) follow the rules and regulations of the federal hazardous waste management program. EPA also limits the amount of *p*-bromodiphenyl ether put into publicly owned waste water treatment plants. To minimize exposure of people to *p*-bromodiphenyl ether, EPA requires that industry tell the National Response Center each time 100 pounds or more of *p*-bromodiphenyl ether have been released to the environment.

For more information on federal and state regulations and guidelines for PBBs and PBDEs, 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
Web site: http://www.atsdr.cdc.gov

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: 1-404-498-0057

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

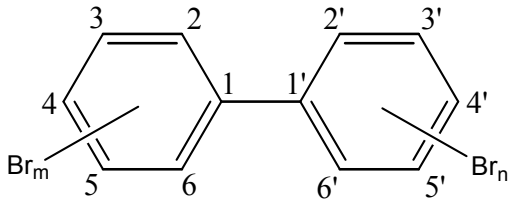
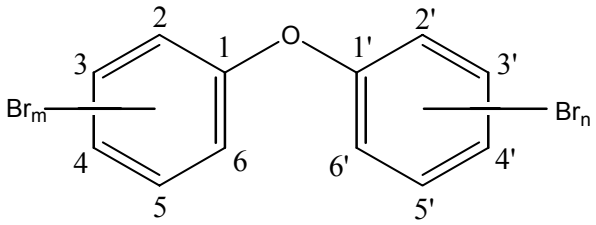
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO POLYBROMINATED BIPHENYLS AND POLYBROMINATED DIPHENYL ETHERS IN THE UNITED STATES

Polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs) are brominated organic compounds used as flame retardant additives in plastics, textiles, and other materials. As additives, they are physically mixed into product applications, rather than chemically bound. Therefore, they have the potential to migrate from the plastic matrix into the environment. Commercial production of PBBs began in approximately 1970 and manufacture was discontinued in the United States in 1976, subsequent to a major agricultural contamination episode that occurred in Michigan in 1973. Concern regarding the health effects of PBBs is mainly related to exposures that have resulted from the regionally localized Michigan episode. Production of PBDEs also began in the 1970s but, unlike PBBs, has continued to the present. Concern for the possible health effects of PBDEs has heightened recently due to evidence that these chemicals are ubiquitously distributed with levels in the environment, biota, and humans tissues and breast milk that are continually increasing.

PBBs and PBDEs are each classes of structurally similar brominated hydrocarbons in which 2–10 bromine atoms are attached to the molecular structure (i.e., biphenyl for PBBs; diphenyl ether for PBDEs). Monobrominated structures (i.e., one bromine atom attached to the molecule) are often included when describing PBBs and PBDEs. There are 209 different molecular combinations, or congeners, that are possible for both PBBs and PBDEs. Based on the number of bromine substituents, there are 10 homologous groups of PBB and PBDE congeners (monobrominated through decabrominated), with each homologous group containing one or more isomers. The mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decabromo-congeners can exist in 3, 12, 24, 42, 46, 42, 24, 12, 3, and 1 isomers, respectively. The general chemical structures of PBBs and PBDEs are similar when viewed in one dimension, differing only in an ether linkage, as shown below, where m+n = 1–10:

 where m + n = 1 to 10	 where m + n = 1 to 10
PBBs	PBDEs

However, due to the ether linkage and position/number of bromine atoms, there are important three-dimensional differences in the structures of PBBs and PBDEs that can influence the molecules' receptor interactions and toxicological properties as discussed in Section 3.5, Mechanisms of Action.

People are environmentally exposed to PBBs and PBDEs of different congeneric composition than the source commercial mixtures, due to differential partitioning and transformation of the individual congeners in the environment, including transformation in food animals (e.g., dairy cattle in the case of PBBs). Additionally, as discussed in Section 3.4, because PBBs and PBDEs are lipophilic and some congeners are not readily metabolized, they are likely to be retained in the body for long periods of time (years).

Polybrominated Biphenyls. Three commercial PBB mixtures were manufactured: hexabromobiphenyl, octabromobiphenyl, and decabromobiphenyl. The two main commercial hexabromobiphenyl PBB mixtures had the trade names FireMaster BP-6 and FireMaster FF-1. FireMaster FF-1 was produced by grinding FireMaster BP-6 and adding 2% calcium polysilicate as an anticaking agent. The hexabrombiphenyl mixtures contained varying proportions of di- through octabrominated homologues. 2,2',4,4',5,5'-Hexabromobiphenyl is the most abundant congener in the mixtures (53.9–68.0%), followed by 7.0–27.3% of 2,2',3,4,4',5,5'-heptabromobiphenyl. Commercial octabromobiphenyl mixtures contained a large proportion (47.4–60.0%) of nonabromobiphenyl congeners, whereas commercial decabromobiphenyls contain predominately (96.8%) decabromobiphenyl congener.

Limited data are available on health effects of commercial decabromobiphenyl and octabromobiphenyl mixtures, although the hexabromobiphenyl mixtures FireMaster BP-6 and FireMaster FF-1 have been extensively tested. Most of the information on human health effects of PBBs comes from studies of Michigan residents who accidentally ingested milk, meat, and eggs that came from farms that used animal feed contaminated with FireMaster FF-1. In 1973, livestock on certain farms in Michigan were exposed

to FireMaster FF-1 after it was mistaken as a feed supplement and mixed with feed that was distributed within the state for several months before being discovered. Health problems in dairy cattle, reported in the fall of 1973, were the first signs that this episode occurred, but the accidental addition of PBBs to animal feed was not identified as the cause of the problem until the spring of 1974.

Available information on the metabolism of PBBs in livestock is insufficient to ascertain whether the people affected in Michigan ingested the original PBB mixtures or metabolic products of the PBBs. Based on limited information in dairy cattle and additional data in laboratory animals as discussed in Section 3.4.2.2, it is reasonable to assume that mainly unchanged penta-, hexa-, and heptabromobiphenyl congeners were consumed in animal products during the contamination episode. PBBs were excreted in cattle manure and, as such, were also environmentally distributed in Michigan via waste disposal on farms. The general population outside of Michigan could possibly have been exposed to PBBs by the oral route via the food chain, and the inhalation and dermal routes represent the most likely routes of exposure to PBBs in occupational settings.

Polybrominated Diphenyl Ethers. Three commercial PBDE mixtures have been and continue to be produced: decabromodiphenyl ether, octabromodiphenyl ether, and pentabromodiphenyl ether. DecaBDE has accounted for more than 80% of PBDE usage. The composition of commercial decaBDE is $97% pure with the remainder mainly nonaBDE. Commercial octaBDE is a mixture of congeners ranging from nona- to hexaBDE, and mixtures of pentaBDE are comprised of tetra-, penta-, and hexaBDE congeners. Congeners with less than four bromine atoms are generally not found in commercial PBDEs. DecaBDE seems to be largely resistant to environmental degradation, whereas differential partitioning and transformation of the octa- and hexaBDE mixture components have more readily yielded the predominance of lower-brominated tetra- and penta-congeners, particularly 2,2',4,4'-tetraBDE and 2,2',4,4',5-pentaBDE, which have been detected in environmental and human tissue samples (including breast milk). The main source of human exposure to PBDEs may be the diet, particularly foods with high fat content such as fatty fish. PBDEs have been detected in air samples, including those taken from remote areas, indicating that inhalation is also an exposure route for the general population.

2.2 SUMMARY OF HEALTH EFFECTS

Polybrominated Biphenyls. Much of the information on human health effects of PBBs comes from studies of Michigan populations where PBBs were accidentally introduced into the feed/food chain. There is also some information on health effects in chemical workers. Although these studies consist largely of observations on groups that are not well defined and lack accurate intake data, they do provide a picture of the health status of the affected people and an indication of potential effects for the general population who may be exposed to lower levels of PBBs. Thus far, there is little convincing evidence linking exposure to PBBs and adverse health effects in Michigan farm residents. Although a variety of symptoms (neurological and neuropsychiatric, gastrointestinal, hepatic, dermal, musculoskeletal) have been reported, the prevalence of these symptoms has not been definitively linked to the extent or types of exposure. Also, neurodevelopmental effects in exposed children and immunological effects were reported. Physical examinations and laboratory tests have shown few abnormalities that corresponded to the complaints, and prevalence of symptoms has not been correlated with serum PBB levels. However, the possibility of long-term effects cannot be ruled out.

Most toxicity studies of PBBs in animals have involved oral exposure, and numerous effects have been documented including hepatic, renal, dermal/ocular, immunological, neurological, and developmental. Other effects of oral PBB exposure include decreased thyroid function, body weight loss, and liver cancer. Adverse hepatic as well as dermal and ocular effects have been observed in a limited number of dermal studies in animals. No significant adverse effects were observed in animal inhalation studies of PBBs, but only two studies have been conducted (one with octabromobiphenyl and one with decabromobiphenyl).

Thyroid Effects. The thyroid gland is an unequivocal target of PBBs in animals, and evidence in humans is suggestive of a similar relationship. Effects in workers exposed to unspecified PBBs and/or decabromobiphenyl included increased serum thyrotropin, low or borderline low serum thyroxine (T_4), and increased thyroid antimicrosomal antibody titers. A spectrum of effects has been observed in rats exposed for acute and intermediate durations, ranging from decreases in serum levels of serum T_4 and serum triiodothyronine (T_3) to histological and ultrastructural changes in the follicles. The preponderance of these studies tested FireMaster FF-1 or FireMaster BP-6 in rats, although chronic exposure to FireMaster FF-1 induced thyroid follicular hyperplasia in mice. Similar thyroid effects also occurred in offspring of treated rats and pigs.

Thyroid effects were produced in rats in acute-duration studies at doses as low as 3 mg/kg/day (reduced serum levels of T_4 hormone) but not at 1 mg/kg/day, in intermediate-duration studies at doses as low as 0.05 mg/kg/day (increased number and decreased size of follicles), and in chronic-duration studies at doses as low as 1.3 mg/kg/day. The no-observed-adverse-effect level (NOAEL) of 1 mg/kg/day is used herein as the basis for an acute-duration minimal risk level (MRL) for oral exposure. The acute-duration lowest-observed-adverse-effect level (LOAEL) for hepatic effects is identical to the LOAEL for acute thyroid toxicity, but is a less appropriate basis for the MRL because organ functional implications are not as clear. The intermediate-duration LOAELs for thyroid and hepatic effects are also comparable to each other, but neither of these LOAELs are suitable for an intermediate MRL because reproductive and developmental toxicity occurred at a lower dosage. The thyroid LOAEL for chronic-duration exposure is unsuitable for deriving a chronic MRL because decreased survival occurred at the same dose (lower doses were not tested), and thyroid, liver, and other effects occurred at lower doses in intermediate-duration studies.

Hepatic Effects. Histologically and ultrastructurally documented liver damage is a consistent and prominent finding among animals exposed to PBBs by the oral route, but studies of Michigan residents who were likely to have ingested PBB-contaminated food are inconclusive. The human studies do not demonstrate any clear association between abnormal liver-associated serum indices (serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactic dehydrogenase [LDH], bilirubin) or liver enlargement and PBB exposure. No information is available on hepatic effects of PBBs in humans exposed by the inhalation or dermal routes. Although the available studies on liver effects in humans are largely inconclusive, the animal data, as summarized below, suggest that humans may also be affected.

Hepatic effects ranging from microsomal enzyme induction and liver enlargement to fatty changes and necrosis have been observed in rodents and other laboratory animal species exposed orally to FireMaster PBBs in acute-, intermediate-, and/or chronic-duration studies. Acute- and intermediate-duration oral data for octabromobiphenyl mixtures are only available for rats and suggest that hepatic histopathologic effects are milder than for FireMaster mixtures at similar doses. Similarly, intermediate-duration oral data for decabromobiphenyl mixture suggest that this PBB mixture is a less potent hepatotoxicant than an octabromobiphenyl mixture. No pathologic effects were reported in the liver of rats exposed to an octabromobiphenyl mixture in acute- and intermediate-duration inhalation studies, or in an intermediate-duration study with a decabromobiphenyl mixture, but it is unclear if histology was evaluated following the intermediate-duration octabromobiphenyl mixture exposure. Acute dermal exposure to commercial

mixtures of hexabromobiphenyl, but not octabromobiphenyl, has been reported to produce gross necrotic changes in the liver of rabbits. Hepatocyte enlargement and degenerative changes (vacuoles or necrosis) are the most sensitive adverse hepatic effects that have been observed in the acute-, intermediate-, and chronic-duration oral studies with FireMaster PBBs. The lowest hepatic LOAELs for acute and intermediate durations are identical or essentially the same as the LOAELs for thyroid effects. The acute-duration LOAEL for thyroid toxicity is used as the basis for an acute oral MRL, but neither hepatic nor thyroid LOAELs for intermediate-duration exposure are suitable for MRL derivation because reproductive and developmental toxicity occurred at a lower dosage. Hepatotoxicity occurred at the lowest dosage tested in chronic studies with rats and mice, and the hepatic LOAEL in mice also caused thyroid effects. Neither the rat nor the mouse LOAEL is a suitable basis for a chronic MRL, however, due to decreased survival at the same dosage and weight loss and developmental toxicity in monkeys at a lower chronic dosage.

Altered vitamin A homeostasis, primarily manifested as decreased hepatic storage of vitamin A, is another established effect of PBBs in animals. Vitamin A is essential for normal growth and cell differentiation, particularly differentiation of epithelial cells, and some PBB-induced epithelial lesions resemble those produced by vitamin A deficiency. Because it is the primary storage site for vitamin A, the liver has a major role in retinol metabolism. Esterification of dietary vitamin A, hydrolysis of stored vitamin A, mobilization and release into the blood of vitamin A bound to retinol-binding protein, and much of the synthesis of retinol-binding protein occurs in the liver.

Immunological and Lymphoreticular Effects. Altered lymphocyte transformation responses among populations exposed to PBB following the Michigan contamination episode have been reported by some investigators. Others have not been able to confirm these findings. However, it is clear that no correlation can be established between altered immune parameters and PBB levels in serum. Some have suggested that PBBs associated with white blood cells is possibly the cause of the immunological dysfunction resulting from exposure to PBBs. This would imply that total PBB in plasma is not necessarily a good marker for immune dysfunction. Continuous examination of this cohort may resolve the controversy.

Studies in animals, mostly intermediate-duration studies in rodents, indicate that a variety of immunological parameters such as spleen and thymus weights, antibody production, and lymphoproliferative responses can be affected by treatment with commercial PBB mixtures. The only chronic study found increased splenic hematopoiesis in mice, but no histological changes in the spleen,

thymus, or lymph nodes of rats. It is apparent, however, that some of these effects are only seen at PBB levels that cause overt toxicity. Steroids are known to influence the immune response. Corticosterone levels were elevated in plasma of mice that were exposed to FireMaster BP-6 in the diet for 30 days, although the increase was not enough to be responsible for the observed immunological effect (reduced antibody-mediated response to sheep red blood cells). Thymic atrophy and a reduction in lymphocyte markers were reported in cows treated with PBB doses of 67 mg/kg/day for #60 days. However, these results should be interpreted with caution since the animals approached death at this dose. Based on the data available, it is difficult to suggest any particular species as the most sensitive. This is because different studies usually examined different end points, using different exposure protocols. It is unclear whether morphological changes in the reticuloendothelial system are more sensitive indicators of altered immune status than are functional changes. Although the limited data on humans are largely inconclusive, PBBs have altered immune responses in a variety of animal species, which suggests that humans may also be affected.

Neurological Effects. Data from studies on Michigan residents exposed to PBBs as a result of the 1973 feed contamination episode and data from a limited number of animal studies both suggest that exposure to PBBs may cause subtle effects on neuropsychological performance and development in humans. Symptoms of neurological effects, including fatigue, weakness, and decrements in the capacity to perform physical or intellectual work, were reported frequently by groups of farm families and residents of Michigan who were likely to have consumed farm products (milk, meat, and eggs) contaminated with PBBs; however, associations between PBB levels in serum or fat and the frequency of subjectively reported neurological symptoms were not found in several studies. The administration of neuropsychological tests to orally-exposed Michigan residents has not revealed abnormalities or associations between test performance and PBB levels in serum or fat. Similarly, no association between performance in neuropsychological tests and serum PBB levels was made in a study of a small number of chemical workers exposed to unspecified PBBs via inhalation and/or dermal contact.

Examinations of a small number of children (19) believed to have been exposed *in utero* or in early infancy during the peak of the Michigan PBB-feed contamination episode have not found consistent or marked effects on neuropsychological development. One study found a statistically significant association between performance in neuropsychological development tests and PBB levels in adipose tissues when the children were . 2.5–4 years old, but a later examination when the children were . 4–6 years old did not find such an association for the same tests.

Studies with rats have shown that oral exposure to PBBs at dose levels of . 10 mg/kg/day for intermediate durations (1–6 months) produced decreased motor activity and weakness of the hind limb , but not operant behavior deficits or histopathological alterations of brain or spinal nerve tissue. Performance deficits in tests of learning behavior were observed in the offspring of female rats and female mice treated with oral doses of PBBs at approximate daily dose levels ranging from 0.2 to 10 mg/kg during gestation and lactation. Effects on acquisition of forward locomotion, cliff avoidance, cage emergence, and open-field activity were found in offspring of rats that were exposed to 2 mg/kg/day from day 6 of gestation through day 24 postpartum and observed until postnatal day 60.

Dermal and Ocular Effects. Dermal lesions characterized as acne have been observed in humans occupationally exposed to PBBs. Increased prevalences of skin disorder symptoms, including rashes, acne, darkening or thickening of the skin, discoloration or deformity of fingernails or toenails, peeling and scaling, erythema, and hair loss, were reported by Michigan residents who were likely to have ingested PBB contaminated food. There was no association between serum PBB levels and prevalence of symptoms in one study, but physical examinations in the other study confirmed a slightly increased incidence of alopecia. Polymer fibers containing octabromobiphenyl mixture caused no dermal effects when placed on covered human skin for 6 days.

Acute-, intermediate-, and chronic-duration oral studies have found no histological alterations in the skin, pinnae, ear canals, or salivary glands of rats or mice exposed to FireMaster FF-1 or FireMaster BP-6. Alopecia, loss of eyelashes, generalized subcutaneous edema, dry scaly skin, and periorbital edema developed in three monkeys that were exposed to low doses of FireMaster FF-1 for several months; related histological findings included sebaceous gland atrophy and metaplasia and keratinization of hair follicles. Uncharacterized dermatosis was observed in similarly treated pigs. Hyperkeratosis of the eyelids and metaplasia of the tarsal glands with keratin cysts developed in cows that ingested FireMaster BP-6 for up to 60 days. Acute dermal application of FireMaster FF-1 induced hyperkeratosis, dilation and keratinization of hair follicles, and partial atrophy of the sebaceous glands in rabbits, but effects of octabromobiphenyl and decabromobiphenyl mixtures were generally mild (slight erythema and edema). Octabromobiphenyl mixture was not a sensitizer when applied to guinea pig skin. Although somewhat limited, the animal and human data are generally consistent and indicate that although PBBs can cause local responses such as irritation by direct dermal contact, exposure does not need to occur by the dermal route to produce cutaneous effects.

Unspecified signs of ocular irritation were observed in rats intermittently exposed to a high (5,000 mg/m^3) dust concentration of decabromobiphenyl mixture for 4 weeks, but severity was not reported, and recovery was not assessed. Octabromobiphenyl and decabromobiphenyl mixtures caused mild eye irritation in rabbits when applied as a dry solid. Histopathological changes have not been observed in the eyes of rats or mice exposed orally to FireMaster FF-1 or FireMaster BP-6 in studies of acute, intermediate, or chronic duration. Xerophthalmia (extreme dryness of the conjunctiva) was reported in rats fed FireMaster BP-6 in an intermediate-duration study. Based on effects in animals, direct exposure to PBBs is likely to be irritating to human eyes.

Body Weight Effects. Animal studies provide strong evidence that oral exposure to FireMaster PBBs causes a wasting syndrome characterized by progressive decreased weight gain, with immediate moderate to severe body weight loss generally preceding death. Effects on body weight have been observed in single dose, intermediate- and chronic-duration oral studies with rats, mice, guinea pigs, mink, monkeys, and/or cows. Changes in body weight were also observed in rabbits following acute dermal exposure to commercial mixtures hexabromobiphenyl, but not octabromobiphenyl, suggesting that the syndrome is independent of exposure route and is a potential effect of PBBs in humans.

Reproductive Effects. A limited amount of data are available regarding the reproductive effects of PBBs in humans. The distribution of sperm counts, sperm motility, and sperm morphology was investigated in a small number (50) of male Michigan residents who ingested food produced on PBB-contaminated farms or who worked in a PBB manufacturing company. The study found no evidence for PBB-related effects compared with a putatively unexposed control group. No relationship was found between serum PBB levels and frequency and duration of breast-feeding in a retrospective study of women exposed to PBBs during the Michigan episode. A study of fetal mortality rates in Michigan counties did not include data for fetal mortalities occurring during the first trimester of pregnancy.

Animal studies provide limited evidence that FireMaster FF-1 and FireMaster BP-6 PBBs cause adverse reproductive effects in a variety of species. Increased menstrual cycle duration and prolonged implantation bleeding were observed in female monkeys fed approximate daily dose levels of 0.012 mg/kg for 7 months before breeding and during pregnancy. A corresponding decrease in serum levels of progesterone suggests that the reproductive effects in the monkeys are related to PBB-induced endocrine imbalance. This dosage (0.012 mg/kg/day) is the lowest tested in any intermediate-duration study and also caused fetal deaths in the monkeys after . 1 year of exposure. Although the reproductive effects are less serious, concern for serious developmental toxicity following exposures of <1 year

precludes deriving an MRL for intermediate-duration exposure. Implantation was completely blocked in 40–67% of female rats treated with gavage dose levels $28.6 mg/kg on alternate days between gestation days 0 and 14 . Alterations in male reproductive organs were observed at doses that caused death in male rats (necrosis of the epithelial lining of the ductus deferens after 100 mg/kg for 4–5 weeks) and in a monkey (hypoactive seminiferous tubules after . 0.73 mg/kg/day for 25 weeks). No alterations in litter size or fertility were observed in a study of male and female minks fed #0.39 mg/kg/day for 6–7 months prior to breeding and during pregnancy or in the F_1 or F_2 generations of female parental rats fed as much as 5 mg/kg/day during the postimplantation phase of gestation and through weaning.

Based on the observations of adverse effects on reproduction in animals exposed to PBBs, the possibility that PBBs may cause reproductive harm in humans cannot be refuted and suggests that exposure of women to PBBs prior to and during the early phases of pregnancy may be of particular concern.

Developmental Effects. Consistent or marked abnormalities have not been found in examinations of the physical and neuropsychological development of children exposed *in utero* or in early infancy during the peak of the Michigan PBB episode. Likewise, a comparison of fetal mortality rates for Michigan counties with a high percentage of quarantined farms and those for Michigan counties with no quarantined farms did not clearly establish or refute the possibility that the Michigan PBB episode caused developmental problems in exposed people.

Fetotoxic and developmental effects have been observed in studies of FireMaster FF-1 or FireMaster BP-6 in several species of laboratory animals. Embryolethal effects or increased mortality among nursing young were observed in rats and mice after oral exposure during gestation and in monkeys after exposure before conception and during pregnancy. Because the dosage (0.012 mg/kg/day) causing these serious developmental effects in monkeys is the lowest tested in any chronic study of PBBs, it is not possible to derive an MRL for chronic-duration exposure. Structural malformations in fetuses, including cleft palate, were also observed in rats and mice after exposure to these PBBs during gestation. Increased incidences of fetuses with extra ribs were reported in a study of rats orally exposed to commercial octabromobiphenyl mixture during gestation, but oral exposure to commercial decabromobiphenyl mixture was not embryotoxic, fetotoxic, or teratogenic in rats. Studies with FireMaster FF-1 and FireMaster BP-6 found that body weight gain was reduced in the offspring of rats and mice after exposure during gestation, in rat offspring after exposure during gestation and lactation, and in mink kits after parental exposure before and during pregnancy. Liver effects, including increased liver weight and hepatic cytochrome P-450 enzymic activity, hepatocyte enlargement, vacuolization, and other

degenerative changes, were observed in the offspring of rats, mice, and/or swine fed FireMaster FF-1 or FireMaster BP-6 during gestation and/or lactation. Performance deficits in tests of operant behavior were observed in offspring of rats and mice after oral exposure to FireMaster FF-1 or FireMaster BP-6 during pregnancy and lactation.

Although the available human data regarding developmental effects of PBBs are inconclusive, the results from animal studies strongly suggest that PBBs may cause mild to severe developmental effects in humans, including growth retardation, alteration of neuropsychological development, and structural malformations.

Cancer. There is no epidemiological evidence of an association between exposure to PBBs and increased prevalence of cancer (all sites) in Michigan residents who were likely to have ingested PBB-contaminated food. These data are inconclusive due to a short latency period of 4 years. Suggestive relationships between increasing serum levels of PBBs and risks of breast cancer, digestive system cancer, and lymphoma (not otherwise specified) were found in case-control studies of Michigan PBB registry enrollees who were followed for approximately 20 years.

Oral studies with rats and mice demonstrate that FireMaster FF-1 is an unequivocal hepatocarcinogen. Hepatocellular adenomas, carcinomas, and/or liver neoplastic nodules were induced in these species following single or repeated (intermediate- and chronic-duration) exposures. These types of liver neoplasms even developed in the offspring of rats administered a single gavage dose during gestation or offspring of mice treated by diet during the perinatal period (throughout gestation and lactation). Liver neoplasm incidences were much higher in rats and mice exposed for up to 2 years in the only chronic bioassay than in the other studies that involved shorter-duration exposures of up to 6 months followed by an observation period of up to 2 years. Based on findings in male rats and mice of both sexes in this study, there is some evidence that combined perinatal and adult dietary exposure to FireMaster FF-1 enhanced the susceptibility of hepatocellular neoplasms in animals receiving adult exposure.

Tumors were not clearly or consistently observed in nonhepatic tissues of animals exposed to FireMaster FF-1. Induction of thyroid follicular cell adenoma was inconclusive in mice in both National Toxicology Program bioassays. Equivocal increases in incidences of mononuclear cell leukemia were observed in adult-only exposed rats in the NTP chronic study, and combined perinatal and adult exposure showed no significant increase. Combined analysis of the incidences of this leukemia in the adult-only, perinatal only, and combined perinatal and adult exposure groups, however, showed an apparent association

between increasing incidences and dose, and incidences in some of the groups exceeded historical control ranges. Evidence is available that oral administration of FireMaster BP-6 promotes development of initiated tumors in rats (liver enzyme-altered foci assays) and hamsters (tracheal papilloma assay).

Based on the results of the oral studies of FireMaster FF-1 in rats, there is sufficient evidence to conclude that PBBs are carcinogenic in animals and potentially carcinogenic in humans. PBBs as a group have been classified as possibly carcinogenic to humans by IARC (Group 2B). This classification is based on sufficient evidence for carcinogenicity to animals and inadequate evidence of carcinogenesis in humans. NTP concluded that PBBs are reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity in animals. The EPA has not classified the carcinogenicity of PBBs. Because there is insufficient information about which constituents of the PBB mixtures are carcinogenic and the congener profile to which people may be exposed environmentally is likely to be different from the original PBB source, it is assumed that PBB mixtures of any composition are potentially carcinogenic. This assumption has uncertainty since it cannot be verified with current knowledge, and because the mechanism of PBB carcinogenesis in rodents has not been definitively elucidated.

Polybrominated Diphenyl Ethers. Information is available on the health effects of all three commercial mixtures of PBDEs (deca-, octa-, and hexaBDEs), although the toxicology of these mixtures is less well characterized than for PBBs. Most of the data are from studies of orally exposed laboratory animals indicating that effects of decaBDE are generally much less pronounced than for octa- and hexaBDE mixtures following acute and repeated-dose exposures. This dissimilar toxicity is likely related to differences in absorption, metabolism, and elimination of the congeners in each mixture as shown by rodent toxicokinetic studies. In particular, in comparison with the other mixtures, decaBDE is minimally absorbed (0.3–2%), has a relatively short half-life (<24 hours), and is rapidly eliminated via fecal excretion (>99% in 72 hours). These toxicokinetic differences correlate with environmental monitoring data indicating that decaBDE has low bioaccumulation potential.

Available intermediate- and chronic-duration oral studies in animals indicate that the thyroid and liver are the main systemic targets of PBDE toxicity as shown by effects mainly including enlargement and histological alterations in both organs and changes in serum levels of thyroid hormones. Several acute-duration studies of pentaBDE suggest that immunosuppression may also be an important health end point. Very little information is available on potential neurotoxic effects of PBDEs, mainly the results of three behavioral tests showing alterations in the developing nervous system of mice following neonatal exposure to low doses of 2,2',4,4'-tetraBDE and 2,2',4,4',5-pentaBDE. Concern for neurodevelopmental

toxicity is raised by the PBDE-induced alterations in thyroid hormone homeostasis because development of the central nervous system is dependent on thyroid hormones. Information on the reproductive toxicity of PBDEs is limited to a one generation study of decaBDE in rats that found no exposure-related functional effects. Developmental toxicity studies have shown no evidence of teratogenicity of deca-, octa-, and pentaBDE in rats and rabbits, although fetotoxic effects, including skeletal ossification variations at maternally toxic doses, have occurred. Information on the carcinogenicity of PBDEs is limited to results of chronic oral bioassays on decaBDE that found limited evidence of cancer based on increased liver neoplasms in rats and mice and equivocal occurrence of thyroid tumors in mice. The weight of available genotoxicity evidence indicates that PBDEs are not genotoxic. Dermal application studies in rabbits showed that decaBDE, octaBDE, and pentaBDE were non-irritating to intact skin and caused some erythematous and edematous responses in abraded skin. DecaBDE was not a skin sensitizer in humans and octaBDE and pentaBDE were non-sensitizing in guinea pigs, indicating that the PBDEs did not cause delayed contact hypersensitivity.

Thyroid Effects. Limited information is available on thyroid effects in PBDE-exposed humans. There are suggestive occupational data as shown by effects that included increased serum FSH, low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers in workers exposed to decaBDE and/or unspecified PBBs. There was no clear association between plasma levels of 2,2',4,4-tetraBDE and thyroid hormone levels (free and total T_3 and T_4, TSH, free testosterone, follicle-stimulating hormone, lutenizing hormone, and prolactin) in men who consumed varying amounts of fatty fish from the Baltic Sea. Based on consistent evidence in animals, as summarized below, the thyroid is particularly sensitive to PBDEs and is a likely target of toxicity in exposed humans.

Thyroid effects that have mainly included reduced serum T_4 hormone levels and follicular cell hyperplasia were consistently observed in rats and mice orally exposed to PBDEs. Accompanying changes in serum TSH levels were not found and the depression of serum T_4 is likely related to hepatic enzyme induction. Acute duration studies showed decreases in serum T_4 in rats exposed to $10 mg/kg/day octaBDE or $30 mg/kg/day pentaBDE for 4 days and in rats and mice exposed to $18 mg/kg/day pentaBDE for 14 days. Effects observed in intermediate-duration studies include thyroid hyperplasia in rats exposed to $8 mg/kg/day octaBDE for 30 days and reduced serum T_4 in rats exposed to $10 mg/kg/day pentaBDE for 90 days. Exposure to pentaBDE on gestation day 6 through postnatal day 21 caused serum T_4 reductions at 30 mg/kg/day in maternal rats and $10 mg/kg/day in their fetuses and neonatal offspring. Intermediate-duration exposure to a 77% decaBDE/22% nonaBDE commercial mixture caused thyroid hyperplasia in rats at doses $80 mg/kg/day for 30 days. Chronic (103-week)

exposure to high-purity decaBDE ($97%) did not induce thyroid histopathological changes in rats at #2,550 mg/kg/day, although follicular cell hyperplasia developed in mice exposed to 2,240 mg/kg/day.

Hepatic Effects. The hepatotoxic potential of PBDE mixtures is well-documented in animals by oral exposure. The spectrum of observed hepatic effects includes microsomal enzyme induction, liver enlargement, and degenerative histopathologic alterations that progress to tumors. Repeated dietary exposure to PBDEs typically caused liver enlargement with or without degenerative changes, and effects were generally dose-related in incidence and severity, more frequent and pronounced in males than females, and more severe with octaBDE and pentaBDE than decaBDE. Hepatic effects induced by chronic exposure to decaBDE included degeneration and thrombosis in rats exposed to 2,240 mg/kg/day and centrilobular hypertrophy and granulomas in mice exposed to $3,200 mg/kg/day. Increased liver weight and hepatocellular enlargement with vacuolation occurred in rats exposed to pentaBDE doses as low as 2–9 mg/kg/day for 4–13 weeks. Increased incidences of degeneration and necrosis of individual hepatocytes were observed 24 weeks following exposure $2 mg/kg/day of pentaBDE for 90 days in rats. No studies are available on hepatic effects of PBDEs in humans. Based on the evidence in animals, PBDEs are potentially hepatotoxic in humans.

Immunological and Lymphoreticular Effects. Information regarding the immunosuppressive potential of PBDE mixtures is essentially limited to evidence from acute-duration oral studies of pentaBDE in animals. The plaque-forming splenic cell antibody response to injected sheep red blood cells was significantly reduced in mice exposed to 72 mg/kg/day pentaBDE for 14 days; single doses as high as 500 mg/kg had no effect. *In vitro* production of IgG immunoglobulin from pokeweed mitogen-stimulated splenocytes was reduced in mice exposed to 36 mg/kg/day pentaBDE for 14 days. Other 14-day studies in mice found no changes in natural killer cell activity to murine YAC-1 target cells at #72 mg/kg/day or numbers of splenic and thymic lymphocyte subsets at #36 mg/kg/day, although 18 mg/kg/day of the single congener 2,2’,4,4’-tetraBDE caused significantly reduced numbers of total lymphocytes and CD4+, CD8+, and CD45R+ subtypes in spleen. Chronic ingestion of decaBDE caused splenic lesions (hematopoiesis, fibrosis, lymphoid hyperplasia) in rats exposed to $1,200 mg/kg/day for 103 weeks. No studies are available on immunological effects of PBDEs in humans. Due to the limited amount of data in animals, insufficient information is currently available to adequately characterize the human immunotoxic potential of PBDEs.

Developmental Effects. Oral developmental toxicity studies of deca-, octa-, and pentaBDE have shown no evidence of teratogenicity in animals. Gestational exposure to a high (1,000 mg/kg/day) but maternally nontoxic dose of decaBDE was fetotoxic in rats as shown by subcutaneous edema and delayed skull bone ossification. Commercial mixtures of octaBDE caused skeletal ossification variations in rats and rabbits at maternally toxic levels and other indications of fetotoxicity at lower doses. Effects of gestational exposure to octaBDE included minimally increased postimplantation loss in rats at $10 mg/kg/day, increased resorptions in rats at 25 mg/kg/day, and increased skeletal variations in rabbits at 15 mg/kg/day and rats at 50 mg/kg/day. No evidence of fetotoxicity was found in the only available study of pentaBDE in rats at maternally toxic doses #200 mg/kg/day. No studies are available on developmental effects of PBDEs in humans. Based on the evidence in animals, PBDEs are unlikely to cause developmental toxicity at expected levels of exposure.

Cancer. The only information regarding carcinogenicity of PBDEs in humans is available from a case-control study that found no clear association between risk of non-Hodgkin's lymphoma and exposure to 2,2'4,4'-tetraBDE in a small group of Swedish men and women.

Cancer data on PBDEs in animals are limited to results of studies on decaBDE mixtures. In a bioassay conducted by the NTP, male and female rats were exposed to decaBDE ($94% pure) in the diet in low doses of 1,120 and 1,200 mg/kg/day, respectively, and high doses of 2,240 and 2,550 mg/kg/day, respectively, for 103 weeks. Male and female mice were similarly exposed to low doses of 3,200 and 3,760 mg/kg/day, respectively, and high doses of 6,650 and 7,780 mg/kg/day, respectively. Incidences of neoplastic nodules in the liver were significantly increased in the male and female rats, and incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in the male mice. Slightly elevated incidences of thyroid gland follicular cell adenoma or carcinoma (combined) were additionally observed in exposed male mice, although the increases were not statistically significant. Carcinogenicity was additionally evaluated in rats that were exposed to 0.01, 0.1, or 1.0 mg/kg/day dietary doses of a 77.4% decaBDE mixture (containing 21.8% nonaBDPO and 0.8% octaDBDPO) for approximately 2 years. No exposure-related neoplastic changes were found, but the power of this study to detect carcinogenic effects is limited by the very low dose levels in comparison to those tested in the NTP bioassay.

Based on the limited evidence of carcinogenicity in animals in the NTP bioassay (significantly increased incidences of neoplastic liver nodules in rats and combined hepatocellular adenomas and carcinomas in mice), as well as the lack of human data, decaBDE has been classified in EPA Group C (possible human

carcinogen) and IARC Group 3 (not classifiable as to its carcinogenicity to humans). EPA Group D classifications (not classifiable as to human carcinogenicity) were assigned to nona-, octa-, hexa-, penta-, tetra-, tri-, and *p,p'*-diBDE based on no human data and no or inadequate animal data. The U.S. Department of Health and Human Services has not classified the carcinogenicity of any PBDE mixture.

2.3 MINIMAL RISK LEVELS (MRLs)

As indicated in Section 2.1, there are three-dimensional structural differences in PBBs and PBDEs that can influence the relative behavior of the chemicals in biological systems. Consequently, although there are some similarities in the health effects of PBBs and PBDEs, it cannot be assumed that corresponding PBDE and PBB congeners necessarily have the same toxicological and toxicokinetic characteristics. PBBs and PBDEs also share some toxicological properties with other structurally similar polyhalogenated aromatic compounds, particularly polychlorinated biphenyls (PCBs), chlorinated dibenzo-*p*-dioxins (CDDs), and chlorinated dibenzofurans (CDFs) (Agency for Toxic Substances and Disease Registry 1994, 1998, 2000). The toxicity of PCBs and PBBs is commonly classified as either "dioxin-like" or "non-dioxin-like" based on evidence that dioxin-like congeners act through the same Ah-receptor initial mechanism involved in 2,3,7,8-TCDD toxicity. The mechanism(s) of toxicity for non-dioxin-like PCB and PBB congeners is less clearly elucidated, but also may involve receptors (e.g., the estrogen receptor, the ryanodine receptor, and others). For PBDEs, the introduction of the ether bridge precludes clearly classifying the congeners as either "dioxin-like" or "non-dioxin-like". As discussed in Section 3.5, available studies of structure-induction properties, structure-affinity binding properties, and structure-toxicity properties suggest that some *ortho* substituted (non-dioxin-like) PBDE congeners can exhibit stronger affinity for the Ah receptor and exhibit stronger dioxin-type toxicity than their corresponding non-*ortho* substituted (dioxin-like) analogs (Chen et al. 2001; Howie et al. 1990). This is contrary to what is expected for the corresponding PCB and PBB congeners, and has been attributed to the greater distance between the two biphenyl rings in PBDE congeners, relative to PCBs and PBBs. In other words, introduction of *ortho* substitutions into PBDEs or PCDEs does not create a spatial impediment for the two phenyl rings to assume a semi-flat position with respect to each other as it does for PCBs or PBBs. This has implications not only for dioxin-type toxicities, but also for non-dioxin-type toxicities. For example, mono- and diortho-substituted PCBs exhibit neurotoxic properties, and structure-activity relationships have been established for various neurological end points (see Agency for Toxic Substances and Disease Registry 2000 for details). Although this has not been adequately examined for PBBs and PBDEs, it is reasonable to speculate that mono- and diortho-substituted PBDEs might not necessarily follow the potency rankings of mono- and diortho-substituted PCBs and PBBs.

The assumption that PBBs and PBDEs share many toxicological characteristics with PCBs also does not consider geometrical differences due to the higher atomic weight and considerably larger molecular volume of bromine compare to chlorine (Hardy 2000, 2002). These differences contribute to dissimilar physical/chemical properties that can influence the relative toxicokinetics and toxicities of the chemicals.

People are environmentally exposed to PBB and PBDE mixtures of different congeneric composition than the original commercial PBB and PBDE mixtures. Although the toxicity or potency of environmental PBB and PBDE mixtures consequently may be greater or less than that of commercial mixtures, there are insufficient mixture toxicity data on which to directly base MRLs for environmental PBBs and PBDEs. Due to the likelihoods that (1) multiple mechanisms (Ah-receptor-dependent mechanisms, Ah-receptor independent mechanisms, or both) may be involved in health effects induced by PBBs/PBDEs, (2) different PBB/PBDE congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PBBs/PBDEs with differing biological activities, as well as to the lack of a suitable approach for quantitatively evaluating joint toxic action from concurrent exposures to PBBs, PBDEs, PCBs, CDDs, and/or CDFs in the environment, data from commercial PBB and PBDE mixtures are used to develop MRLs for assessing health risks from environmental exposures to PBBs or PBDEs.

Polybrominated Biphenyls

Inhalation MRLs

No MRLs have been derived for inhalation exposure to PBBs because human and animal data for all durations are either insufficient or lacking. Insufficiencies in the human inhalation data include mixed-chemical and unquantified exposures. The animal inhalation database is limited by inadequately reported studies and lack of any information on the mixtures likely to be most toxic (i.e., FireMaster PBBs).

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute oral exposure (14 days or less) to PBBs.

The acute oral MRL was based on a NOAEL for decreased serum levels of thyroid T_4 hormone identified in groups of 8–11 male rats that were treated with 0, 1, 3, or 6 mg/kg/day doses of an unspecified mixture of PBBs in lecithin liposomes by gavage for 10 days (Allen-Rowlands et al. 1981). The MRL was

estimated by dividing the NOAEL by an uncertainty factor of 100 (component factors of 10 for animal to human extrapolation and 10 for human variability). Levels of serum T_4 were significantly ($p<0.05$) reduced at $3 mg/kg/day, indicating that the lowest dose (1 mg/kg/day) is the NOAEL. Decreased serum T_4 is considered adverse due to unequivocal evidence from numerous studies that the thyroid is a target of PBBs with a spectrum of effects, including decreases in serum T_3 and T_4 hormone, thyroid enlargement, effects in the follicular cells (e.g., reduced size, hyperplasia with columnar appearance and papillary projections), and accumulation of colloid droplets (Akoso et al. 1982b; Byrne et al. 1987; NTP 1983; Gupta and Moore 1979; Kasza et al. 1978a; Norris et al. 1975a, 1975; Sepkovic and Byrne 1984; Sleight et al. 1978). Additional information on the derivation of the acute-duration oral MRL for PBBs is provided in Appendix A.

Intermediate- and chronic-duration oral MRLs were not derived because serious developmental and reproductive effects were observed in monkeys that had been exposed to PBBs for durations that spanned the intermediate and chronic categories at the lowest dose tested in the database. This dose (0.012 mg/kg/day) caused increased menstrual cycle duration and implantation bleeding after 6–7 months of exposure and fetal deaths (fetal abortion and stillbirth) after . 1 year of exposure in monkeys, with surviving infants having decreased birth weight and decreased postnatal weight gain (Allen et al. 1978, 1979; Lambrecht et al. 1978). Additionally, weight loss occurred in the maternal monkeys. The 0.012 mg/kg/day serious LOAEL for developmental and reproductive effects is lower than the lowest less serious LOAELs for thyroid effects in rats (0.05 mg/kg/day) (Akoso et al. 1982b) and hepatic effects in guinea pigs (0.04 mg/kg/day) (Sleight and Sanger 1976). Concern for serious developmental and reproductive toxicity following exposures of <1 year therefore precludes deriving an MRL for intermediate-duration exposure. Derivation of an MRL for chronic oral exposure is precluded by the serious developmental effect (stillbirth) that occurred following exposures exceeding 1 year in duration. The serious LOAEL in monkeys is lower than the lowest chronic dosages tested in other species (0.5 and 1.3 mg/kg/day in rats and mice, respectively) that caused decreased survival (NTP 1992). ATSDR's classification of LOAELs into less serious and serious effects is discussed in the introduction to Section 3.2.

Polybrominated Diphenyl Ethers

Available information on the toxicity of PBDEs indicates that the health effects of commercial decaBDE is generally much less pronounced than for the octa- and hexaBDE mixtures following acute and repeated-dose exposures. This dissimilar toxicity is likely related to the comparatively poor uptake and

rapid elimination of decaBDE, and is consistent with environmental monitoring data indicating that decaBDE has a low potential to degrade and bioaccumulate relative to the other mixtures. In contrast to commercial decaBDE, which typically contains $97% of the single congener, octaBDE and pentaBDE are comprised of multiple congeners that appear to more readily yield the lower-brominated tetraBDEs and pentaBDEs that predominate in the environment. Consequently, due to the lower toxicity and lower potential for environmental degradation and bioaccumulation of decaBDE in comparison to the octaBDE and pentaBDE mixtures, MRLs for PBDEs are based on health effects data for the lower-brominated mixtures.

Inhalation MRLs

No MRLs have been derived for inhalation exposure to PBDEs because available human and animal data for all durations are either insufficient or lacking.

Oral MRLs

- An MRL of 0.03 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to PBDEs.

The acute oral MRL is based on a NOAEL of 1 mg/kg/day for reduced serum levels of thyroid T_4 hormone in fetal rats that were exposed to octaBDE on days 4–20 of gestation (Zhou et al. 2002). The MRL was estimated by dividing the NOAEL by an uncertainty factor of 30 (component factors of 10 for animal to human extrapolation and 3 for human variability). A component factor of 10 was not used for human variability because the MRL is based on effects observed in a sensitive subgroup. Thyroid hormone levels were determined in Long-Evans rats that were administered a technical pentaBDE mixture (DE-71) in corn oil by gavage from gestation day (Gd) 6 through postnatal day (Pnd) 21, except for Pnd 0 (day of birth) (Zhou et al. 2002). Dams were sacrificed on Gd 20 and Pnd 22 and offspring were sacrificed on Gd 20 and Pnd 4, 14, 36, and 90). Study end points included serum total T_4 and T_3 concentrations measured at each age point. The maternal exposure to pentaBDE caused reductions in serum total T_4 that were significantly ($p<0.05$) different from controls in dams at 30 mg/kg/day on Gd 20 and Pnd 22 (48 and 44%, respectively, relative to controls), and in fetuses and offspring at $10 mg/kg/day on Gd 20 (at least 15% reduced) and Pnds 4 and 14 (50 and 64% maximal in the 10 and 30 mg/kg/day groups, respectively). The effect on T_4 concentrations in the offspring was age-dependent as values returned to control levels by Pnd 36. There were no exposure-related effects on serum total T_3 concentrations in the dams or offspring at any time, although T_3 was not be measured in fetuses on Gd 20

due to insufficient serum sample volume. The critical NOAEL of 1 mg/kg/day and LOAEL of 10 mg/kg/day for reduced serum T_4 hormone levels in fetal rats that were exposed to pentaBDE (Zhou et al. 2002) are supported by a NOAEL of 3 mg/kg/day and a LOAEL of 10 mg/kg/day for reduced serum T_4 levels in weanling (28-day-old) rats that were exposed to octaBDE for 4 days (Zhou et al. 2001). Data from other acute-duration studies of PBDEs that support the selection of the critical NOAEL and LOAEL include a NOAEL of 2.5 mg/kg/day and LOAEL of 10 mg/kg/day for fetotoxicity in rats exposed to octaBDE for 10 days during gestation (Life Science Research Israel Ltd. 1987), a NOAEL of 5 mg/kg/day and LOAEL of 15 mg/kg/day for fetotoxicity in rabbits exposed to octaBDE for 13 days during gestation (Breslin et al. 1989), and LOAELs of 18 mg/kg/day for reduced serum T_4 in rats and mice exposed to pentaBDE for 14 days (Fowles et al. 1994; Hallgren et al. 2001). Additional information on the derivation of the acute-duration oral MRL for PBDEs is provided in Appendix A.

- An MRL of 0.007 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to PBDEs.

The intermediate oral MRL is based on a LOAEL of 2 mg/kg/day for minimal liver effects in rats that were exposed to pentaBDE for 90 days (WIL Research Laboratories 1984). The MRL was estimated by dividing the LOAEL by an uncertainty factor of 300 (component factors of 3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability). Groups of 30 male and 30 female Sprague-Dawley rats were exposed to pentaBDE (commercial mixture DE-71) in the diet at dosage levels of 0, 2, 10, or 100 mg/kg/day for up to 90 days. Study end points included clinical signs, body weight, food consumption, hematology, clinical chemistry (including serum T_3 and T_4), urine indices, gross pathology, and selected organ weights (brain, gonads, heart, liver, kidneys, thymus, and thyroid). Histological examinations were performed on liver, thyroid, thymus, kidney, and lung in all dose groups and in all tissues (comprehensive evaluation) at 0 and 100 mg/kg/day. Hepatocytomegaly was observed in males at 2 mg/kg/day and both sexes at $10 mg/kg/day. The hepatocytomegaly was similar in incidence and severity after 4 and 13 weeks of exposure, was dose-related with respect to severity (some affected hepatocytes had vacuoles that likely contained lipid), and was still observed in males at $10 mg/kg/day and females at 2 and 100 mg/kg/day at 24 weeks postexposure (in lessened severity and incidence). Examinations at 24 weeks following exposure also showed an increase in individual hepatocytes with degeneration and necrosis, effects that were considered to be likely exposure-related and indicative of final loss of previously damaged cells. No NOAEL was identified because liver changes were observed at all dose levels. Nonhepatic effects included increases in serum T_4 levels at $10 mg/kg/day and thyroid follicular cell hyperplasia at 100 mg/kg/day. Based on the observations of hypertrophy, mild degeneration, and slight necrosis, 2 mg/kg/day is considered to be a minimal LOAEL

for liver effects. Data from other intermediate-duration studies that support selection of the 2 mg/kg/day minimal LOAEL include hepatic LOAELs of 5 mg/kg/day for cytomegaly (with vacuolation and necrosis at higher doses) in rats exposed to octaBDE for 13 weeks (IRDC 1977), 8 mg/kg/day for hepatocellular enlargement and vacuolation in rats exposed to octaBDE for 30 days (Norris et al. 1973, 1975a), and 9 mg/kg/day for hepatocellular enlargement and increased liver weight in rats exposed to octaBDE or pentaBDE for 28 days (IRDC 1976). Other relevant effect levels from intermediate-duration studies include thyroid LOAELs of 8 mg/kg/day for hyperplasia in rats exposed to octaBDE for 30 days (Norris et al. 1973, 1975a), and 10 mg/kg/day for reduced serum T_4 levels in fetuses and neonatal offspring of rats that were exposed to pentaBDE from gestation day 6 through postnatal day 21 (Zhou et al. 2002). Additional information on the derivation of the intermediate-duration oral MRL for PBDEs is provided in Appendix A.

A chronic-duration oral MRL was not derived for PBDEs due to insufficient data. Two chronic studies of PBDEs were conducted. In one of the studies, Sprague-Dawley rats (25/sex/dose level) were fed a 77.4% pure decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for approximately 2 years (Kociba et al. 1975; Norris et al. 1975a). Evaluations that included clinical signs, body weight, food consumption, hematology, clinical chemistry, urine indices, and comprehensive histological examinations showed no exposure-related effects. In the other chronic study, decaBDE (94–97% pure) was fed to F344 rats (50/sex/dose level) in doses of 1,120/1,200 mg/kg/day (males/females) or 2,240/2,550 mg/kg/day, and B6C3F1 mice (50/sex/dose level) in doses of 3,200/3,760 mg/kg/day or 6,650/7,780 mg/kg/day, for 103 weeks (NTP 1986). Histopathological changes occurred in both species and included liver effects (degeneration and thrombosis) in male rats at 2,240 mg/kg/day, and liver (centrilobular hypertrophy and granulomas) and thyroid effects (follicular cell hyperplasia) in male mice at 3,200 mg/kg/day. The highest chronic NOAELs that can be identified in these studies are 1 mg/kg/day for the decaBDE/nonaBDE mixture (Kociba et al. 1975; Norris et al. 1975a) and 1,120 mg/kg/day for decaBDE (NTP 1986). Neither of these NOAELs is appropriate for estimation of a chronic MRL for all PBDEs due to insufficient sensitivity of the studies. In particular, using the NOAELs of 1 and 1,120 mg/kg/day and an uncertainty factor of 100, chronic oral MRLs derived from these studies would be 1.4 and 1,600 times higher, respectively, than the 0.007 mg/kg/day intermediate MRL. The relative insensitivity of the chronic studies appears to be related to low potency of decaBDE compared to the pentaBDE mixture tested in the critical intermediate-duration study. The low toxicity of decaBDE relative to lower-brominated mixtures is illustrated by comparison of liver effect levels in 13-week rat studies: LOAELs of 2 and 5 mg/kg/day were identified for pentaBDE and octaBDE, respectively, whereas 8,000 mg/kg/day (highest tested dose) is a NOAEL for decaBDE (IRDC 1977; NTP 1986; WIL Research Laboratories

1984). A similar pattern was observed for thyroid effects in the study used to derive the acute-duration oral MRL (Zhou et al. 2001) as summarized above. Due to the insufficiencies of the chronic data for MRL derivation, the intermediate oral MRL could also be used as a value for chronic exposure.

3. HEALTH EFFECTS

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 of polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs). It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

Polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs) are classes of brominated hydrocarbons that are used as flame retardant additives in plastics, textiles, and other materials. Both classes of chemicals are comprised of compounds in which 1–10 bromine atoms are attached to the biphenyl structure in up to 209 different combinations. Based on the number of bromine substituents, there are 10 homologous groups of PBBs and PBDEs (monobrominated through decabrominated), each containing one or more isomers. PBBs and PBDEs are structurally similar when viewed in one dimension, differing only in the ether linkage between the two phenyl rings in PBDEs, but the oxygen bridge confers three-dimensional conformational differences that can influence toxicological properties. Consequently, on the basis of chemical structure, it cannot be assumed that the health effects of PBBs and PBDEs are necessarily similar.

Commercial production of PBBs began in approximately 1970, and manufacture was discontinued in the United States in 1976 following a contamination episode that occurred in Michigan in 1973–1974. Three main commercial mixtures of PBBs were produced: hexabromobiphenyl, octabrombiphenyl, and decabromobiphenyl. The most prevalent hexabromobiphenyl PBB mixtures had the trade names FireMaster BP-6 and FireMaster FF-1. FireMaster FF-1 was produced by grinding FireMaster BP-6 and adding 2% calcium polysilicate as an anticaking agent. The hexabromobiphenyl mixtures contained varying proportions (depending on lot number) of di- through octabrominated homologues, and 2,2',4,4',5,5'-hexabromobiphenyl was the most abundant congener (53.9–68.0%) followed by 2,2',3,4,4',5,5'-heptabromobiphenyl (7.0–27.3%). Commercial octabromobiphenyl PBB mixtures contained a large proportion (47.4–60.0%) of nonabromobiphenyl congeners, whereas commercial

decabromobiphenyls contained predominately (96.8%) decabromobiphenyl congener. The general names hexabromobiphenyl, octabromobiphenyl, and decabromobiphenyl are used in this profile to refer to unspecified commercial mixtures of these PBBs.

Concern regarding the health effects of PBBs is largely related to exposures that resulted from the Michigan contamination episode. Livestock on farms in Michigan were exposed to FireMaster FF-1 over a period of approximately 10 months after it was accidentally mistaken for the feed supplement magnesium oxide and mixed with animal feed that was distributed within the state. Health problems in dairy cattle (decreased feed consumption and decreased milk production), reported in the fall of 1973, were the first signs that the contamination episode occurred, but accidental addition of PBBs to animal feed was not identified as the cause of the problem until late spring of 1974 (Fries 1985a; Jackson and Halbert 1974). The U.S. Food and Drug Administration (FDA) established tolerances of 1 ppm in milk and meat fat and 0.1 ppm in eggs in May 1974, which were revised downward to 0.3 and 0.05 ppm, respectively, in November 1974 due to improved analytical sensitivity (Dunckel 1975; Fries 1985a). The Michigan Department of Agriculture (MDA) subsequently lowered the FDA tolerance in meat fat from 0.3 to 0.02 ppm, but there currently are no FDA or MDA tolerances for PBBs (FDA 1989; Fries 1985a). As a result of a farm animal testing and quarantining program established by the MDA in May 1974, about 30,000 dairy cattle, 2,000 swine, 400 sheep, and over 2,000,000 chickens were found to contain PBBs at concentrations requiring their destruction (Dunckel 1975; Fries 1985a; Mercer et al. 1976).

Most of the information that is available on health effects of PBBs in humans comes from studies of Michigan residents who ingested milk, meat, and eggs that were produced on farms that used the FireMaster-contaminated animal feed. In the interval of more than 9 months between the accident, the detection and identification of its cause, and the beginning of testing and the establishment of quarantines, PBB-contaminated food products were consumed, not only by farm families and people that acquired produce directly from PBB-contaminated farms, but also by people who purchased food from markets (Anderson et al. 1979). The Michigan PBB contamination episode led to the establishment of epidemiological studies (that are still ongoing) of Michigan residents who were expected to have consumed PBB-contaminated food, as well as to a substantial increase in research activity regarding the health effects of PBBs in cattle, poultry, and laboratory animals. Compared to the FireMaster (commercial hexabromobiphenyl) PBBs, relatively limited data are available on health effects of commercial mixtures of octabromobiphenyl and decabromobiphenyl. Reviews of the research results on the toxicity of PBBs include those by Damstra et al. (1982), DiCarlo et al. (1978), Fries (1985a), Kay (1977), Kimbrough (1987), Kimbrough et al. (1978a), and WHO (1994a).

3. HEALTH EFFECTS

This profile discusses information regarding health effects of PBBs in humans and laboratory animals; some research on cattle and poultry is also discussed, but its relevance to human health effects is uncertain due to interspecies physiological differences. Although livestock toxicity at high-level farms is generally concluded to have been due to PBBs, data regarding effects at farms with low levels of PBBs have generated some controversy because signs of toxicosis reported in Michigan cattle have not been reproduced in animals exposed to PBBs in controlled experiments that led to residue concentrations in tissues 100 times greater than those reported in the Michigan animals (Jackson and Halbert 1974; Moorhead et al. 1977). This led some investigators to suggest that some signs of toxicosis reported in Michigan cattle reflected farm management procedures, nutritional deficiencies, microbial and parasitic infections, or exposure to unknown contaminants in the feed (Durst et al. 1977; Fries 1985a; Moorhead et al. 1977). Although exposure by ingestion occurred during the Michigan contamination episode, existing information on the metabolism of PBBs in livestock is insufficient to ascertain whether the people ingested PBBs or metabolic products of PBBs. However, based on available data discussed in Section 3.4.2.2, it is reasonable to assume that mainly unchanged penta-, hexa-, and heptabromobiphenyl congeners in animal products were consumed.

Unlike PBBs, PBDEs have been continuously produced and used as flame-retardant additives since the 1970s. Concern for health effects of PBDEs has heightened due to relatively recent evidence that they have become ubiquitously distributed in the environment and are present in tissues and breast milk of the general population at levels that continue to increase. Three commercial PBDE mixtures have been and continue to be produced: decabromodiphenyl ether (decaBDE), octabromodiphenyl ether (octaBDE), and pentabromodiphenyl ether (pentaBDE). DecaBDE has accounted for more than 80% of PBDE usage. The composition of commercial decaBDE is $97% of the pure congener with the remainder mainly nonaBDE. Commercial octaBDE is a mixture of congeners ranging from nona- to hexaBDE, and mixtures of pentaBDE are comprised of tetra-, penta-, and hexaBDE congeners. Congeners with less than four bromine atoms are generally not found in commercial PBDEs. Reviews on the health effects and other aspects of PBDEs include those by Darnerud et al. (2001), de Boer et al. 2000, de Wit (2002), Hardy (1999, 2002a, 2002b), McDonald (2002), NAS (2002), Rahman et al. (2001), Silberhorn et al. (1990), and WHO (1994b).

Toxicity data for individual PBB and PBDE congeners are included in some discussions in this profile when these data corroborate or provide information on effects not documented for the PBB and PBDE mixtures. Congener-specific toxicity data are currently not practical for determining exposure levels of PBB and PBDE mixtures associated with adverse health effects at hazardous waste sites. This is due in

part to the fact that standardized analytical procedures for congener mixtures and commercially available standards for all congeners are lacking, and congener-specific analyses are not routinely performed. Additionally, using current health effects evaluation procedures, toxicity data for individual congeners may overestimate or underestimate the actual health risk of PBB and PBDE mixtures because congeners vary in toxic potency and may be influenced by other congeners in an additive or less-than-additive way. It is also important to recognize that the PBBs and PBDEs to which people may be exposed are likely to be different from the original PBB and PBDE source because of changes in congener composition resulting from differential partitioning and transformation in the environment and differential biological metabolism and retention.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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 route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). 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 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 (LOAELs) or exposure levels 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 PBBs and PBDEs are indicated in Tables 3-1, 3-2 and 3-3 and Figures 3-1 and 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-1 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 PBBs and PBDEs. 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.

3.2.1 Inhalation Exposure

A few studies have examined groups of chemical workers involved in the manufacture and distribution of PBBs and/or PBDEs (Bahn et al. 1980; Brown et al. 1981; Chanda et al. 1982; Landrigan et al. 1979; Rosenman et al. 1979; Stross et al. 1981). These people are believed to have been exposed predominately by dermal contact and inhalation, although the oral route cannot be ruled out. Results from these studies, therefore, are discussed in this section as well as in Section 3.2.3.

3.2.1.1 Death

Polybrominated Biphenyls. No studies were located regarding death in humans after inhalation exposure to PBBs.

Nose-only exposure to the highest attainable dust concentration of octabromobiphenyl mixture for 4 hours (960 mg/m^3 as a time-weighted average) was not lethal to six male rats observed for 7 days (Waritz et al. 1977). No deaths occurred in groups of five male and five female rats that were exposed to a decabromobiphenyl dust mixture at concentrations ranging from 5 to 5,000 mg/m^3 concurrently with starch dust (6 mg/m^3) for 6 hours/day, 5 days/week for 4 weeks (Millischer et al. 1980). Information on lethality of inhaled hexabromobiphenyl PBB mixtures was not located.

Polybrominated Diphenyl Ethers. No studies were located regarding death in humans after inhalation exposure to PBDEs.

No deaths occurred in groups of five male and five female rats that were chamber-exposed to pentaBDE aerosol (compound dissolved in corn oil), octaBDE dust, or decaBDE dust in concentrations as high as 200,000, 60,000, or 48,200 mg/m^3, respectively, for 1 hour and observed for the following 14 days (IRDC 1974, 1975a, 1975b). Confidence in these studies is limited by a lack of control data. There was no mortality in rats that were exposed to #174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978).

3.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, or musculoskeletal effects in humans or animals after inhalation exposure to PBBs.

No studies were located regarding musculoskeletal or dermal effects in humans or animals after inhalation exposure to PBDEs.

Systemic effects that have been observed in humans and animals following inhalation exposure to PBBs and PBDEs are described below.

Respiratory Effects.

Polybrominated Biphenyls. No studies were located regarding respiratory effects in humans after inhalation exposure to PBBs.

Slight dyspnea was observed in five male and five female rats that were exposed to a decabromobiphenyl dust mixture at 5,000 mg/m^3 concurrently with starch dust (6 mg/m^3) for 6 hours/day, 5 days/week for 4 weeks (Millischer et al. 1980). This effect was not observed at 500 mg/m^3 and lower concentrations or in air only-exposed controls, and there were no changes in pulmonary resistance and compliance in urethane-anesthetized rats, blood gases, and lung histology at any of the exposure levels. Lung function and blood gases were not evaluated in starch-exposed controls, but this is unlikely to be a serious study deficiency as the ratio of PBB to starch was . 1,000 in the high exposure group.

Polybrominated Diphenyl Ethers. No studies were located regarding respiratory effects in humans after inhalation exposure to PBDEs.

Transient signs of respiratory distress that included tachynpea or dyspnea developed in rats that were chamber-exposed to pentaBDE aerosol (compound dissolved in corn oil), octaBDE dust, or decaBDE dust in very high concentrations of 200,000, 60,000, and 48,200 mg/m^3, respectively, for 1 hour (IRDC 1974, 1975a, 1975b). Confidence in these effect levels is low due to a small number of tested animals and lack of control data. Increased respiration rate also occurred in rats that were exposed to $24.4 mg/m^3 concentrations of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978). The effect was observed by the end of each exposure period, always disappeared by the following morning,

and was not observed at lower concentrations of #3.68 mg/m^3. Histological examinations of rats exposed to 174 mg/m^3 in the 14-day study showed no effects in the nasal turbinates, trachea, or lungs.

Cardiovascular Effects.

Polybrominated Diphenyl Ethers. No studies were located regarding cardiovascular effects in humans after inhalation exposure to PBDEs.

No histopathological changes were observed in the hearts of rats that were exposed to 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978).

Gastrointestinal Effects.

Polybrominated Diphenyl Ethers. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to PBDEs.

No histopathological changes were observed in the stomach, duodenum, or colon of rats that were exposed to 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978).

Hematological Effects.

Polybrominated Biphenyls. No studies were located regarding hematological effects in humans after inhalation exposure to PBBs.

Hematology was normal in groups of five male and five female rats that were exposed to a decabromobiphenyl dust mixture at concentrations of 5 or 5,000 mg/m^3 concurrently with starch dust (6 mg/m^3) for 6 hours/day, 5 days/week for 4 weeks (Millischer et al. 1980). The evaluation included erythrocyte and leucocyte counts, differential leukocyte count, hematocrit, and hemoglobin level.

Polybrominated Diphenyl Ethers. No studies were located regarding hematological effects in humans after inhalation exposure to PBDEs.

No adverse hematological changes were observed in rats that were exposed to 24.4 or 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978). Evaluation of hemoglobin,

hematocrit, total erythrocyte count, and total and differential leukocyte counts showed no remarkable responses except for an elevation in leukocyte numbers. The observed increase in leukocyte counts was considered to be an unusual response by the investigators, although it was within the normal range for control rats in their laboratory.

Hepatic Effects.

Polybrominated Biphenyls. No studies were located regarding hepatic effects in humans after inhalation exposure to PBBs.

No significant ($p<0.05$) increase in relative liver weight or hepatic histological changes were found in six male rats nose-only exposed to a octabromobiphenyl dust mixture at 960 mg/m^3 for 4 hours (time-weighted average, highest attainable concentration), and observed for 7 days (Waritz et al. 1977). Toxicity of octabromobiphenyl mixture vapor was investigated in groups of six rats almost continuously exposed (23 hours/day, 7 days/week) for 2, 4, 7, 9, 11, 13, or 15 weeks (Waritz et al. 1977). The exposure level was 0.00035 µg/m^3, which is the reported equilibrium concentration at 28 EC. Gross pathologic examination and measurement of relative liver weight showed no exposure-related changes at any of the sacrifices, but it is unclear if liver histology was evaluated.

Relative liver weight was increased . 25% in groups of 5 or 10 rats that were exposed to a decabromobiphenyl dust mixture at concentrations of 50–5,000 mg/m^3 concurrently with starch dust (6 mg/m^3) for 6 hours/day, 5 days/week for 4 weeks (Millischer et al. 1980). The increased liver weight was not accompanied by hepatic histologic changes, and therefore may be an adaptive response because PBBs are hepatic inducers and cause cellular proliferation (see Section 3.2.2.2 Hepatic Effects). No effects on liver weight or histology were observed at 5 mg/m^3.

Polybrominated Diphenyl Ethers. No studies were located regarding hepatic effects in humans after inhalation exposure to PBDEs.

Increased liver weight and hepatic histological changes were observed in rats that were exposed to $3.6 mg/m^3 concentrations of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978). At 3.6 mg/m^3, the liver lesions consisted of very slight to slight, focal to multifocal cytoplasmic enlargement of the hepatocytes, accompanied by focal acidophilic degeneration of individual to small groups of cells. The liver lesions were similar at higher concentrations (24.4 or 174 mg/m^3), except that the hepatocyte

enlargement was multifocal to diffuse in distribution and was accompanied by focal, small to large areas of hepatocellular necrosis of very slight to marked degree. No liver effects were found at 0.58 mg/m^3 (lowest tested concentration).

Renal Effects.

Polybrominated Biphenyls. No studies were located regarding renal effects in humans after inhalation exposure to PBBs.

Groups of six rats were exposed to 0.00035 µg/m^3 of octabromobiphenyl mixture vapor (equilibrium concentration) 23 hours/day, 7 days/week for 2, 4, 7, 9, 11, 13, or 15 weeks (Waritz et al. 1977). Gross pathologic examination at each sacrifice and measurement of relative kidney weight at the last sacrifice showed no exposure-related changes, but it is unclear if kidney histology was evaluated.

Urinalysis was normal in groups of five male and five female rats that were exposed to a decabromobiphenyl dust mixture at concentrations ranging from 5 to 5,000 mg/m^3 concurrently with starch dust (6 mg/m^3) for 6 hours/day, 5 days/week for 4 weeks (Millischer et al. 1980). The analysis included pH, specific gravity, proteins, glucose, ketone bodies, biliary pigments, urobilinogen, blood, and microscopic examination of sediment. A comprehensive histology evaluation was performed in this study, but the only tissues specifically mentioned as having been examined are the liver and lungs. However, a total of 21 tissues were examined; therefore, it is probable that the kidney was examined, but was not discussed because no histological alterations were found.

Polybrominated Diphenyl Ethers. No studies were located renal respiratory effects in humans after inhalation exposure to PBDEs.

No histopathological changes were observed in the kidneys or urinary bladder of rats that were exposed to 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978).

Endocrine Effects.

Polybrominated Biphenyls. Hypothyroidism was diagnosed in 4 of 35 men who were occupationally exposed to unspecified PBBs and/or decaBDE (Bahn et al. 1980). The cohort consisted of workers (mean age 35.9 years) who had been employed at a production plant for at least 6 weeks during a 52-month

period during which PBBs and decaBDE were the only chemicals manufactured and who had volunteered for a comprehensive medical evaluation performed 3 months after the end of the 52-month period. There was no further description of exposure, and it was assumed to have occurred by both inhalation and dermal routes. The cohort was matched by sex, race, and age to 89 unexposed control subjects. Four subjects (22–50 years old, employed for 9–46 months not entirely during the 52-month production period) had elevated serum thyrotropin levels (mean 37.5 versus #1.5–8 μU/ml normal range), low or borderline low serum thyroxine (T_4) levels (4.4 versus 4.5–11.5 μg/dL) and free-thyroxine indices (3.7 versus 3.8–10.8), and markedly elevated thyroid antimicrosomal antibody titers (1:6,400 or above). Serum T_4 levels measured 7 months earlier in two of the four men were normal. Antithyroglobulin antibodies were elevated in one of the four subjects (not evaluated in other workers). The exposed cohort had significantly more subjects with elevated serum thyrotropin (p=0.006), but free thyroxine index (p=0.06), serum T_4 level (p=0.11) and antimicrosomal antibody titer (p=0.06) did not differ significantly from the controls. Questioning about exposure to 74 occupational toxicants showed that three of the four hypothyroid subjects had only three common chemical exposures (PBBs, decaBDE, and bromine); the fourth worker was hired after PBB production ceased and was exposed only to decaBDE and bromine, but it is not clear if PBBs were still present in the work environment. Except for one control subject who had an enlarged thyroid, none of the exposed or control subjects had signs of thyroid enlargement, thyroid nodularity or hypothyroidism on physical examination, or had reported taking thyroid medication or having thyroid problems within the previous 5 years. Reevaluation of three of the four subjects 1 year later (none had been treated with thyroid hormone) showed that two still had low free-thyroxine indices and high serum thyrotropin, one had a normal free-thyroxine index and a high-normal serum thyrotropin, and all three still had markedly elevated thyroid antimicrosomal antibody titers. The findings of this study suggest that occupational exposure to PBBs, decaBDE, and/or bromine affected the thyroid, but the mixed chemical exposure and a lack of data on serum or tissue levels of the chemicals preclude attributing effects solely to any particular congener or mixture of congeners.

Polybrominated Diphenyl Ethers. There is suggestive evidence of hypothyroidism in a small group of workers who were occupationally exposed to decaBDE as well as PBBs (Bahn et al. 1980), as summarized in the preceding subsection on endocrine effects of PBBs.

No histopathological changes were observed in the thyroid, parathyroid, adrenal, or pituitary of rats that were exposed to 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978).

Dermal Effects.

Polybrominated Biphenyls. In a medical history survey study, 7 of 10 (70%) workers in the production department of a PBB manufacturing plant reported that they experienced symptoms of skin disorders, compared with 31% of 45 workers in other departments in the same plant and 18% in a control group of 153 Wisconsin farm residents (Chanda et al. 1982). The survey covered a period of 3 years of potential exposure, but exposure levels were not reported. The dermatological symptoms were described as "almost uniformly" halogen acne (bromacne). Mean serum PBB levels for the respective PBB groups (with ranges listed in parentheses) were 603.9 ppb (11.4–1,729 ppb) and 16.5 ppb (4–234 ppb); PBBs were not detected in serum of the control subjects (Chanda et al. 1982). Physical examination confirmed the occurrence of bromacne in 13% of PBB workers compared with no acne in the control group. No other studies were located regarding dermal effects in humans after occupational exposure to PBBs.

No studies were located regarding dermal effects in animals after inhalation exposure to PBBs.

Ocular Effects.

Polybrominated Biphenyls. No studies were located regarding ocular effects in humans after inhalation exposure to PBBs.

Signs of ocular irritation (no further description) were observed in five male and five female rats that were exposed to a decabromobiphenyl dust mixture at 5,000 mg/m^3 concurrently with starch dust (6 mg/m^3) for 6 hours/day, 5 days/week for 4 weeks (Millischer et al. 1980). The seriousness of this effect is unclear as severity was not reported and recovery was not assessed. Ocular irritation was not observed at 500 mg/m^3 and lower concentrations.

Polybrominated Diphenyl Ethers. No studies were located regarding ocular effects in humans after inhalation exposure to PBDEs.

Transient signs of ocular irritation that included eye squint, erythema, and/or ocular discharge were observed in rats that were chamber-exposed to pentaBDE aerosol (compound dissolved in corn oil), octaBDE dust, or decaBDE dust in concentrations of 2,000, 2,000, and 48,200 mg/m^3, respectively, for 1 hour (IRDC 1974, 1975a, 1975b). Confidence in these effect levels is low due to a small number of

tested animals and lack of control data. No histopathological changes were observed in eyes of rats that were exposed to 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978).

3.2.1.3 Immunological and Lymphoreticular Effects

Polybrominated Biphenyls. Several immunological parameters were evaluated in a group of 28 workers from the Michigan Chemical Company who were involved in manufacturing and distributing PBBs (Stross et al. 1981). This company manufactured the FireMaster FF-1 that was involved in the agricultural contamination episode in Michigan in 1973–1974. The subjects had worked directly with PBBs during the previous 5 years, but exposure levels were not reported. Immunological analyses included determination of immunoglobulin levels, skin testing, and lymphocyte transformation studies. No abnormalities in lymphocyte number or function could be determined when compared to an unexposed group. One of three blastogenic responses (pokeweed mitogen [PWM]) was significantly reduced ($p<0.01$) relative to concurrent controls, but was within the normal control range for the laboratory. PWM is a mitogenic lectin that stimulates both human T and B cells. No specific information was provided regarding the skin testing and immunoglobulin levels.

No studies were located regarding immunological or lymphoreticular effects in animals after inhalation exposure to PBBs.

Polybrominated Diphenyl Ethers. No studies were located regarding immunological or lymphoreticular effects in humans after inhalation exposure to PBDEs.

No histopathological changes were observed in lymph nodes or bone marrow from rats that were exposed to 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978).

3.2.1.4 Neurological Effects

Polybrominated Biphenyls. Twenty-five workers at a PBB-manufacturing plant (exposure duration and levels not reported) displayed mean scores on tests of memory and learning that were typical for people of their age, and educational, occupational, and cultural backgrounds, even though they had an elevated mean PBB concentration in adipose tissue (9.33 ppm) (Brown et al. 1981). Workers with the highest concentrations of PBBs in adipose tissue showed no evidence of memory dysfunction in these tests.

No studies were located regarding neurological effects in animals after inhalation exposure to PBBs.

Polybrominated Diphenyl Ethers. No studies were located regarding neurological effects in humans or animals after inhalation exposure to PBDEs.

3.2.1.5 Reproductive Effects

Polybrominated Biphenyls. Eleven workers in a PBB manufacturing company (exposure duration and levels not reported) displayed no differences in the distribution of sperm counts, motility, or sperm morphology compared with a control group of 52 nonexposed men (Rosenman et al. 1979). PBBs were detected in the serum of all exposed subjects and in only one nonexposed subject, but no mean or individual serum PBB values were reported.

No studies were located regarding reproductive effects in animals after inhalation exposure to PBBs.

Polybrominated Diphenyl Ethers. No studies were located regarding reproductive effects in humans after inhalation exposure to PBDEs.

No histopathological changes were observed in ovaries or testes from rats that were exposed to 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (IRDC 1978).

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to PBBs or PBDEs.

3.2.1.7 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to PBBs or PBDEs.

3.2.2 Oral Exposure

No studies were located regarding cancer in humans or animals after inhalation exposure to PBBs.

3.2.2.1 Death

Polybrominated Biphenyls. No studies were located regarding death in humans after oral exposure to PBBs.

Limited information is available on lethal amounts of PBBs in animals. In general, dosing regimen and magnitude affect response. The lack of decreased survival in some studies does not necessarily indicate low toxicity because observation periods may not be sufficient to observe effects that develop slowly.

Except as noted below, acute-duration studies administered PBBs by gavage in oil vehicle. A single 1,000 mg/kg dose of FireMaster FF-1 did not significantly increase mortality in rats observed for #2 years posttreatment (Kimbrough et al. 1978b, 1981). Exposing pregnant rats to #800 mg/kg FireMaster BP-6 on one of gestation days 6–14 did not significantly increase mortality, but the animals were not observed beyond pregnancy (Beaudoin 1977). Administration of 1,000 mg/kg/day FireMaster FF-1 for 6–10 doses (5 days/week), however, caused 100% mortality in rats; the mean time to death was 12.3 days in females and 11.0 days in males (Gupta and Moore 1979). The cause of death was not specifically reported, but a general statement indicated that the rats had hunchback posture, rough coat, and sunken eyes, were lethargic, and appeared dehydrated and emaciated. No deaths occurred in rats administered octabromobiphenyl mixture in a single dose #1,000 mg/kg with 4 weeks of observation (Lee et al. 1975a), 2,000 mg/kg with 2 weeks of observation (Norris et al. 1975a), 17,000 mg/kg with 1 week of

observation (Lee et al. 1975a; Waritz et al. 1977), or 3,000 mg/kg/day on 2 consecutive days with 4 weeks of observation (Lee et al. 1975a). The 17,000 mg/kg dose was the highest that was feasible to administer, apparently due to gavage volume because it had to be administered as divided doses given in a 4-hour period. Dietary administration of octabromobiphenyl mixture in estimated dosages of #70 mg/kg/day for 2 weeks was not lethal in rats, but there was no posttreatment observation period (Lee et al. 1975b; Waritz et al. 1977). In the only study of a decabromobiphenyl mixture, a single dose as high as 5,000 mg/kg caused no deaths in rats observed for 14 days (Millischer et al. 1980). In mice, dietary administration of FireMaster BP-6 for 2 weeks produced death (cause not reported) at estimated doses of 130 mg/kg/day, but not #36 mg/kg/day (Cagen et al. 1977; Fraker 1980; Fraker and Aust 1980). Information on acute oral lethality in species other than rats and mice was not located.

In intermediate-duration studies with rats, no deaths were induced by dietary administration of FireMaster BP-6 at estimated dosages of #5 mg/kg/day for #82 days (Darjono et al. 1983) or #10 mg/kg/day for 30 days (Akoso et al. 1982a). No deaths were observed in rats fed #50 mg/kg/day of an unspecified PBB mixture for 30 or 60 days (Sleight and Sanger 1976). Twice weekly gavage with 100 mg/kg FireMaster FF-1 in corn oil for two 3-week dosing periods, separated by . 6 weeks, was not lethal in rats observed for 2 years (Kimbrough et al. 1981). Twenty-two gavage doses of 100 mg/kg FireMaster FF-1 in corn oil (5 days/week for 4.5 weeks) produced 38 and 100% mortality in male and female rats, respectively; the average times to death were 46.7 and 60.3 days, respectively (Gupta and Moore 1979). Similar treatment with 30 mg/kg/day FireMaster FF-1 was not lethal in rats observed for . 5 months. Based on these gavage data, the calculated LD_{50} in rats observed for . 60 days posttreatment (i.e., 90-day $LD_{50)}$ was 149 and 65 mg/kg/day for male and female rats, respectively (Gupta and Moore 1979). This study did not specifically address the cause of death, but emaciated appearance and gross loss of subcutaneous and visceral adipose tissue indicate wasting was a contributing factor. Rats that were treated with FireMaster FF-1 in corn oil by gavage on 5 days/week for 25 weeks exhibited dose-related decreased survival at $0.3 mg/kg/day (cause of death not discussed), but not at 0.1 mg/kg/day (NTP 1983). The decreased survival was only apparent when the rats were observed for a lifetime (. 15–22 months posttreatment) and consistent only in males. Survival was also decreased in male but not female rats given $0.5 mg/kg/day FireMaster FF-1 in the diet for up to 104 weeks (Chhabra et al. 1993; NTP 1992). The decreased survival appeared to be related to increased incidences of mononuclear cell leukemia. No deaths were observed in rats treated with octabromobiphenyl mixture in the diet at estimated dosages of #71 mg/kg/day for 4 weeks and observed for #18 weeks (Lee et al. 1975b; Waritz et al. 1977). Rats treated with #1 mg/kg/day dietary octabromobiphenyl mixture for 8 months did not die, but there were some deaths (number and cause not reported) in rats treated with higher dietary dosages (8–800 mg/kg/day) for

30 days (Norris et al. 1975a). Insufficient information is available to determine if the deaths were treatment-related, since incidences and other pertinent information were not reported.

Survival data for intermediate-duration exposure to PBBs are less extensive for species other than rat, but indicate that guinea pigs and mink are particularly susceptible. High mortality occurred in guinea pigs fed estimated dosages of 2 mg/kg/day FireMaster BP-6 for 45 days (Vos and van Genderen 1973, 1974) or $4 mg/kg/day of an unspecified PBB mixture for 30 days (Sleight and Sanger 1976); dosages of #0.4 mg/kg/day of either mixture were not lethal. The Litchfield and Wilcoxon procedure was used to calculate dietary LD_{50} values of 0.47 and 0.61 mg/kg/day (estimated dosages) for male and female mink, respectively, exposed to FireMaster FF-1 for life (63–294 days) (Aulerich and Ringer 1979; Ringer et al. 1981). Dosages #0.18 mg/kg/day did not significantly increase mortality in the mink. Dietary administration of FireMaster BP-6 in an estimated dosage of 21.7 mg/kg/day for 12 weeks caused some deaths in mice (number not reported), leading to sacrifice of other test animals (Martino et al. 1981; Wilson-Martino et al. 1980). Mean survival time decreased significantly in female mice treated with 10 mg/kg/day of FireMaster FF-1 in corn oil by gavage on 5 days/week for 25 weeks, but not #3 mg/kg/day (NTP 1983). Decreased survival was only apparent when the mice were observed for #24 months posttreatment (lifetime observation) and not observed in similarly treated males. Survival was also decreased in female mice given $1.3 mg/kg/day FireMaster FF-1 in the diet for up to 105 weeks; decreased survival occurred in similarly treated male mice at 3.9 mg/kg/day (Chhabra et al. 1993; NTP 1992). The cause of death was not discussed in the NTP(1983, 1992) mouse studies, but hepatocellular tumors increased significantly in both sexes at dosages that decreased survival.

No deaths occurred in two swine that ingested estimated dosages of #8 mg/kg/day for 16 weeks; one pig was observed for 102 days following exposure and the other for 14 weeks following exposure (Ku et al. 1978). An adult male monkey died after consuming 0.73 mg/kg/day FireMaster FF-1 in the diet for 25 weeks (Allen et al. 1978; Lambrecht et al. 1978). The death was attributed to severe gastrointestinal changes, including ulcerative colitis. The only other animal in this study was a juvenile female who survived 50 weeks of a dietary dosage of 1.43 mg/kg/day. In another study, one juvenile female monkey that consumed 18 mg/kg/day FireMaster FF-1 in the diet died after 137 days of continuous exposure (Allen et al. 1978). Although only one or two monkeys were tested in these studies, effects characteristic of PBB poisoning (e.g., dermal changes, body weight loss) indicate that the deaths were exposure-related. Pregnant cows given 67 mg/kg/day FireMaster BP-6 in capsules for 60 days (dosing began $10 days after pregnancy diagnosis) were sacrificed between days 33 and 66 because of impending death (Moorhead et al. 1977). Clinical signs developed progressively and included anorexia, emaciation, and depressed

general condition. No mortality occurred in cows treated with #0.65 mg/kg/day and observed for 1 or 140 days following the end of treatment.

The LD_{50} value and reliable LOAEL values for death in each species in the acute- and intermediate-duration categories are recorded in Table 3-1 and plotted in Figure 3-1.

Polybrominated Diphenyl Ethers. No deaths occurred in rats that were treated with a single gavage dose of #5,000 mg/kg of decaBDE or #2,000 mg/kg of 77.4% decaBDE (containing 21.8% nonaBDE and 0.8% octaDBE) and observed for the following 14 days (IRDC 1974; Norris et al. 1975b). No mortality was observed in rats and mice that were exposed to decaBDE via diet in estimated doses of #16,000 and #19,000 mg/kg/day, respectively, for 14 days (NTP 1986).

In intermediate-duration dietary studies with decaBDE, there was no exposure-related mortality in rats that were exposed to estimated dietary doses of #90 mg/kg/day for 28 days (IRDC 1976) or rats and mice fed estimated doses of #8,000 and #9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986). In chronic studies, there were no effects on survival in rats that were fed 0.01–1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaDBE) for 2 years (Kociba et al. 1975; Norris et al. 1975b), or in rats and mice fed decaBDE in estimated doses of #2,550 and #7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986).

No deaths occurred in rats that were administered octaBDE by gavage in single doses #5,000 mg/kg and observed for the following 14 days (IRDC 1975a). Intermediate-duration dietary studies with octaBDE, observed no mortality in rats exposed to estimated dietary doses of #90 mg/kg/day for 28 days or #750 mg/kg/day for 13 weeks (IRDC 1976, 1977).

Single-dose gavage LD_{50} values of 5,000 and 6,200 mg/kg were determined for pentaBDE (Saytex 115 and DE-71, respectively) in rats that were observed for 14 days (British Industrial Biological Research Association 1977; Pharmakon Research International Inc. 1984). Another study found that a single 5,000 mg/kg dose of pentaBDE caused deaths in four of five rats in the 14 days following treatment,

Table 3-1. Levels of Significant Exposure to PBBs - 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 (Fischer 344/N)	2 wk 5d/wk 1x/d (GO)				1000 (18/18 died)	Gupta and Moore 1979 (FF-1)
2	Mouse (Balb/c)	14 d ad lib (F)				130 F (63% lethality)	Fraker 1980 Fraker and Aust 1978 (BP-6)
	Systemic						
3	Rat (Sprague-Dawley)	10 d 1x/d (GO)	Endocr	1[b]	3 M (decreased thyroid plasma T4 hormone)		Allen-Rowlands et al. 1981 (NS)
4	Rat (Sprague-Dawley)	once (GO)	Endocr	286 M			Allen-Rowlands et al. 1981 (NS)
5	Rat (Wistar)	once Gd 6-14 (GO)	Bd Wt	400 F	800 F (unknown percent maternal weight loss)		Beaudoin 1977 (BP-6)
6	Rat (Sherman)	once 18 mo observation (GO)	Hepatic		500 M (increased hepatic phospholipids and serum cholesterol)		Bernert et al. 1983 (FF-1)

Table 3-1. Levels of Significant Exposure to PBBs - 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
7	Rat (Fischer 344/N)	2 wk 5 d/wk 1x/d (GO)	Hepatic		1000	(hepatocytic swelling, fatty infiltration, multinucleation, necrosis, and cytolysis)			Gupta and Moore 1979 (FF-1)
			Renal		1000	(darkened kidneys)			
			Endocr		1000	(darkened adrenal glands)			
			Bd Wt				1000	(unknown percent weight loss, emaciation)	
8	Rat (Fischer 344/N)	2 wk 5 d/wk 1x/d (GO)	Resp	30					Gupta et al. 1981 (FF-1)
			Cardio	30					
			Gastro	30					
			Hemato	30					
			Musc/skel	30					
			Hepatic	0.3	3	(dose-related hepatocyte enlargement and single-cell necrosis)			
			Renal	30					
			Endocr	30					
			Derm	30					
			Ocular	30					
			Bd Wt	30					

Table 3-1. Levels of Significant Exposure to PBBs - 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
9	Rat (Sherman)	once 2-14 mo observa-tion (GO)	Resp	1000			Kimbrough et al. 1978 (FF-1)
			Cardio	1000			
			Gastro	1000			
			Hepatic			1000 (vacuolation, necrosis, and fibrosis, porphyria, multinucleation)	
			Renal	1000			
			Endocr	1000			
			Bd Wt	1000			
10	Rat (Sherman)	once 15wk observa-tion (GO)	Hepatic		500 M (vacuolation of hepatocytes)		Kimbrough et al. 1980 (FF-1)
			Bd Wt	500 M			
11	Rat (Sherman)	once 18-22mo observa-tion (GO)	Resp	200 F			Kimbrough et al. 1981 (FF-1)
			Cardio	200 F			
			Hepatic		200 F (porphyrin accumulation)		
			Renal	200 F			
			Endocr	200 F			
			Derm	200 F			
			Bd Wt	200 F			

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Table 3-1. Levels of Significant Exposure to PBBs - 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
12	Rat (Sherman)	once 23mo observation (GO)	Resp	1000 F			Kimbrough et al. 1981 (FF-1)
			Cardio	1000 F			
			Gastro	1000 F			
			Musc/skel	1000 F			
			Hepatic		1000 F (hepatomegaly, hepatocyte enlargement and vacuolation, porphyrin accumulation)		
			Renal	1000 F			
			Endocr	1000 F			
			Ocular	1000 F			
			Bd Wt		1000 F (12% decreased body weight gain)		
13	Rat (Sprague-Dawley)	once 28d observation (GO)	Hepatic		1000 M (fatty changes in centrilobular hepatocytes)		Lee et al. 1975a (OBB)
			Bd Wt	1000 M			
14	Rat (Sprague-Dawley)	2 d 1x/d (GO)	Hepatic		3000 M (fatty changes in centrilobular hepatocytes)		Lee et al. 1975a (OBB)
			Bd Wt	1000 M			
15	Rat (Sprague-Dawley, Spartan)	once (GO)	Bd Wt	2000 F			Norris et al. 1975 (OBB)
16	Rat (Fischer 344)	10 d ad lib (F)	Hepatic		5 M (hepatomegaly and fatty changes in weanlings)		Raber and Carter 1986 (BP-6)
			Bd Wt	5 M			

Table 3-1. Levels of Significant Exposure to PBBs - 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
17	Rat (Sprague-Dawley)	2 wk ad lib (F)	Hepatic	0.66 M	6.53 M (hyperplasia and fatty changes)		Waritz et al. 1977; Lee et al. 1975b (OBB)
			Renal	71 M			
			Endocr	71 M			
			Bd Wt	71 M			
18	Mouse (Swiss-Webster)	2 wk ad lib (F)	Hepatic	36 F			Cagen et al. 1977 (BP-6)
19	Mouse (Swiss/ IRC)	11 d ad lib (F)	Hepatic		130 F (focal areas of coagulative necrosis)		Corbett et al. 1975 (BP-6)
20	Mouse (Swiss/ IRC)	4-14 d ad lib (F)	Bd Wt			130 M (30% decreased body weight)	Corbett et al. 1978 (BP-6)
21	Mouse (Balb/c)	14 d ad lib (F)	Bd Wt			130 F (23% weight loss)	Fraker 1980 Fraker and Aust 1978 (BP-6)

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Table 3-1. Levels of Significant Exposure to PBBs - 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
22	Mouse (B6C3F1)	2 wk 5 d/wk 1x/d (GO)	Resp	30			Gupta et al. 1981 (FF-1)
			Cardio	30			
			Gastro	30			
			Hemato	30			
			Musc/skel	30			
			Hepatic	0.3	3 (dose-related increase in incidence of hepatocyte enlargement and single-cell necrosis)		
			Renal	30			
			Endocr	30			
			Ocular	30			
			Bd Wt	30			
			Other	30			
	Reproductive						
23	Rat (Sherman)	once 23mo observation (GO)			1000 F (9% increased incidence of uterine polyps)		Kimbrough et al. 1981 (FF-1)
24	Mouse (C57BL)	9 d Gd 6-15 1x/d (F)		21 F		63 F (29% reduction in success of pregnancy)	Welsch and Morgan 1985 (HBB)
	Developmental						
25	Rat (Wistar)	once Gd 6-14 (GO)		40		200 (9.1-31.4% resorptions)	Beaudoin 1977 (BP-6)

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Table 3-1. Levels of Significant Exposure to PBBs - 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
26	Rat (Sprague-Dawley)	14 d Gd 7-20 (F)		5	50 (12% decrease in fetal body weight)		Corbett et al. 1975 (BP-6)
27	Rat (Sherman)	Gd 7-14 1x/d (GO)				200 (increased mortality and liver neoplasms in offspring)	Groce and Kimbrough 1984 (FF-1)
28	Rat (NS)	9 d Gd 7-15 1x/d (GO)			42.9 (12-20% decreased mean body weight in treated pups at post-parturition day 60)		Harris et al. 1978 (BP-6)
29	Rat (Sprague-Dawley, Iffa credo)	10 d Gd 6-15 1x/d (GO)		1000			Millischer et al. 1980 (DBB)
30	Rat (ChR-CD)	10 d Gd 6-15 ad lib (F)		9.1	86 (increased incidence of extra ribs)		Waritz et al. 1977 (OBB)
31	Mouse (Swiss/ IRC)	12 d Gd 7-18 (F)		5		50 (cleft palate)	Corbett et al. 1975 (BP-6)
	Cancer						
32	Rat (Sherman)	Gd 7-14 1x/d (GO)				200 (CEL: hepatocellular carcinoma in offspring)	Groce and Kimbrough 1984 (FF-1)

Table 3-1. Levels of Significant Exposure to PBBs - 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
33	Rat (Sherman)	once (GO)				1000 F (CEL: hepatocellular carcinoma)	Kimbrough et al. 1981 (FF-1)
	Immuno/Lymphor						
34	Rat (Fisher 344/N)	10 d 5 d/wk 1x/d (GO)				1000 (atrophy of thymus; necrosis of splenic lymphoblasts)	Gupta and Moore 1979 (FF-1)
35	Mouse (Balb/c)	14 d ad lib (F)				130 F (suppressed antibody-mediated response to SRBC, thymic atrophy)	Fraker 1980 Fraker and Aust 1978 (BP-6)

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Table 3-1. Levels of Significant Exposure to PBBs - 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
	INTERMEDIATE EXPOSURE						
	Death						
36	Rat (Fischer 344/N)	4.5 wk 5 d/wk 22 d (GO)				65[e] F (90-day LD50)	Gupta and Moore 1979 (FF-1)
						149 M (90-day LD50)	
37	Rat (Fischer 344/N)	25 wk 5 d/wk 1x/d (GO)				0.3 M (decreased mean survival time)	NTP 1983 (FF-1)
38	Mouse (B6C3F1)	25 wk 5 d/wk 1x/d (GO)				10 F (decreased mean survival time)	NTP 1983 (FF-1)
39	Gn pig (NS)	30 d ad lib (F)				4 M (4/6 died)	Sleight and Sanger 1976 (NS)
40	Gn pig (NS)	45 d ad lib (F)				2.0 F (7/8 died)	Vos and van Genderen 1973, 1974 (BP-6)
41	Mink (NS)	313 d ad lib (F)				0.47[e] M (LD50)	Aulerich and Ringer 1979 (FF-1)
						0.61 F (LD50)	

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Table 3-1. Levels of Significant Exposure to PBBs - 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
	Systemic						
42	Monkey (Rhesus)	137 d ad lib (F)	Gastro		18 F (hyperplastic gastroenteritis)		Allen et al. 1978 (FF-1)
			Hemato		18 F (decreased RBC, PCV, and WBC)		
			Hepatic		18 F (enlarged hepatocytes, hyperplasia of bile duct epithelium, increased SGPT, decreased serum cholesterol)		
			Renal		18 F (hyperplasia of bladder epithelium)		
			Endocr			18 F (adrenal hemorrhage)	
			Derm		18 F (edema, atrophy, and squamous metaplasia of sebaceous glands)		
			Bd Wt			18 F (27% body weight loss)	

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Table 3-1. Levels of Significant Exposure to PBBs - 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
43	Monkey (Rhesus)	25-50 wk ad lib (F)	Cardio		0.73 M (enlarged heart at necropsy)		Allen et al. 1978; Lambrecht et al. 1978 (FF-1)
			Gastro			0.73 M (proliferation of mucosal cells, chronic inflammatory cells, severe ulcerative colitis)	
			Hemato		0.73 M (decreased PCV and total serum protein)		
			Hepatic		0.73 (enlarged hepatocytes with increased lipid droplets, increased SGPT, decreased serum cholesterol, hyperplasia of bile duct epithelium)		
			Derm			0.73 (edema and alopecia, keratinization of hair follicles and sebaceous glands)	
			Bd Wt			0.73 (34% weight loss in adult male, 0% weight gain in juvenile)	

Table 3-1. Levels of Significant Exposure to PBBs - 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
44	Rat (Sprague-Dawley)	30 d ad lib (F)	Resp	10 M			Akoso et al. 1982a (BP-6)
			Cardio	10 M			
			Gastro	10 M			
			Hemato	10 M			
			Musc/skel	10 M			
			Hepatic		0.1 M (hepatocyte swelling, vacuolation)		
			Renal	10 M			
			Endocr	10 M			
			Derm	10 M			
			Ocular	10 M			
			Bd Wt	10 M			
45	Rat (Sprague-Dawley)	30 d ad lib (F)	Endocr		0.05 M (altered thyroid follicular ultrastructure)		Akoso et al. 1982b (BP-6)
46	Rat (Sprague-Dawley)	20 d 1x/d (GO)	Endocr		1 M (decreased serum thyroid hormone T4)		Allen-Rowlands et al. 1981 (NS)
47	Rat (Sprague-Dawley)	7 mo ad lib (F)	Endocr		0.45 F (decreased thyroid serum T3 and T4 hormones)		Byrne et al. 1987 (BP-6)
48	Rat (Sprague-Dawley)	5-7 mo ad lib (F)	Endocr	0.05 F	0.25 F (decreased adrenal serum corticosterone B, DHEA and DHS hormones)		Byrne et al. 1988 (BP-6)

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Table 3-1. Levels of Significant Exposure to PBBs - 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)	20 d 1x/d (GO)	Endocr	6 M			Castracane et al. 1982 (NS)
50	Rat (Sprague-Dawley)	28 d ad lib (F)	Resp	2 M			Chu et al. 1980 (BP-6)
			Cardio	2 M			
			Gastro	2 M			
			Hemato	2 M			
			Hepatic		2 M (increased liver weight, increased liver microsomal enzymes, fatty degeneration of liver)		
			Renal	2 M			
			Endocr		2 M (reduction of follicular size and colloid density and exfoliation of epithelium in thyroid)		
			Derm	2 M			
			Bd Wt	2 M			
51	Rat (Sprague-Dawley)	82 d ad lib (F)	Hepatic		0.5 M (bile duct hyperplasia)		Darjono et al. 1983 (BP-6)
			Ocular		5 M (xerophthalmia)		
			Bd Wt	5 M			

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Table 3-1. Levels of Significant Exposure to PBBs - 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
52	Rat (Fischer 344/N)	4.5 wk 5 d/wk 1x/d (GO)	Cardio	1000			Gupta and Moore 1979 (FF-1)
			Gastro	1000			
			Hemato		30 (decreased hemoglobin, PCV, and platelet count)		
			Hepatic		30 (hepatocyte enlargement, fatty infiltration and multinucleation, porphyrin accumulation)		
			Renal		30 (dilation of Bowman's capsule with serous fluid)		
			Endocr		30 (unspecified altered thyroid histology)		
			Bd Wt		30 (19% decreased body weight gain)	100 (emaciation)	
53	Rat (Fischer 344/N)	30 d 5 d/wk 1x/d (GO)	Resp	30			Gupta et al. 1981 (FF-1)
			Cardio	30			
			Gastro	30			
			Hemato	30			
			Musc/skel	30			
			Hepatic	0.3	3.0 (increased liver weight, hepatocyte swelling, and necrosis)		
			Renal	30			
			Bd Wt	3	30 (significant decrease in body weight)		

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Table 3-1. Levels of Significant Exposure to PBBs - 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 (Holtz-man)	5 wk ad lib (F)	Hepatic	0.25 M	2.5 M (hepatocyte hypertrophy and degeneration)		Kasza et al. 1978 (BP-6)
55	Rat (Holtz-man)	5 wk ad lib (F)	Endocr		0.25 M (colloid droplets, abnormal microvilli and other changes in thyroid follicle ultrastructure)		Kasza et al. 1978 (BP-6)
56	Rat (Fischer 344)	6 mo 5 d/wk (GO)	Hemato		10 F (increased white blood cell count)		Luster et al. 1980 (FF-1)
			Bd Wt	1.0 F	3.0 F (15% decreased weight gain)		
57	Rat (Sprague-Dawley)	3 mo ad lib (F)	Hepatic		5 F (enlarged and vacuolated hepatocytes, focal necrosis)		McCormack et al. 1978 (BP-6)
			Renal		5 F (degenerative changes in glomeruli)		
			Bd Wt		5 F (10% decreased body weight gain)		
58	Rat (Sprague-Dawley CFY)	13 wk (F)	Gastro	100			Millischer et al. 1980 (DBB)
			Hemato	100			
			Hepatic	25	100 (11% increased liver weight, hepatocyte hypertrophy and vacuolization, slightly increased liver lipids)		
			Renal	100			
			Bd Wt	100			

Table 3-1. Levels of Significant Exposure to PBBs - 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
59	Rat (Sprague-Dawley)	30 d ad lib (F)	Cardio	800 M			Norris et al. 1975 (OBB)
			Hemato	80 M	800 M (decreased PCV and RBC counts)		
			Hepatic		8 M (enlargement and vacuolation)		
			Renal		8 M (hyaline degenerative changes)		
			Endocr		8 M (thyroid hyperplasia)		
			Bd Wt	800 M			
60	Rat (Sprague-Dawley)	8 mo ad lib (F)	Cardio	1			Norris et al. 1975 (OBB)
			Hemato	1			
			Hepatic	1			
			Renal	1			
			Endocr	1			
			Bd Wt	1			

Table 3-1. Levels of Significant Exposure to PBBs - 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
61	Rat (Fischer 344/N)	25 wk 5 d/wk 1x/d (GO)	Resp	10			NTP 1983 (FF-1)
			Cardio	10			
			Gastro	0.3	1 (gastric ulcers)		
			Hemato	0.1	0.3 (decreased hemoglobin, MCH, PCV, and MCV)		
			Musc/skel	10			
			Hepatic	0.1	0.3 (lipid accumulation; increased atypical foci; porphyrin accumulation)		
			Renal	0.3		1 (chronic progressive nephropathy)	
			Endocr	0.1	0.3 (decreased serum thyroid T4 hormone)		
			Ocular	10			
			Bd Wt	10			
62	Rat (Sprague-Dawley)	7 mo ad lib (F)	Endocr	2.5 F			Sepkovic and Byrne 1984 (HBB)
63	Rat (Sprague-Dawley)	7 mo ad lib (F)	Hepatic	2.5 F			Sepkovic and Byrne 1984 (OBB)
			Endocr	2.5 F			

Table 3-1. Levels of Significant Exposure to PBBs - 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
64	Rat (Sprague-Dawley)	30 d ad lib (F)	Resp	50 M			Sleight and Sanger 1976 (NS)
			Cardio	50 M			
			Gastro	50 M			
			Hemato	50 M			
			Musc/skel	50 M			
			Hepatic		1 M (hepatocyte vacuolation)		
			Renal	10 M	50 M (unquantified, but significantly increased BUN)		
			Endocr	50 M			
			Bd Wt	10 M	50 M (16% decreased weight gain)		
65	Rat (Sprague-Dawley)	30 d ad lib (F)	Resp	5 M			Sleight et al. 1978 (BP-6)
			Cardio	5 M			
			Gastro	5 M			
			Hemato	5 M			
			Hepatic	0.5 M	5 M (hepatocyte swelling and vacuolation)		
			Renal	5 M			
			Endocr	0.5 M	5 M (hyperplasia of thyroid follicular epithelium)		
			Bd Wt	0.5 M	5 M (27-36% reduced body weight gain)		

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Table 3-1. Levels of Significant Exposure to PBBs - 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
66	Rat (Sprague-Dawley)	4 wk ad lib (F)	Hepatic	0.66 M	6.53 M (hyperplasia and progressive lipid changes)		Waritz et al. 1977; Lee et al. 1975b (OBB)
			Renal	71 M			
			Endocr	71 M			
			Bd Wt	71 M			
67	Mouse (Balb/c)	30 d ad lib (F)	Bd Wt	13 F			Fraker 1980 Fraker and Aust 1978 (BP-6)
68	Mouse (B6C3F1)	30 d 5 d/wk 1x/d (GO)	Resp	30			Gupta et al. 1981 (FF-1)
			Cardio	30			
			Gastro	30			
			Hemato		30 F (decreased PCV)		
			Musc/skel	30			
			Hepatic	0.3	3 (hepatocyte enlargement and necrosis)		
			Renal	30			
			Ocular	30			
			Bd Wt	3	30 M (significant decrease in weight gain)		
			Other	30			

Table 3-1. Levels of Significant Exposure to PBBs - 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
69	Mouse (Balb/ cBYJ)	6 wk ad lib (F)	Resp	21.7 M			Loose et al. 1981 (FF-1)
			Cardio	21.7 M			
			Hepatic	0.65 M		21.7 M (hepatocellular necrosis and vacuolation)	
			Renal	21.7 M			
			Endocr	0.65 M			
			Bd Wt	0.65 M		21.7 M (33% reduction in body weight)	
70	Mouse (B6C3F1)	6 mo 5 d/wk (GO)	Hemato	10			Luster et al. 1980 (FF-1)
			Endocr		10 (increased adrenal weight gain)		
			Bd Wt	10			

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Table 3-1. Levels of Significant Exposure to PBBs - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL	LOAEL Less serious	LOAEL Serious	Reference Chemical Form
71	Mouse (B6C3F1)	25 wk 5 d/wk 1x/d (GO)	Resp	10			NTP 1983 (FF-1)
			Cardio	10			
			Gastro	10			
			Hemato	0.1	0.3 (decreased erythrocyte count and MCV)		
			Musc/skel	10			
			Hepatic	0.1	0.3 (increased liver weight, SGOT and porphyrin accumulation)		
			Renal	10			
			Endocr	10			
			Ocular	10			
			Bd Wt	3 M		10 M (25% decreased body weight gain)	
72	Gn pig (NS)	30 d ad lib (F)	Resp	20 M			Sleight and Sanger 1976 (NS)
			Hepatic		0.04 M (vacuolation and fatty changes)		
			Bd Wt	0.4 M		4 M (severe weight loss prior to death)	

Table 3-1. Levels of Significant Exposure to PBBs - 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
73	Pig (NS)	16 wk ad lib (F)	Cardio	8			Ku et al. 1978 (NS)
			Gastro	1	8 (gross hyperplasia glandular stomach)		
			Hemato	8			
			Hepatic		1 (LDH increased)		
			Renal	8			
			Endocr		8 (increased adrenal weight)		
			Derm	1	8 (dermatosis)		
			Bd Wt		1 (12.9% reduced weight gain and food intake)		
74	Pig (NS)	12 wk Gwk 8-ppwk 4 ad lib (F)	Hepatic	0.125 F	1.25 F (fatty changes and necrosis)		Werner and Sleight 1981 (BP-6)
			Endocr	1.25 F	2.5 F (significant decrease in thyroid serum T3 and T4 hormones)		
75	Mink (NS)	313 d ad lib (F)	Cardio	2.4			Aulerich and Ringer 1979 Ringer and Aulerich 1981 (FF-1)
			Hepatic		0.24 F (48% increased relative liver weight, fatty infiltration)		
			Renal	2.4			
			Bd Wt		0.39 F (14% decreased prebreeding body weight gain)	1.86 F (up to 19% mean body weight loss prior to death)	

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Table 3-1. Levels of Significant Exposure to PBBs - 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						
76	Rat (NS)	6 mo 5 d/wk 1x/d (GO)			10 (decreased limb strength)		Cabe and Tilson 1978 (FF-1)
77	Rat (Sprague-Dawley Holtz-man)	4 wk 5 d/wk 1x/d (G)		3 M		6 M (decreased motor activity)	Geller et al. 1979 (FF-1)
78	Rat (Sprague-Dawley)	40d Gd 6-Ppd 24 (F)		0.2	2 (delayed acquisition of locomotion and reduced open field activity in offspring)		Henck et al. 1994 (BP-6)
79	Rat (Fischer 344/N)	6 mo 5 d/wk (GO)				3 (decreased motor activity, grip strength, and startle responsiveness)	Tilson and Cabe 1979 (FF-1)
80	Rat (Fischer 344/N)	4 wk 5 d/wk 1x/d (GO)				30 (decreased open field motor activity and grip strength)	Tilson and Cabe 1979 (FF-1)
	Reproductive						
81	Monkey (Rhesus)	25-50 wk ad lib (F)			0.73 M (hypoactive seminiferous tubules)		Allen et al. 1978; Lambrecht et al. 1978 (FF-1)

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Table 3-1. Levels of Significant Exposure to PBBs - 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
82	Monkey (Rhesus)	6 mo ad lib (F)				0.012 F (increased menstrual cycle duration in 4/7; implantation bleeding in 2/7)	Lambrecht et al. 1978; Allen et al. 1978; 1979 (FF-1)
83	Rat (Wistar)	15 d Gd 0-14 8x (GO)		14.3 F		28.6 F (no implantations in 2/5 rats)	Beaudoin 1979 (BP-6)
84	Rat (Fischer 344/N)	4-5 wk 5 d/wk 22 d (GO)		30 M 1000 F	100 M (squamous metaplasia, hyperplasia, and necrosis in epithelium of ductus deferens)		Gupta and Moore 1979 (FF-1)
85	Rat (Sprague-Dawley)	42 d Gd 8-ppd 28 ad lib (F)		5 F			McCormack et al. 1981 (BP-6)
86	Mouse (B6C3F1)	4-5 wk 5 d/wk 1x/d (GO)		30			Gupta et al. 1981 (FF-1)
87	Mink (NS)	313 d ad lib (F)		0.24	0.39 F (10% reduction in body weight)		Aulerich and Ringer 1979 (FF-1)

Table 3-1. Levels of Significant Exposure to PBBs - 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
	Developmental						
88	Rat (Wistar)	15 d Gd 0-14 8x (GO)		2.9		14.3 (increased resorptions)	Beaudoin (BP-6)
89	Rat (Holtz-man Sprague-Dawley)	4 wk 5 d/wk (G)		5			Geller et al. 1985 (FF-1)
90	Rat (Sprague-Dawley)	40 d Gd 6- ppd24 ad lib (F)				0.2 (deficits in learning behavior in offspring, 6 months after prenatal and lactational exposure)	Henck and Rech 1986 (BP-6)
91	Rat (Sprague-Dawley)	40d Gd 6-Ppd 24 (F)			0.2 M (reduced crown-rump length)		Henck et al. 1994 (BP-6)
92	Rat (Sprague-Dawley)	42 d Gd 8-ppd 28 ad lib (F)			0.5 (increased liver weight, hepatocyte vacuolation, decreased hepatic vitamin A content in F1 but not F2)	5 (decreased pup survival during lactation in F1)	McCormack et al. 1981 (BP-6)
93	Rat (Sprague-Dawley)	42-126 d Gd 8-ppd 28-112 ad lib (F)			5 (20% decrease in pup body weight gain, 50% decreased hepatic vitamin A, 256-285% decreased urinary uro- and coproporphyrins in pups)		McCormack et al. 1982a (BP-6)

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Table 3-1. Levels of Significant Exposure to PBBs - 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
94	Rat (Sprague-Dawley)	37 d Gd 0-ppd 15 ad lib (F)			2.5	(decreased body weight, increased relative liver weight, and decreased serum T4 in offspring)			Meserve et al. 1992 (BP-6)
95	Rat (Fischer 344/N)	77 d Gd 0-ppd 56 ad lib (F)			0.5	(hepatic vacuolization and altered foci in pups)			NTP 1992 Chhabra et al. 1993 (FF-1)
96	Mouse (B6C3F1)	42 d Gd 0- weaning 1x/2d (GO)		2	3	(decreased hematocrit in offspring)	10	(early postnatal death; no details provided)	Luster et al. 1980 (FF-1)
97	Mouse (B6C3F1)	77 d Gd 0- ppd 56 ad lib (F)			1.5	(hepatic cytomegaly and altered foci in pups)			NTP 1992 Chhabra et al. 1993 (FF-1)
98	Mouse (C57B1/6)	Gd 0-ppd 21 1x/2d (GO)			3	(performance deficits in offspring in a learned task)			Tilson 1992 (FF-1)
99	Pig (NS)	12 wk Gwk 8- ppwk 4 ad lib (F)		0.125			1.25	(increased relative liver weight, decreased serum thyroid hormone levels, and slight thyroid hyperplasia in offspring)	Werner and Sleight 1981 (BP-6)
100	Mink (NS)	313 d (F)			0.155	(decreased birth and 4-week weights in kits)			Aulerich and Ringer 1979 Ringer and Aulerich 1981 (FF-1)

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Table 3-1. Levels of Significant Exposure to PBBs - 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
	Cancer						
101	Rat (Sherman)	4 mo 12 x (GO)				100 (CEL: hepatocellular carcinoma)	Kimbrough et al. 1981 (FF-1)
102	Rat (Fischer 344/N)	25 wk 5 d/wk 1x/d (GO)				3 (CEL: hepatocellular carcinoma)	NTP 1983 (FF-1)
103	Mouse (B6C3F1)	25 wk 5 d/wk 1x/d (GO)				10 (CEL: hepatocellular carcinomas)	NTP 1983 (FF-1)
104	Mouse (B6C3F1)	77 d Gd 0-ppd 56 ad lib (F)				1.5 (CEL: hepatocullular adenoma and carcinoma in offspring)	NTP 1992 Chhabra et al. 1993 (FF-1)
	Immuno/Lymphor						
105	Rat (Fischer 344)	5 wk 5 d/wk (GO)		0.03 M	3.0 M (decreased lymphocytic response to mitogen stimulation; decrease in absolute and relative thymus weight)		Luster et al. 1978 (FF-1)
106	Rat (Fischer 344)	6 mo 5 d/wk 1x/d (GO)		1 F	3 F (decreased lymphoproliferative responses and decreased delayed hypersensitivity responses)		Luster et al. 1980 (FF-1)

Table 3-1. Levels of Significant Exposure to PBBs - 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
107	Mouse (Balb/c)	30 d ad lib (F)		0.13 F	1.3 F (reduced antibody mediated response to SRBC and 21% reduction in thymus weight)		Fraker 1980 Fraker and Aust 1978 (BP-6)
108	Mouse (Balb/ cBYJ)	6 wk ad lib (F)		0.65 M		21.7 M (increased lethality due to endotoxin challenge)	Loose et al. 1981 (FF-1)
109	Mouse (B6C3F1)	6 mo 5 d/wk 1x/d (GO)		3.0		10 (increased lethality due to infection with L monocytogenes; decreased response to mitogen stimulation)	Luster et al. 1980 (FF-1)
110	Gn pig (NS)	45 d ad lib (F)			0.4 F (reduced antitoxin titers following toxoid challenge)	4.0 F (thymic atrophy and follicular depletion in spleen)	Vos and van Genderen 1973, 1974 (BP-6)
111	Pig (NS)	12 wk Gwk 8- ppwk 4 ad lib (F)		1.25 F	2.5 F (reduced lymphocyte response to mitogen stimulation)		Howard et al. 1980 (BP-6)

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Table 3-1. Levels of Significant Exposure to PBBs - 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							
112	Rat (Fischer 344/N)	115 wks Gd 0-ppd 56 (weaning) 104 wks post-weaning ad lib (F)				0.5 M (18% decreased survival)	NTP 1992 Chhabra et al. 1993 (FF-1)
113	Mouse (B6C3F1)	116 wks Gd 0-ppd 56 (weaning) 105wks post-weaning ad lib (F)				1.3 F (44% decreased survival)	NTP 1992 Chhabra et al. 1993 (FF-1)
Systemic							
114	Monkey (Rhesus)	66 wk ad lib (F)	Hemato	0.012			Lambrecht et al. 1978 (FF-1)
			Bd Wt		0.012 (7.4% weight loss)		

Table 3-1. Levels of Significant Exposure to PBBs - 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
115	Rat (Fischer 344/N)	115 wks Gd 0-ppd 56; 104 wks post-weaning (F)	Resp	1.5			NTP 1992 Chhabra et al. 1993 (FF-1)
			Cardio	1.5			
			Gastro	0.5	1.5 M (forestomach hyperplasia, inflammation, ulceration)		
			Hemato	0.5	1.5 F (mild anemia)		
			Musc/skel	1.5			
			Hepatic		0.5 (hypertrophy, vacuolation, altered foci, increased serum cholesterol, decreased serum triglycerides)		
			Renal	1.5			
			Endocr	1.5			
			Derm	1.5			
			Bd Wt		0.5 (11-18% decreased final body weight)		

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Table 3-1. Levels of Significant Exposure to PBBs - 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
116	Mouse (B6C3F1)	116 wks Gd 0-ppd 56 (weaning) 105 wks post-weaning ad lib (F)	Resp	3.9			NTP 1992 Chhabra et al. 1993 (FF-1)
			Cardio	3.9			
			Gastro	3.9			
			Musc/skel	3.9			
			Hepatic		1.3 (hypertrophy, vacuolization, single-cell necrosis, altered foci, bile duct hyperplasia)		
			Renal	1.3		3.9 (increased chronic nephropathy)	
			Endocr		1.3 (thyroid follicular cell hyperplasia)		
			Derm	3.9			
			Bd Wt	3.9			
	Reproductive						
117	Rat (Fischer 344/N)	115 wks Gd 0- ppd-56 (weaning) 104 wks post-weaning ad lib (F)		0.5 F 1.5 M	1.5 F (cystic endometrial hyperplasia)		NTP 1992 Chhabra et al. 1993 (FF-1)

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Table 3-1. Levels of Significant Exposure to PBBs - 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
118	Mouse (B6C3F1)	116 wks Gd 0-ppd 56 (weaning) 105 wks post-weaning ad lib (F)		3.9			NTP 1992 Chhabra et al. 1993 (FF-1)
	Developmental						
119	Monkey (Rhesus)	359-469 d ad lib (F)				0.012 (1/7 fetuses were aborted, 1/7 fetuses stillborn, 12% decreased birth weight and 22% decreased postnatal weight gain in 4/7 survivors)	Lambrecht et al. 1978; Allen et al. 1978; Allen et al. 1979 (FF-1)
	Cancer						
120	Rat (Fischer 344/N)	115 wks Gd 0- ppd 56 104 wks post-weaning (F)				0.5 (CEL: hepatocellular adenoma and carcinoma)	NTP 1992 Chhabra et al. 1993 (FF-1)
						1.5 (CEL: leukemia)	
121	Mouse (B6C3F1)	116 wks Gd 0- ppd 56 105wks post-weaning (F)				1.3 (CEL: hepatocellular adenoma and carcinoma)	NTP 1992 Chhabra et al. 1993 (FF-1)
						3.9 (thyroid follicular cell adenoma)	

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Table 3-1. Levels of Significant Exposure to PBBs - 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
	Immuno/Lymphor						
122	Rat (Fischer 344/N)	115 wks Gd 0- ppd 56 (weaning) 104 wks post-weaning ad lib (F)		0.5 M	1.5 M (splenic fibrosis)		NTP 1992 Chhabra et al. 1993 (FF-1)
123	Mouse (B6C3F1)	116 wks Gd 0-ppd 56 (weaning) 105 wks post-weaning ad lib (F)		1.3	3.9 (increased splenic hematopoiesis)		NTP 1992 Chhabra et al. 1993 (FF-1)

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

[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.01 mg/kg/day. The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for extrapolation from animals to humans, 10 for human variability).

[c] Differences in levels of helath effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect fot the most sensitive gender are presented.

ad lib - ad libitum; Bd Wt = body weight; BP-6 = FireMaster BP-6; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); DBB = decabromobiphenyl; DHEA = dehydroepiandrosterone; DHS = dehydroepiandrosterone sulfate; Endocr = endocrine; (F) = feed; F = Female; FF-1= FireMaster FF-1; G) = gavage; Gastro = gastrointestinal; gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; HBB = hexabromobiphenyl; hemato = hematological; hr = hour(s); LDH = lactic dyhydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; OBB = Octabromobiphenyl; PCV = packed cell volume; pmd = pre-mating day; pnd = post-natal day; occup = occupational; RBC = red blood cell; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase ; SRBC = sheep red blood cells; x = time(s); (W) = drinking water; WBC = white blood cell; wk = week(s)

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Figure 3-1. Levels of Significant Exposure to PBBs - Oral

Acute (≤14 days)

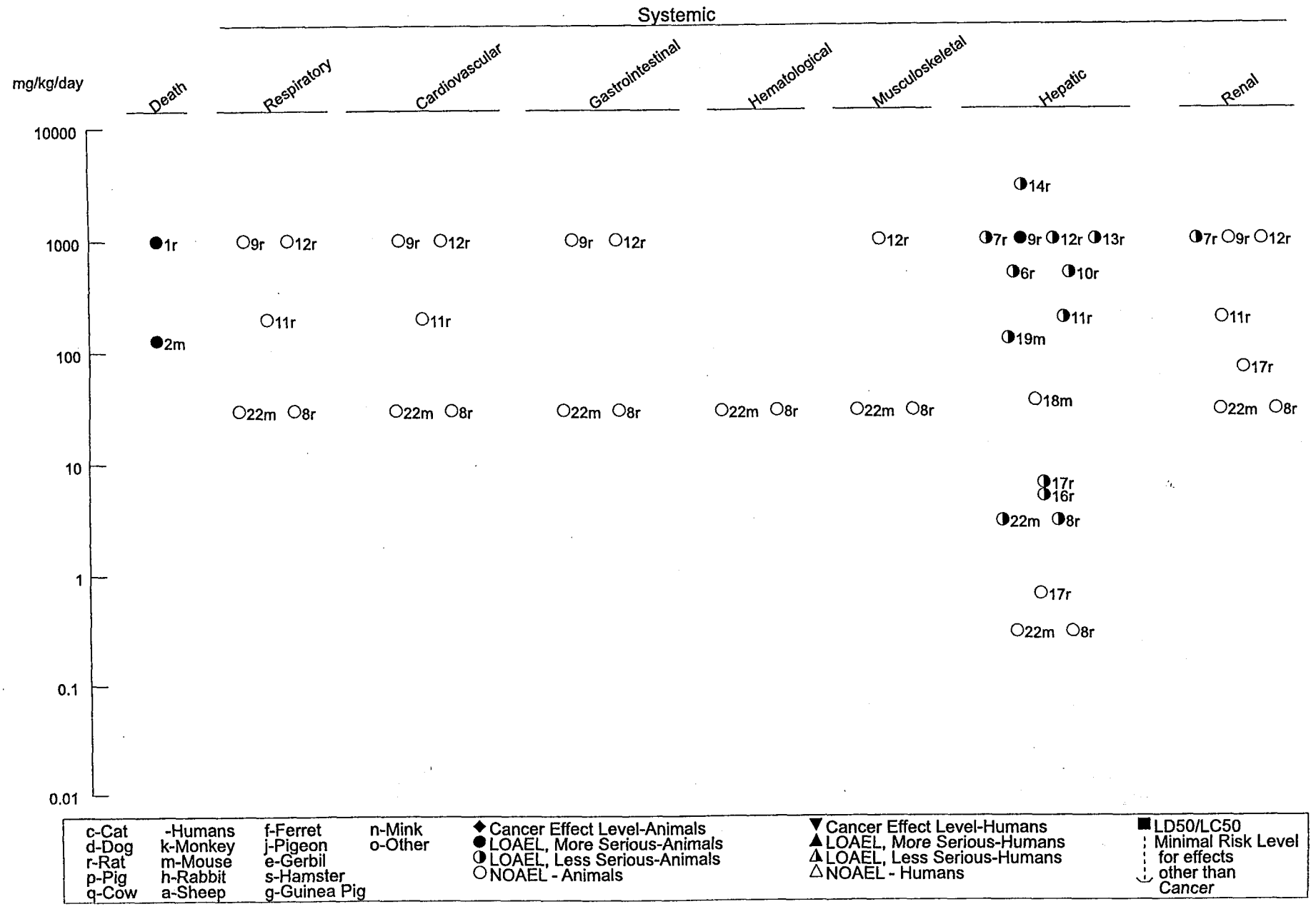

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Figure 3-1. Levels of Significant Exposure to PBBs - Oral (*Continued*)

Acute (≤14 days)

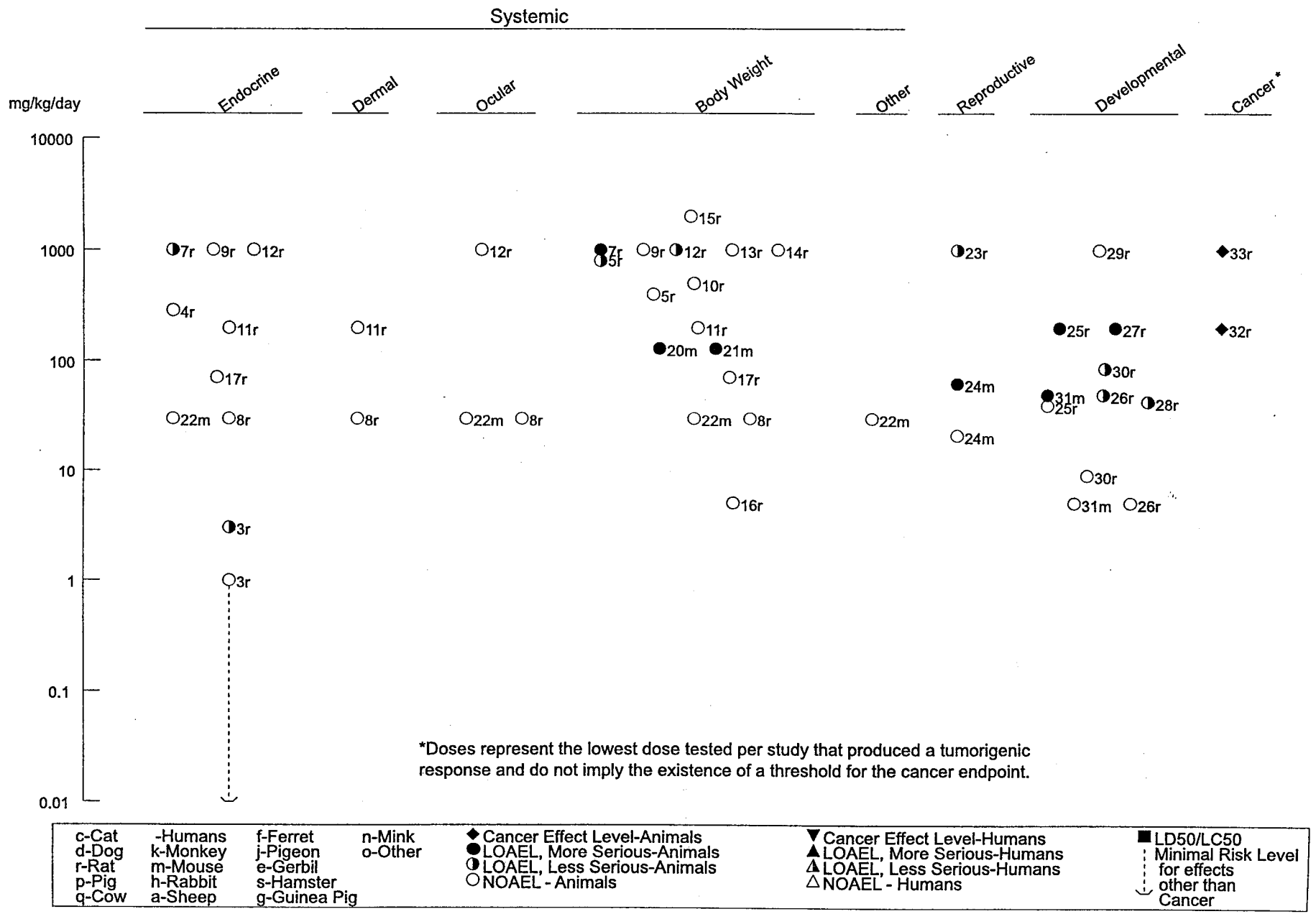

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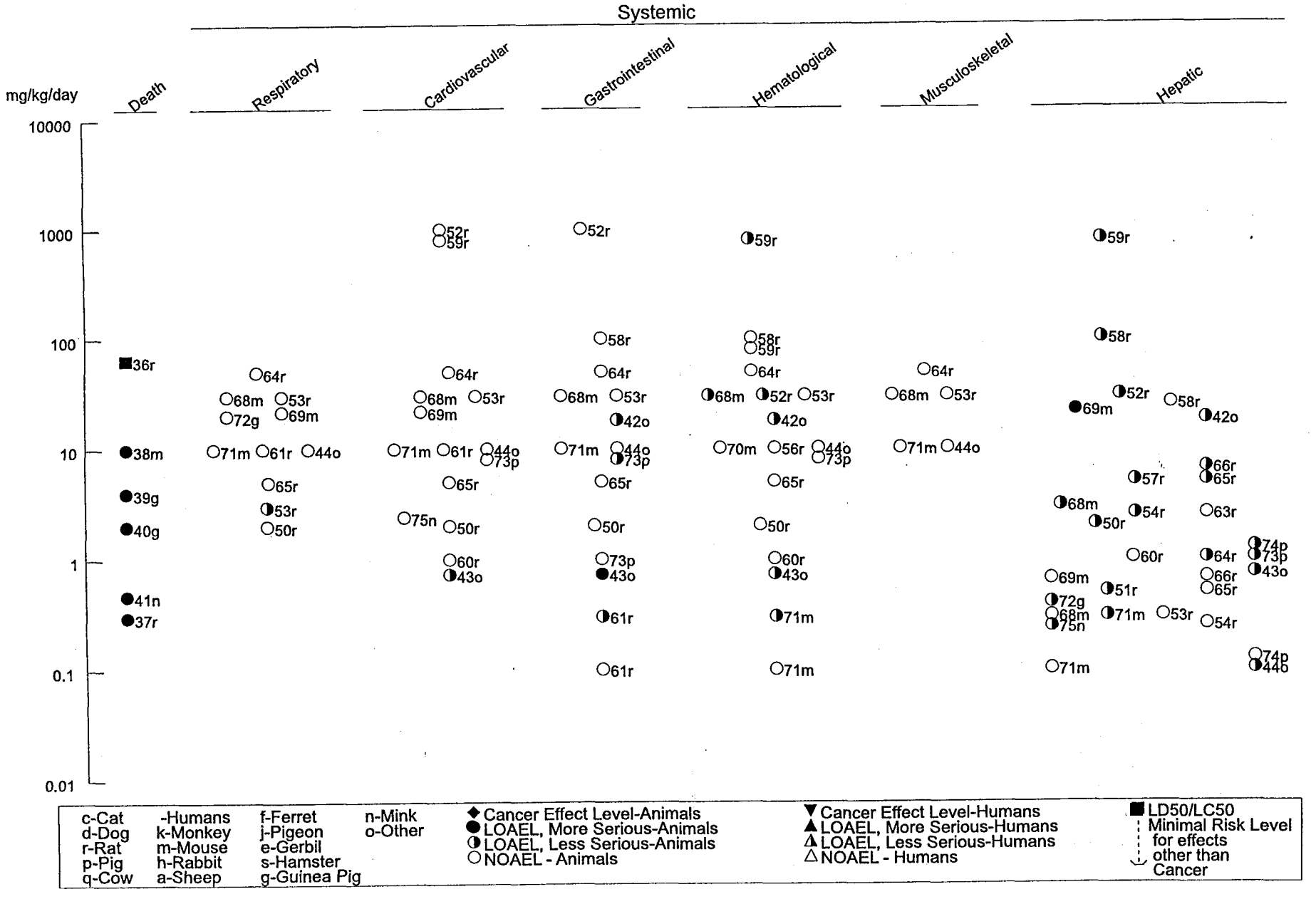
Figure 3-1. Levels of Significant Exposure to PBBs - Oral (*Continued*)

Intermediate (15-364 days)



c-Cat d-Dog r-Rat p-Pig q-Cow
-Humans k-Monkey m-Mouse h-Rabbit a-Sheep
f-Ferret j-Pigeon e-Gerbil s-Hamster g-Guinea Pig
n-Mink o-Other

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

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Figure 3-1. Levels of Significant Exposure to PBBs - Oral (*Continued*)

Intermediate (15-364 days)

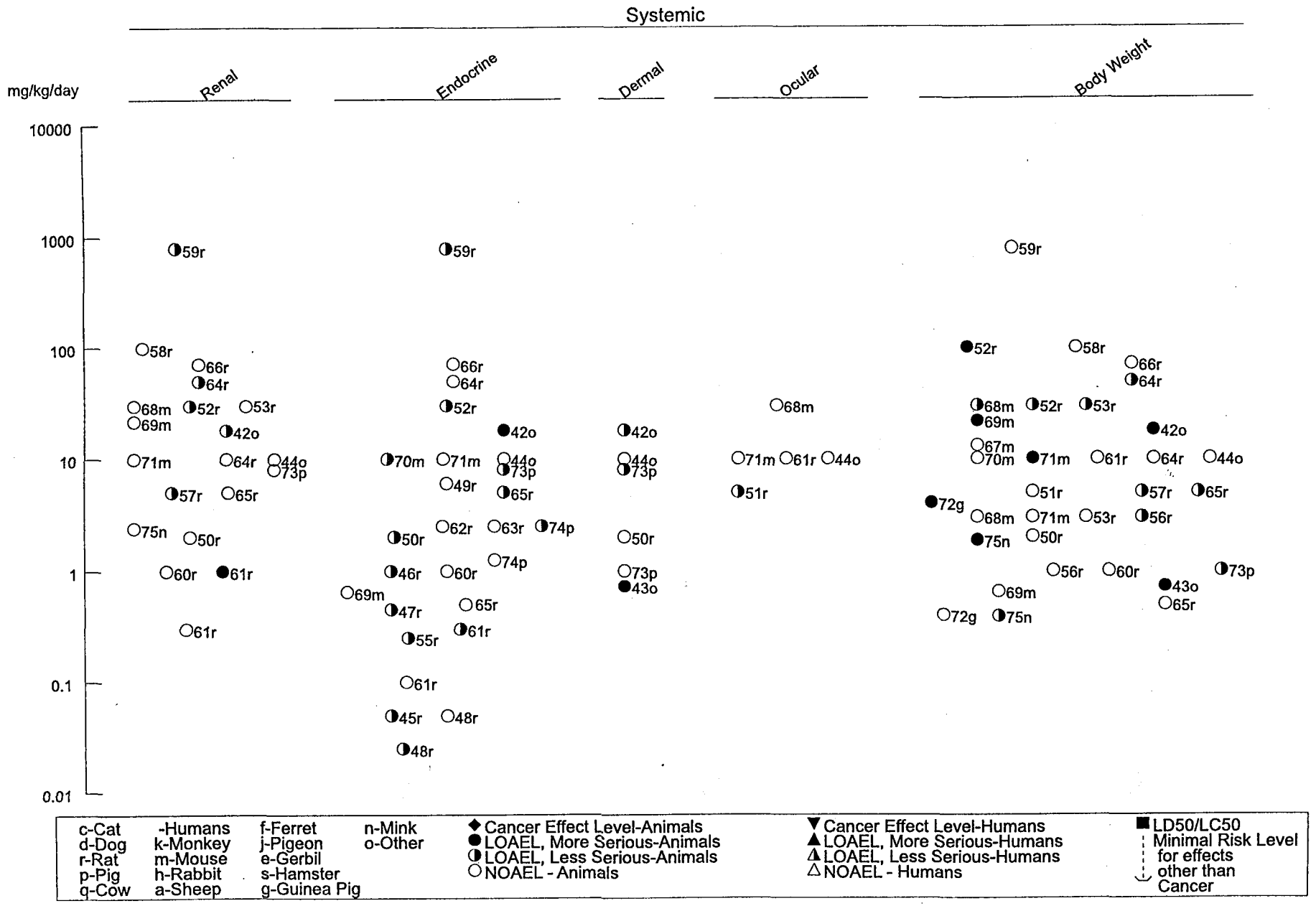

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Figure 3-1. Levels of Significant Exposure to PBBs - Oral (*Continued*)

Intermediate (15-364 days)

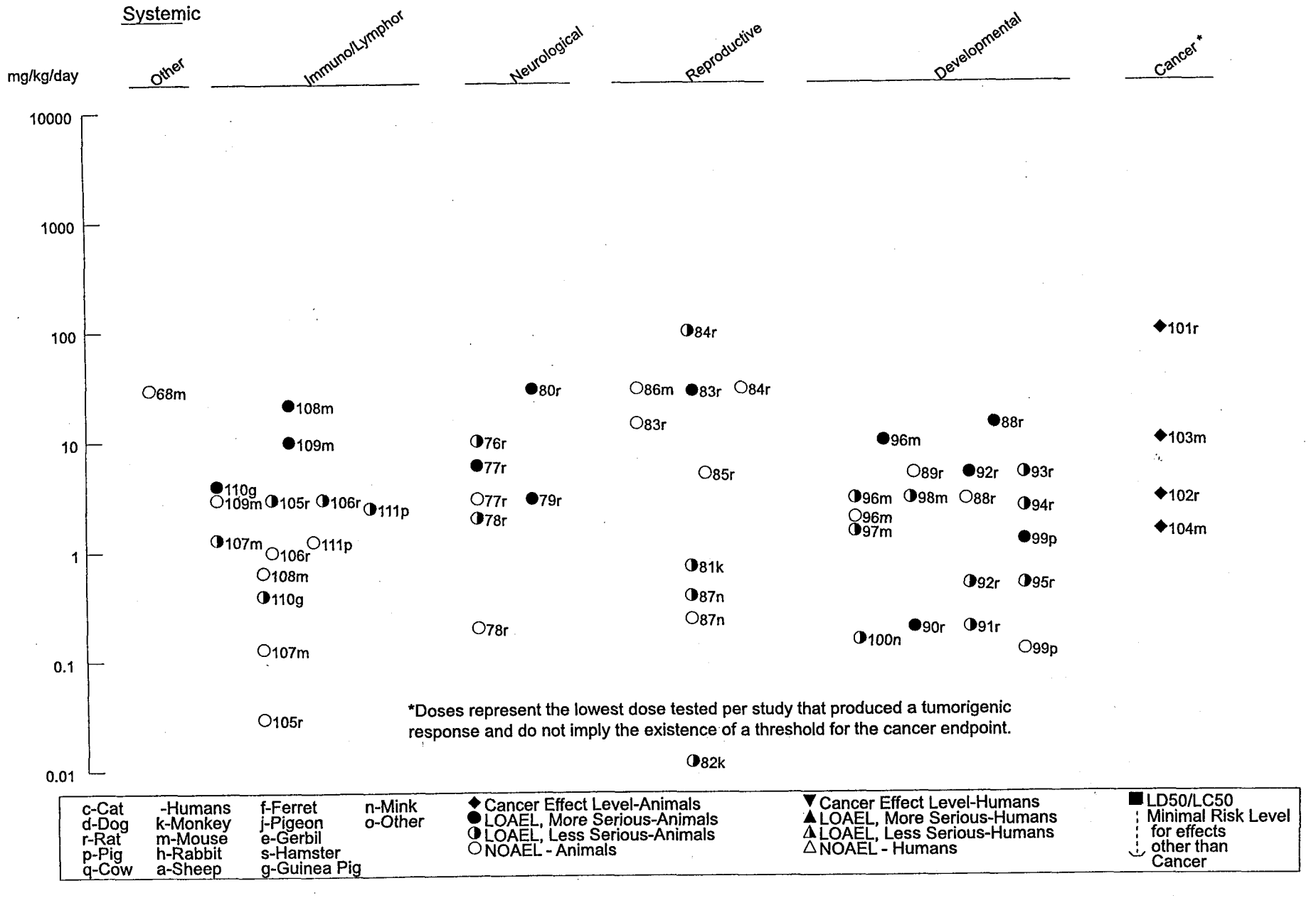

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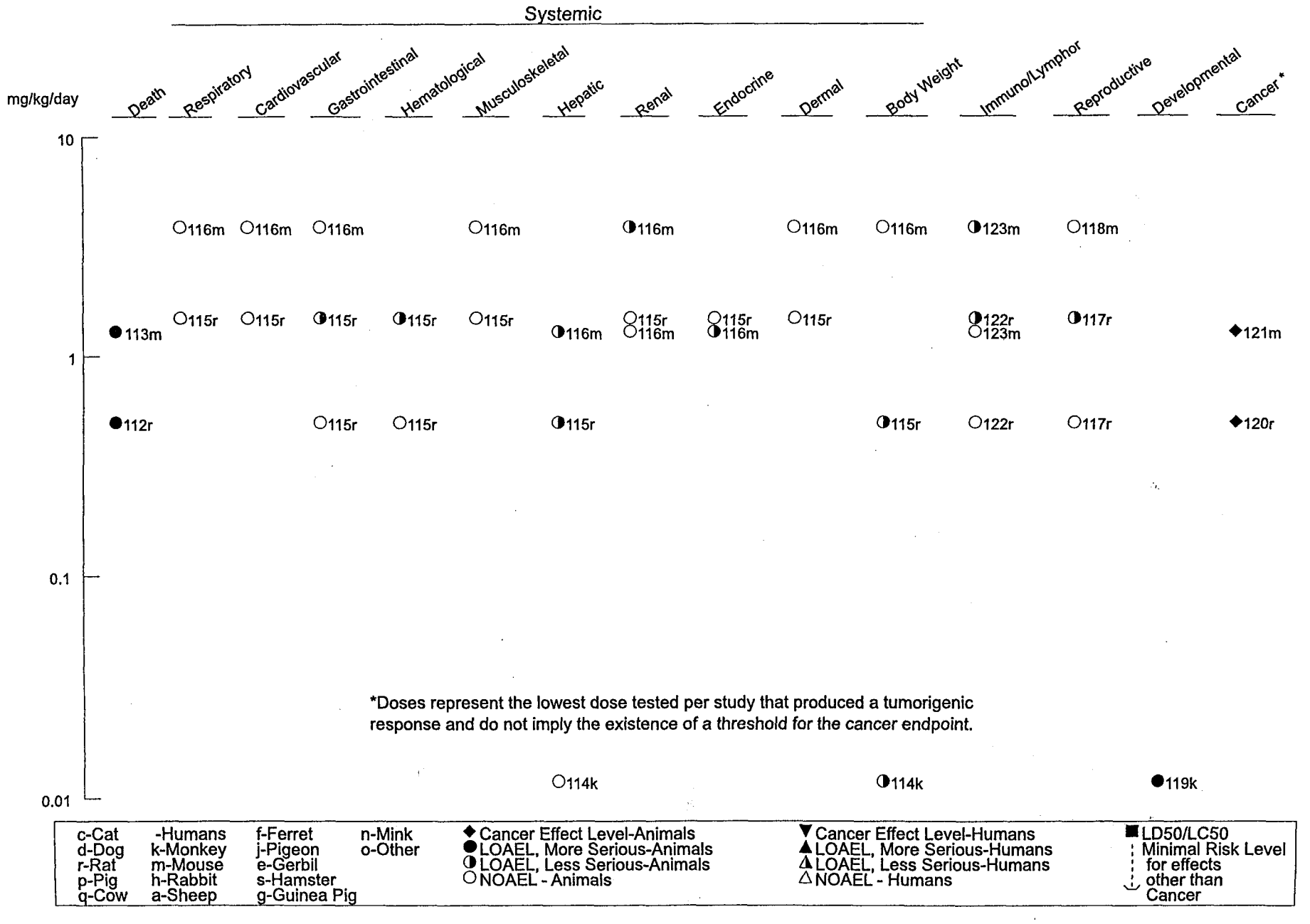
Figure 3-1. Levels of Significant Exposure to PBBs - Oral (*Continued*)

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 endpoint.

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				

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whereas doses #500 mg/kg caused no mortality (IRDC 1975b). No deaths occurred in rats exposed to pentaBDE in estimated dietary doses of #90 mg/kg/day for 28 days (IRDC 1976) or #100 mg/kg/day for 90 days (WIL Research Laboratories 1984).

The LD_{50} and LOAEL values for death in the acute-duration pentaBDE studies in rats are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The systemic effects in humans and animals following oral exposure to PBBs and PBDEs are described below. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2.

Respiratory Effects.

Polybrominated Biphenyls. No studies were located regarding respiratory effects in humans after oral exposure to PBBs.

The preponderance of data does not indicate that PBBs are respiratory system toxicants in animals, even at doses sufficient to cause death. No exposure-related histological changes were observed in the lungs or trachea of rats that were administered FireMaster FF-1 in a single dose of 200 or 1,000 mg/kg and observed for 2–23 months posttreatment (Kimbrough et al. 1978b, 1981). Rats and mice exposed to #30 mg/kg/day FireMaster FF-1 for 2 weeks also showed no histological alterations in the lung, trachea, or nasal turbinates (Gupta et al. 1981). Information on acute-duration respiratory effects in other species was not located.

In intermediate- and chronic-duration studies with rats, histology of the lung, trachea, or nasal turbinate was not altered by FireMaster FF-1 or FireMaster BP-6 dosages of #30 mg/kg/day by gavage for 30 days (Gupta et al. 1981), #10 mg/kg/day in the diet for 30 days (Akoso et al. 1982a; Sleight et al. 1978), #10 mg/kg/day by gavage for 25 weeks (NTP 1983), or #1.5 mg/kg/day in the diet for up to 104 weeks (NTP 1992). Rat lung histology also was not affected by exposure to 50 mg/kg/day of an unspecified PBB mixture in the feed for 30 days (Sleight and Sanger 1976). In studies with mice, FireMaster FF-1 produced no histopathological changes in the lungs, trachea, or nasal turbinates following gavage

Table 3-2. Levels of Significant Exposure to PBDEs - Oral

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg)	LOAEL Less serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	once (GO)				6200 (44-day LD50)	British Industrial Biological Research Association 1977 PentaBDE
2	Rat Spartan	once (GO)				5000 (4/5 died)	IRCD 1975b PentaBDE
3	Rat (Sprague-Dawley)	once (GO)				5000 (14-day LD50)	Pharmakon Research International Inc. 1984 PentaBDE
Systemic							
4	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic	95.9 M			Carlson 1980b DecaBDE
5	Rat Spartan	once (GO)	Bd Wt	5000			IRCD 1974 DecaBDE
6	Rat (Fischer- 344)	14d 1x/d (F)	Bd Wt	16,000			NTP 1986 DecaBDE
7	Rat (Long-Evans)	4 d 1x/d (GO)	Endocr	100			Zhou et al. 2001 DecaBDE

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Table 3-2. Levels of Significant Exposure to PBDEs - 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
8	Mouse (B6C3F1)	14d 1x/d (F)	Bd Wt	19,000			NTP 1986 DecaBDE
9	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic	76.6 M			Carlson, 1980b OctaBDE
10	Rat Spartan	once (GO)	Bd Wt	5000			IRCD 1975a OctaBDE
11	Rat (CD)	10 d Gd 6-15 (GO)	Bd Wt	25			Life Science Research Israel Ltd. (1987) OctaBDE
12	Rat (CD)	10 d Gd 6-15 (GO)	Bd Wt	25	50 (40% reduced maternal body weight gain)		WIL Research Laboratories 1986 OctaBDE
13	Rat (Long-Evans)	4 d 1x/d (GO)	Endocr	3	10 (reduced serum T4)		Zhou et al. 2001 OctaBDE
14	Rat (CD)	10 d Gd 6-15 (GO)	Bd Wt	10	100 (30% reduced maternal body weight gain)		Argus Research Laboratories 1985a PentaBDE
15	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic	56.4 M			Carlson, 1980b PentaBDE

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Table 3-2. Levels of Significant Exposure to PBDEs - 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
16	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Endocr		18 (reduced serum T4)		Darnerud and Sinjari 1996 PentaBDE
17	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic		18 (reduced liver vitamin A)		Hallgren et al. 2001 PentaBDE
			Endocr		18 (reduced serum T4)		
18	Rat Spartan	once (GO)	Bd Wt	500			IRCD 1975b PentaBDE
19	Rat (Long-Evans)	4 d 1x/d (GO)	Endocr	10	30 (reduced serum T4)		Zhou et al. 2001 PentaBDE
20	Mouse (C57BL/6N)	14 d 1x/d (GO)	Endocr		18 (reduced serum T4)		Darnerud and Sinjari 1996 PentaBDE
21	Mouse C57BL/6J	once (GO)	Hepatic	500			Fowles et al. 1994 PentaBDE
			Endocr	100	500 (reduced serum T4)		
22	Mouse (C57BL/6N)	14d 1x/d (GO)	Hepatic	72			Fowles et al. 1994 PentaBDE
			Endocr		18 (reduced serum T4)		
			Bd Wt	72			
23	Mouse (C57BL/6N)	14 d 1x/d (GO)	Hepatic	18	36 (reduced liver vitamin A)		Hallgren et al. 2001 PentaBDE
			Endocr		18 (reduced serum T4)		

Table 3-2. Levels of Significant Exposure to PBDEs - 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
	Immunological/Lymphoreticular						
24	Rat (Sprague-Dawley)	14 d 1x/d (GO)		36			Darnerud and Thuvander 1998 PentaBDE
25	Mouse (C57BL/6N)	14 d 1x/d (GO)		18	36 (reduced in vitro production of IgG in mitogen- stimulated splenocytes)		Darnerud and Thuvander 1998 PentaBDE
26	Mouse (C57BL/6N)	once (GO)		500			Fowles et al. 1994 PentaBDE
27	Mouse (C57BL/6N)	14d 1x/d (GO)		36	72 (reduced antibody response to sheep red blood cells, decreased thymus weight)		Fowles et al. 1994 PentaBDE
	Developmental						
28	Rat (Sprague-Dawley)	10 d Gd 6-15 (GO)		100 F		1000 F (subcutaneous edema, delayed skull bone ossification)	Norris et al. 1975; Dow Chemical Co. 1985 77% decaBDE, 22% nonaBDE
29	Rat (CD)	10 d Gd 6-15 (GO)		10	25 (increased resorptions and reduced fetal body weight)		Argus Research Laboratories 1985b OctaBDE

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Table 3-2. Levels of Significant Exposure to PBDEs - 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 (CD)	10 d Gd 6-15 (GO)		2.5	10 (minimal increased post-implantation loss)		Life Science Research Israel Ltd. (1987) OctaBDE
31	Rat (CD)	10 d Gd 6-15 (GO)		25	50 (reduced fetal weight and increased skeletal variations associated with maternal tox)		WIL Research Laboratories 1986 OctaBDE
32	Rabbit (New Zealand)	13 d Gd 7-19 (GO)		5 F	15 F (delayed ossification of sternebrae with decreased maternal weight gain)		Breslin et al. 1989 OctaBDE
33	Rat (CD)	10 d Gd 6-15 (GO)		200			Argus Research Laboratories 1985a PentaBDE
34	Rat (Long-Evans)	14 d Gd 6-Gd 20 (GO)		1[b]	10 (reduced serum T4 in fetuses)		Zhou et al. 2002 PBDPE

Table 3-2. Levels of Significant Exposure to PBDEs - 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
	INTERMEDIATE EXPOSURE						
	Systemic						
35	Rat (CD)	28 d (F)	Hepatic	90			IRDC 1976 DecaBDE
			Renal	90			
			Endocr	90			
			Bd Wt	90			
36	Rat (Fischer- 344)	13 wk (F)	Resp	8000			NTP 1986 DecaBDE
			Cardio	8000			
			Gastro	8000			
			Hemato	8000			
			Musc/skel	8000			
			Hepatic	8000			
			Renal	8000			
			Endocr	8000			
			Bd Wt	8000			
37	Mouse (B6C3F1)	13 wk (F)	Resp	9500			NTP 1986 DecaBDE
			Cardio	9500			
			Gastro	9500			
			Hemato	9500			
			Musc/skel	9500			
			Hepatic	9500			
			Renal	9500			
			Endocr	9500			
			Bd Wt	9500			

Table 3-2. Levels of Significant Exposure to PBDEs - 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
38	Rat (Sprague-Dawley)	30 d (F)	Hemato	800 M			Norris et al., 1973, 1975 77% decaBDE, 22% nonaBDE
			Hepatic	80	800 M (centrilobular cytoplasmic enlargement and vacuolation)		
			Renal	80	800 M (hyaline degenerative cytoplasmic changes)		
			Endocr	8 M	80 M (thyroid hyperplasia)		
			Bd Wt	800			
39	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	2.4 M			Carlson, 1980a OctaBDE
40	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	19.2 M			Carlson, 1980a OctaBDE
41	Rat (CD)	28 d (F)	Hepatic		9 (increased liver weight and enlarged parenchymal cells)		IRDC 1976 OctaBDE
			Renal	90			
			Endocr	90			
			Bd Wt	90			

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Table 3-2. Levels of Significant Exposure to PBDEs - 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
42	Rat (CD)	13 wk (F)	Resp	750 F			IRDC 1977 OctaBDE
			Cardio	750 F			
			Gastro	750 F			
			Hemato	70 F	750 F (reduced erythrocytes, hematocrit and hemoglobin)		
			Hepatic		5 M (cytomegaly with vacuolation and necrosis at higher doses)		
			Renal	50 M	600 M (minimal increase in tubular degenerative changes)		
			Endocr	7 F	50 M (increased thyroid weight with follicular epithelial changes at higher doses)		
			Dermal	750 F			
			Ocular	750 F			
			Bd Wt	70 F	600 M (12% reduced body weight gain)		
43	Rat (Sprague-Dawley)	30 d (F)	Hemato	80 M	800 M (decreased RBC count and packed cell volume)		Norris et al., 1973, 1975 OctaBDE
			Hepatic		8 M (cytoplasmic enlargement and vacuolation)		
			Renal		8 M (hyaline degenerative cytoplasmic changes)		
			Endocr		8 M (thyroid hyperplasia)		
			Bd Wt	800 M			

Table 3-2. Levels of Significant Exposure to PBDEs - 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
44	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	1.77 M			Carlson 1980a PentaBDE
45	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	14.1 M			Carlson 1980a PentaBDE
46	Rat (CD)	28 d (F)	Hepatic		9 (increased liver weight and enlarged parenchymal cells)		IRDC 1976 PentaBDE
			Renal	90			
			Endocr	90			
			Bd Wt	90			
47	Rat (Sprague-Dawley)	90d (F)	Resp	100			WIL Research Laboratories 1984 PentaBDE
			Cardio	100			
			Gastro	100			
			Hemato	100			
			Musc/skel	100			
			Hepatic		2[c] (minimal LOAEL for hypertrophy, mild degeneration, and slight necrosis)		
			Renal	100			
			Endocr	2	10 (reduced serum T4)		
			Dermal	100			
			Ocular	100			
			Bd Wt	10	100 (reduced weight gain)		

Table 3-2. Levels of Significant Exposure to PBDEs - 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
48	Rat (Long-Evans)	37 d Gd 6-Pnd 21 (GO)	Endocr	10	30 (reduced maternal serum T4)		Zhou et al. 2002 PentaBDE
	Immunological/Lymphoreticular						
49	Rat (Fischer- 344)	13 wk (F)		8000			NTP 1986 DecaBDE
50	Mouse (B6C3F1)	13 wk (F)		8000			NTP 1986 DecaBDE
51	Rat (CD)	13 wk (F)		750 F			IRDC 1977 OctaBDE
52	Rat (Sprague-Dawley)	90d (F)		100			WIL Research Laboratories 1984 PentaBDE
	Reproductive						
53	Rat (Fischer- 344)	13 wk (F)		8000			NTP 1986 DecaBDE
54	Mouse (B6C3F1)	13 wk (F)		8000			NTP 1986 DecaBDE
55	Rat (Sprague-Dawley)	117 d Pmd 60-Pnd 21 (F)		100			Norris et al. 1975; Dow Chemical Co. 1975 77% decaBDE, 22% nonaBDE

Table 3-2. Levels of Significant Exposure to PBDEs - 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
56	Rat (CD)	13 wk (F)		600[d] M 750 F			IRDC 1977 OctaBDE
57	Rat (Sprague-Dawley)	90d (F)		100 M 100 F			WIL Research Laboratories 1984 PentaBDE
	Developmental						
58	Rat (Sprague-Dawley)	117 d Pmd 60-Pnd 21 (F)		100			Norris et al. 1975; Dow Chemical Co. 1975 77% decaBDE, 22% nonaBDE
59	Rat (Long-Evans)	37 d Gd 6-Pnd 21 (GO)		1	10 (reduced serum T4 in fetuses and offspring on Gd 20 and Pnd 4 and 14)		Zhou et al. 2002 PBDPE

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Table 3-2. Levels of Significant Exposure to PBDEs - 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						
	Systemic						
60	Rat (Fischer- 344)	103 wk (F)	Resp	2550 F			NTP 1986 DecaBDE
			Cardio	2550 F			
			Gastro	1120 M	2240 M (acanthosis of forestomach)		
			Hemato	2550 F			
			Musc/skel	2550 F			
			Hepatic	1120 M	2240 M (degeneration and thrombosis)		
			Renal	2550 F			
			Endocr	2550 F			
			Bd Wt	2550 F			
61	Mouse (B6C3F1)	103 wk (F)	Resp	7780 F			NTP 1986 DecaBDE
			Cardio	7780 F			
			Gastro	3760 F	7780 F (ulcers)		
			Hemato	7780 F			
			Musc/skel	7780 F			
			Hepatic		3200 M (centrilobular hypertrophy and granulomas)		
			Renal	7780 F			
			Endocr		3200 M (follicular cell hyperplasia)		
			Bd Wt	7780 F			

Table 3-2. Levels of Significant Exposure to PBDEs - 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
62	Rat (Sprague-Dawley)	2 yr (F)	Resp	1.0			Kociba et al. 1975; Norris et al. 1975 77% decaBDE, 22% nonaBDE
			Cardio	1.0			
			Gastro	1.0			
			Hemato	1.0			
			Musc/skel	1.0			
			Hepatic	1.0			
			Renal	1.0			
			Endocr	1.0			
			Ocular	1.0			
			Bd Wt	1.0			
	Immunological/Lymphoreticular						
63	Rat (Fischer-344)	103 wk (F)			1200[d] F (splenic hematopoiesis) 2240 M (splenic fibrosis and lymphoid hyperplasia)		NTP 1986 DecaBDE
64	Mouse (B6C3F1)	103 wk (F)		7780 F			NTP 1986 DecaBDE
65	Rat (Sprague-Dawley)	2 yr (F)		1.0			Kociba et al. 1975; Norris et al. 1975 77% decaBDE, 22% nonaBDE
	Reproductive						
66	Rat (Fischer-344)	103 wk (F)		2240[d] M 2550 F			NTP 1986 DecaBDE

Table 3-2. Levels of Significant Exposure to PBDEs - 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 (B6C3F1)	103 wk (F)		6650[d] M 7780 F			NTP 1986 DecaBDE
68	Rat (Sprague-Dawley)	2 yr (F)		1.0 M 1.0 F			Kociba et al. 1975; Norris et al. 1975 77% decaBDE, 22% nonaBDE
	Cancer						
69	Rat (Fischer- 344)	103 wk (F)				1120 M (CEL: liver neoplastic nodules)	NTP 1986 DecaBDE
70	Mouse (B6C3F1)	103 wk (F)				3200 M (CEL: hepatocellular adenomas and carcinomas)	NTP 1986 DecaBDE

[a]The number corresponds to entries in Figure 3-2.

[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.03 mg/kg/day. The MRL was derived by dividing the NOAEL by an uncertainty factor of 30 (10 for extrapolation from animals to humans, 3 for human variability because effects were observed in a sensitive subgroup).

[c]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.007 mg/kg/day. The MRL was derived by dividing the LOAEL by an uncertainty factor of 300 (3 for converting a minimal LOAEL to a NOAEL, 10 for extrapolation from animals to humans, 10 for human variability).

[d] Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

BDE = brominated diphenyl ethers; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; pmd = pre-mating day; pnd = post-natal day; occup = occupational; RBC = red blood cell; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s)

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Figure 3-2. Levels of Significant Exposures to PBDEs - Oral

Acute (≤14 days)

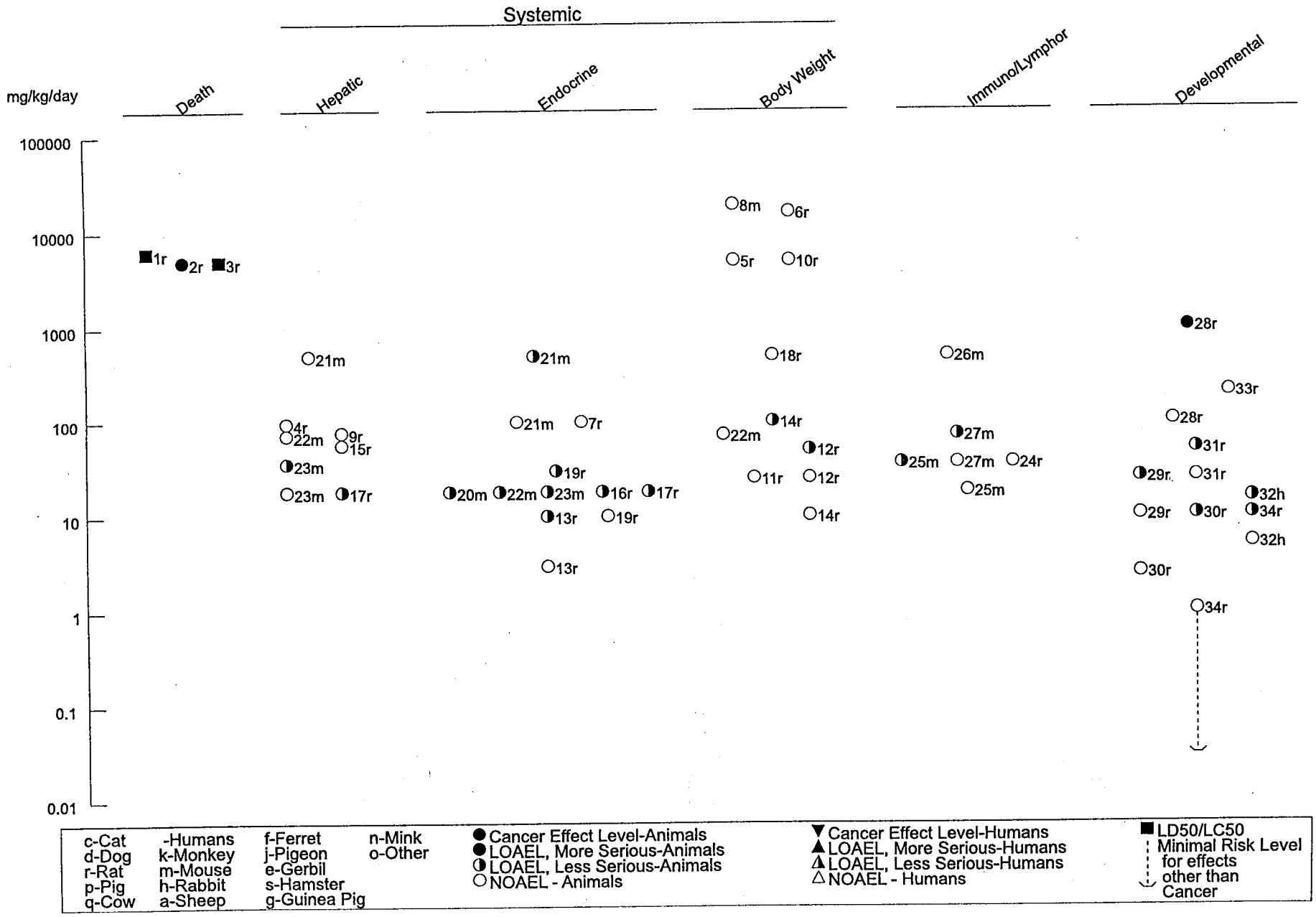

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Figure 3-2. Levels of Significant Exposures to PBDEs - Oral (*Continued*)

Intermediate (15-364 days)

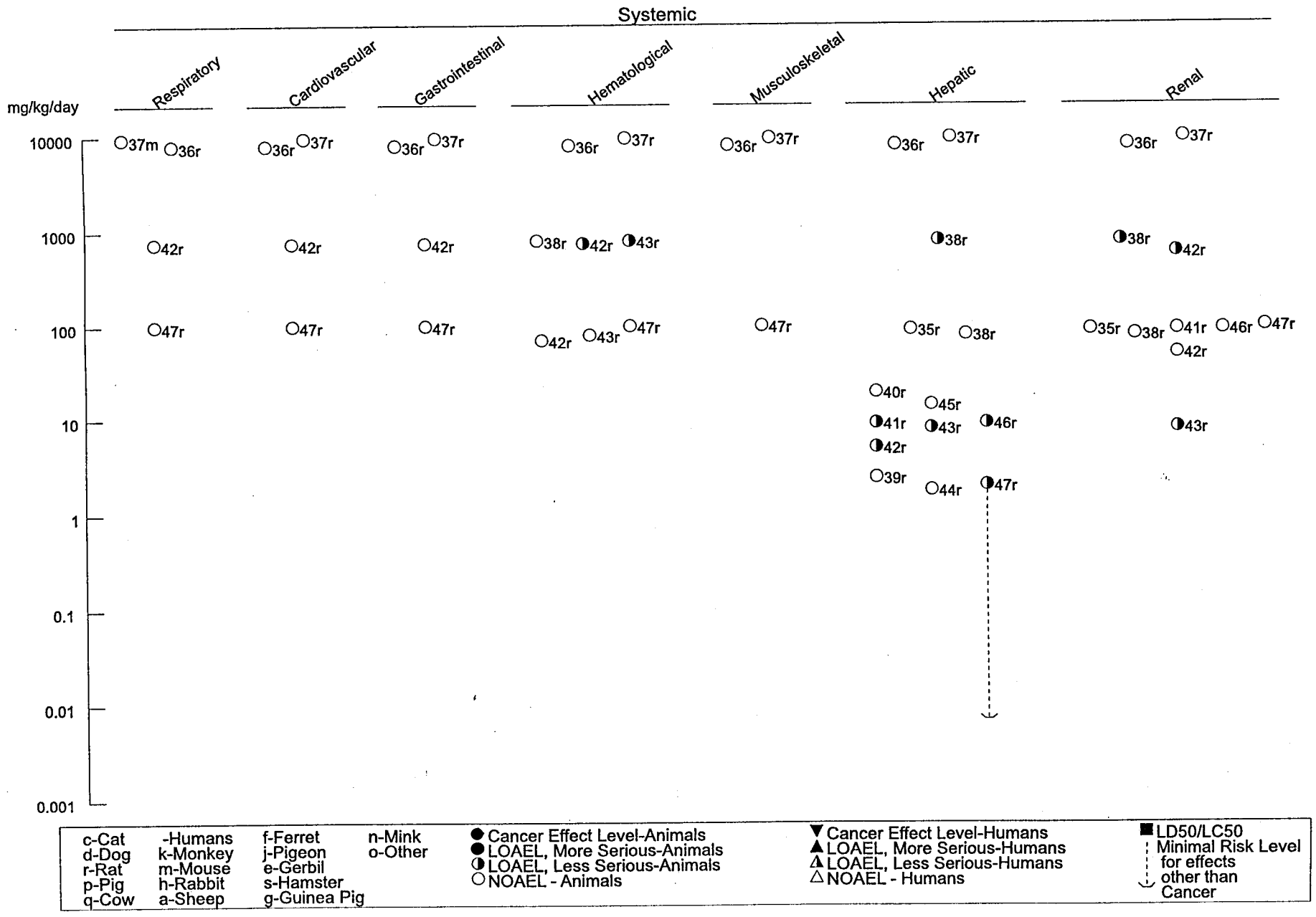

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Figure 3-2. Levels of Significant Exposures to PBDEs - Oral (Continued)

Intermediate (15-364 days)

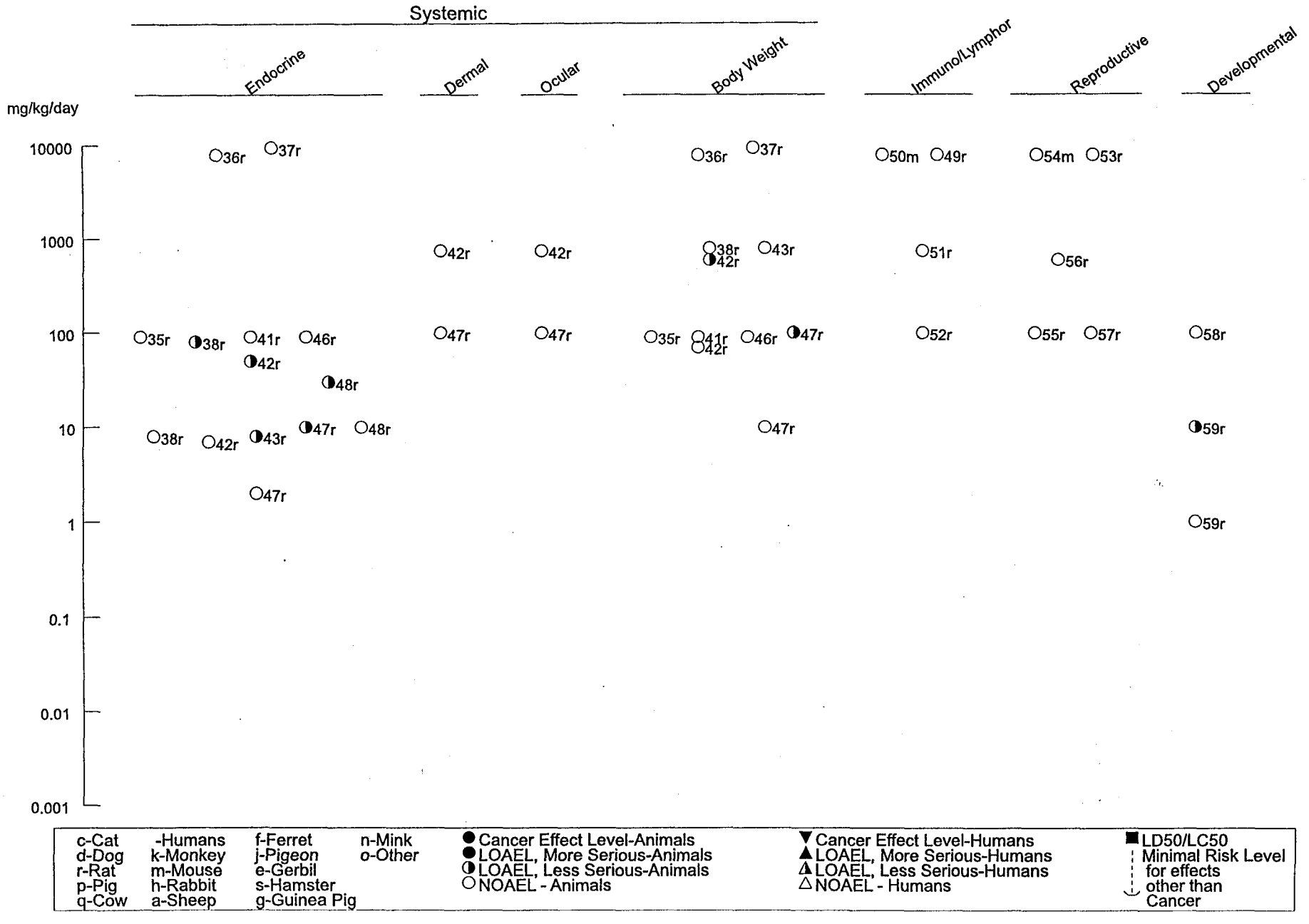

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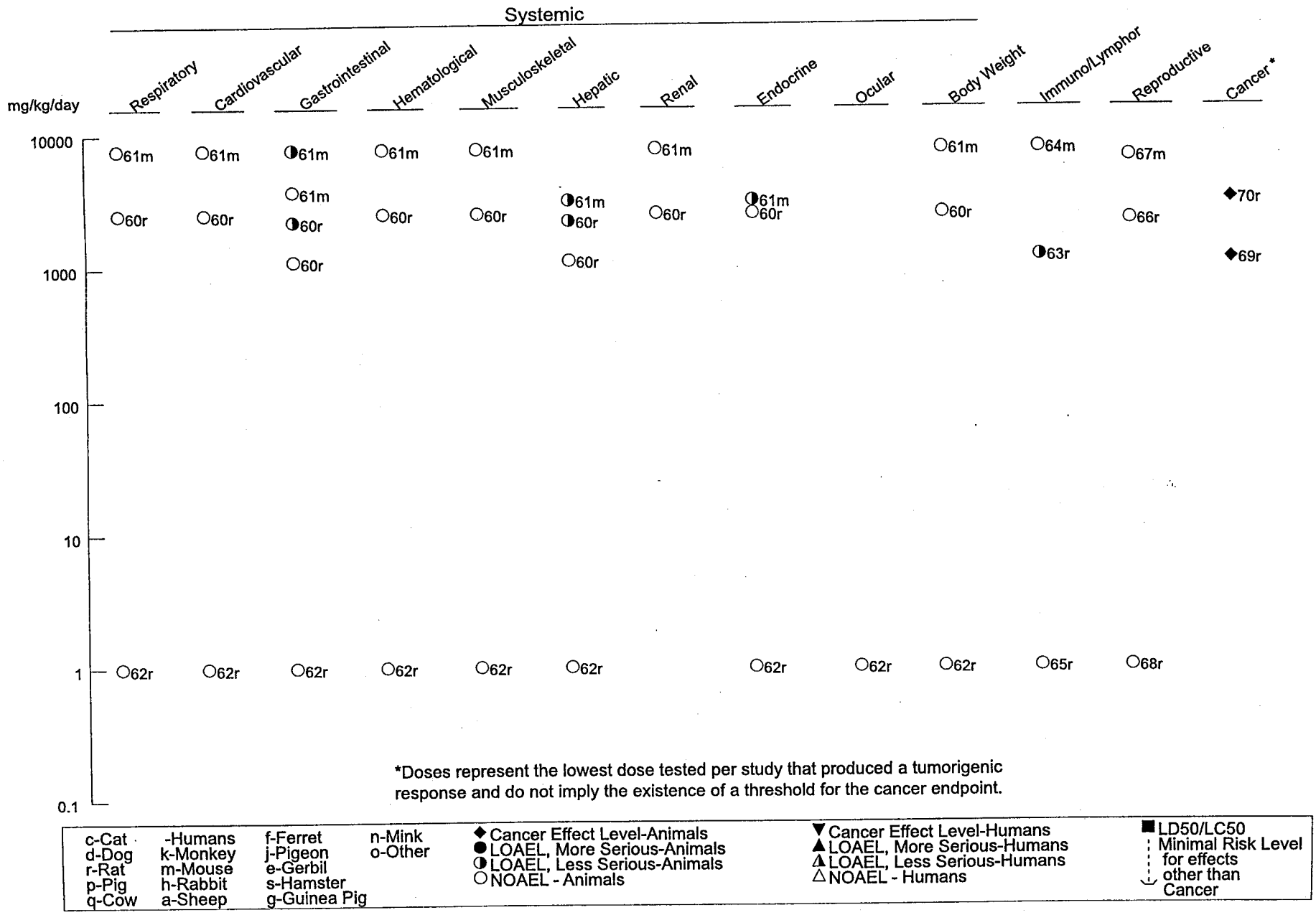
Figure 3-2. Levels of Significant Exposures to PBDEs - Oral (*Continued*)

Chronic (≥365 days)



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exposure to #10 mg/kg/day for 25 weeks (NTP 1983) or #30 mg/kg/day for 30 days (Gupta et al. 1981), or dietary exposure to #3.9 mg/kg/day for up to 105 weeks (NTP 1992). Guinea pig lung histology was unaffected by exposures of #20 mg/kg/day of an unspecified PBB mixture in the feed for 30 days (Sleight and Sanger 1976). Relative lung weights increased in mink that died following exposure to #2.4 mg/kg/day FireMaster FF-1 for 313 days, but it is unclear if this effect is adverse because the animals had lost weight and histopathology was not reported (Aulerich and Ringer 1979; Ringer et al. 1981). Effects in six pregnant cows given 67 mg/kg/day of FireMaster BP-6 in capsules for up to 60 days included increased respiratory rate and occasional nasal discharge (Moorhead et al. 1977). Necropsy following sacrifice between days 33 and 66 because of impending death due to poor health showed gross pneumonia (one cow), microscopic lesions of early purulent bronchopneumonia (two cows), and petechial hemorrhages of the tracheal mucosa (one cow). No histological changes were observed in the trachea or lungs treated with #0.65 mg/kg/day and observed for 1–140 days following the end of treatment. Information on respiratory effects of octabromobiphenyl mixture or other PBB mixtures in animals was not located.

Polybrominated Diphenyl Ethers. No studies were located regarding respiratory effects in humans after oral exposure to PBDEs.

Effects of PBDEs on respiratory function have not been studied in orally-exposed animals. No histopathological changes in respiratory tract tissues were found in rats and mice fed decaBDE in estimated doses of #8,000 and #9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986). In chronic dietary studies, there was no respiratory tract histopathology in rats that were fed #1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaDBDE) for 2 years (Kociba et al. 1975; Norris et al. 1975b), or in rats and mice exposed to decaBDE at estimated doses of #2,550 and #7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986).

No histopathological changes in the respiratory tract were found in dietary studies of rats exposed to #750 mg/kg/day of octaBDE for 13 weeks (IRDC 1977) or #100 mg/kg/day of pentaBDE for 90 days (WIL Research Laboratories 1984).

Cardiovascular Effects.

Polybrominated Biphenyls. No studies were located regarding cardiovascular effects in humans after oral exposure to PBBs.

Animal data do not generally indicate cardiovascular toxicity of PBBs even at lethal doses, but cardiovascular function was not evaluated in most studies. No exposure-related histological changes in the heart were observed in rats administered FireMaster FF-1 in a single dose of 200 or #1,000 mg/kg and observed for 2–23 months posttreatment (Kimbrough et al. 1978a, 1981), or #30 mg/kg/day for 2 weeks (Gupta et al. 1981; Kimbrough et al. 1978b, 1981). Mice exposed to #30 mg/kg/day FireMaster FF-1 for 2 weeks also showed no histological alterations in the heart (Gupta et al. 1981). In intermediate-and chronic-duration studies with rats, FireMaster FF-1 or FireMaster BP-6 dosages of #30 mg/kg/day by gavage for 30 days (Gupta et al. 1981), #10 mg/kg/day in the diet for 30 days (Akoso et al. 1982a; Sleight et al. 1978), #10 mg/kg/day by gavage for 25 weeks (NTP 1983), or #1.5 mg/kg/day in the diet for up to 104 weeks (NTP 1992) did not alter heart weight or histology. Rat heart histology also was unaffected by exposure to 50 mg/kg/day of an unspecified PBB mixture for 30 days (Sleight and Sanger 1976). Rats exposed to #5 mg/kg/day FireMaster BP-6 for 30 days exhibited no exposure-related changes in blood pressure, but histology or other cardiovascular end points were not evaluated (McCormack et al. 1978). Rats exposed to octabromobiphenyl mixture in dosages of #1 mg/kg/day for 8 months or #800 mg/kg/day for 30 days showed no changes in heart weight, but histology or function was not evaluated (Norris et al. 1975a). In studies with mice, FireMaster FF-1 produced no changes in heart weight or histology following gavage exposure to #10 mg/kg/day for 25 days (Gupta et al. 1981), #30 mg/kg/day for 30 days (NTP 1983), or dietary exposure to #3.9 mg/kg/day for up to 105 weeks (Chhabra et al. 1993; NTP 1992). No effects on heart relative weight or histology were reported in mink that died following exposure to #2.4 mg/kg/day FireMaster FF-1 for 313 days (Aulerich and Ringer 1979; Ringer et al. 1981). Relative heart weights were increased in swine exposed to #8 mg/kg/day of an unspecified PBB mixture for 16 weeks, but gross pathology was normal and histology was not evaluated (Ku et al. 1978). Necropsy of a monkey that died following ingestion of 0.73 mg/kg/day FireMaster FF-1 for 25 weeks showed an enlarged heart, but histology was not evaluated and a similar effect was not reported in two other monkeys exposed to higher dosages (Allen et al. 1978; Lambrecht et al. 1978). Mean heart rate was 32% lower than the pre-exposure value in pregnant cows that were treated with 67 mg/kg/day of FireMaster BP-6 in capsules for 10 days (Moorhead et al. 1977). Necropsy following sacrifice between days 33 and 66 because of impending death due to poor health showed petechial and ecchymotic hemorrhages of the myocardium and endocardium in two of six cows. No cardiovascular effects were observed in cows given #0.65 mg/kg/day and observed for 1–140 days following the end of treatment.

Polybrominated Diphenyl Ethers. No studies were located regarding cardiovascular effects in humans after oral exposure to PBDEs.

Effects of PBDEs on cardiovascular function have not been studied in orally exposed animals. No histopathological changes in the heart were found in rats and mice fed decaBDE in estimated doses of #8,000 and #9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986). In chronic dietary studies, there was no cardiac histopathology in rats that were fed #1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaDBDE) for 2 years (Norris et al. 1975b), or in rats and mice exposed to decaBDE in estimated doses of #2,550 and #7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986).

No histopathological changes in the heart were found in dietary studies of rats exposed to #750 mg/kg/day of octaBDE for 13 weeks (IRDC 1977) or #100 mg/kg/day of pentaBDE for 90 days (WIL Research Laboratories 1984).

Gastrointestinal Effects.

Polybrominated Biphenyls. No symptoms of gastrointestinal effects were reported by residents of quarantined Michigan farms in an epidemiological study conducted by the U.S. Center for Disease Control and the Michigan Department of Public Health (Landrigan et al. 1979). In a medical history survey conducted by the Environmental Science Laboratory of the Mount Sinai School of Medicine, no statistically significant difference was observed between the prevalence rates of gastrointestinal symptoms for 933 Michigan residents who were likely to have ingested PBB-contaminated food and the rates for a control group of 229 Wisconsin farm residents (Anderson et al. 1978c). The Michigan residents were examined . 3 years after the contamination episode occurred. No other studies were located regarding gastrointestinal effects in humans after oral exposure to PBBs.

Gastric lesions have developed in various animals that ingested PBBs, particularly after prolonged exposure to FireMaster FF-1 or FireMaster BP-6. No exposure-related histological changes in the gastrointestinal tract or esophagus were observed in rats administered FireMaster FF-1 in a single dose #1,000 mg/kg and observed for 2–23 months posttreatment (Kimbrough et al. 1978b, 1981). Rats or mice exposed to #30 mg/kg/day FireMaster FF-1 for 2 weeks also showed no histological alterations in the gastrointestinal tract (esophagus not examined) (Gupta et al. 1981). In intermediate-duration studies, the gastrointestinal tract of rats exposed to FireMaster BP-6 or FireMaster FF-1 by gavage or diet at #50 mg/kg/day for 4–4.5 weeks showed no histopathological changes (esophagus not examined) (Akoso et al. 1982a; Gupta and Moore 1979; Gupta et al. 1981; Sleight and Sanger 1976; Sleight et al. 1978). Histological examination of the gastrointestinal tract of rats administered FireMaster FF-1 by gavage for

25 weeks showed significantly increased incidences of gastric ulcers at $1 mg/kg/day and hyperplastic gastropathy at $3 mg/kg/day after lifetime observation (23 months). These gastric effects were not observed in rats examined at the end of the gavage treatment period, although similar changes (forestomach hyperplasia, inflammation, and ulceration) occurred in rats exposed to 1.5 mg/kg/day FireMaster FF-1 in the diet for up to 104 weeks (Chhabra et al. 1993; NTP 1992). In the only study of a decabromobiphenyl mixture, rats were fed estimated dosages as high as 100 mg/kg/day for 13 weeks (Millischer et al. 1980). A comprehensive histology evaluation was performed in this study, but the liver is the only tissue specifically mentioned as having been examined. Due to the total number of tissues examined (21) and route of exposure, it is probable that the gastrointestinal tract was examined but not discussed because no histopathologic changes were observed.

Gastrointestinal tract histology was normal in mice exposed to FireMaster FF-1 dosages of #10 mg/kg/day by gavage for 25 weeks or #3.9 mg/kg/day in the diet for up to 105 weeks (NTP 1983, 1992). FireMaster FF-1 produced no histological changes in the gastrointestinal tract of mice exposed to #30 mg/kg/day for 30 days (Gupta et al. 1981). Gross pathologic examination of swine administered an unspecified PBB mixture for 16 weeks showed that the glandular portion of the stomach "appeared somewhat hyperplastic" (additional details were not reported, and histology was not evaluated) at 8 mg/kg/day, but not at 1 mg/kg/day (Ku et al. 1978). Biopsies of two monkeys performed following their ingestion of 0.73 or 1.43 mg/kg/day FireMaster FF-1 for 12 weeks showed proliferation of gastric mucosal cells, focal areas of infiltration of chronic inflammatory cells, and isolated penetrations of the gastric mucosa into the underlying submucosa (Allen et al. 1978; Lambrecht et al. 1978). Necropsies performed after 25 or 50 weeks of exposure also showed hyperplastic gastroenteritis and, in the low-dose monkey (that died of "severe gastrointestinal changes"), severe ulcerative colitis. Hyperplastic gastroenteritis was described in another monkey exposed to a higher dosage (18 mg/kg/day) of FireMaster FF-1 for 137 days (Allen et al. 1978). Gastrointestinal effects in six pregnant cows that were administered 67 mg/kg/day of FireMaster BP-6 in capsules for up to 60 days included diarrhea, dehydration (possibly a result of the diarrhea), and occasional constipation (Moorhead et al. 1977). Necropsy following sacrifice between days 33 and 66 because of impending death due to poor health showed edema and hemorrhage of the colon and rectum mucosa, although histology was normal in the esophagus, rumen, omasum, and reticulum. No histological changes were observed in the gastrointestinal tract of cows with #0.65 mg/kg/day and observed 1 or 140 days following the end of treatment.

Polybrominated Diphenyl Ethers. No studies were located regarding gastrointestinal effects in humans after oral exposure to PBDEs.

No histopathological changes in gastrointestinal tract tissues were found in rats and mice fed decaBDE in estimated doses of #8,000 and #9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986). In chronic dietary studies, there was no gastrointestinal tract histopathology in rats that were fed #1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaDBDE) for 2 years (Kociba et al. 1975; Norris et al. 1975b). Higher dietary doses of decaBDE for 103 weeks caused acanthosis of the forestomach in rats exposed to 2,240 mg/kg/day (no effects at #1,200 mg/kg/day) and stomach ulcers in mice exposed to 7,780 mg/kg/day (no effects at #3,760 mg/kg/day) (NTP 1986).

No histopathological changes in the gastrointestinal tract were found in dietary studies of rats exposed to #750 mg/kg/day of octaBDE for 13 weeks (IRDC 1977) or #100 mg/kg/day of pentaBDE for 90 days (WIL Research Laboratories 1984).

Hematological Effects.

Polybrominated Biphenyls. No studies were located regarding hematological effects in humans after oral exposure to PBBs.

In animals, hematologic changes indicative of possible anemia are common findings in animals resulting from longer-term exposure to PBBs. Comprehensive hematological examinations in rats and mice administered #30 mg/kg/day FireMaster FF-1 for 2 weeks showed no exposure-related changes (Gupta et al. 1981). No additional information on hematology in animals following acute-duration exposure to PBBs was located. In intermediate-duration studies, no consistent hematological changes were found in rats exposed to #10 mg/kg/day FireMaster BP-6 for 30 days (Akoso et al. 1982a; Sleight et al. 1978). Some hematologic effects occurred in rats at higher dosages or longer durations. Exposure to 30 mg/kg/day FireMaster FF-1 for 4.5 weeks significantly reduced hemoglobin concentration, packed cell volume (PCV), and platelet count in rats evaluated up to . 60 days postexposure (Gupta and Moore 1979). In another study in which rats were administered the same dosages of FireMaster FF-1 (#30 mg/kg/day) for 30 days, longer postexposure (up to 90 days) evaluation revealed transient responses (Gupta et al. 1981). Transitory and slight but significant ($p<0.05$) decreases in red blood cell count, hemoglobin concentration, and PCV values were found; they returned to control levels by 60-days post-dosing. No consistent hematological changes were observed in rats administered #50 mg/kg/day of an unspecified PBB mixture for 30 days (Sleight and Sanger 1976) or #10 mg/kg/day FireMaster FF-1 for 6 months (Luster et al. 1980). Rats exposed to FireMaster FF-1 for 25 weeks showed no hematological changes at 0.1 mg/kg/day, but had dose-related, significantly decreased hemoglobin, mean corpuscular hemoglobin

(MCH), mean corpuscular volume (MCV), and PCV at $0.3 mg/kg/day, and increased total leukocytes at $1 mg/kg/day; there were no effects on erythrocyte or platelet counts (NTP 1983). Mice similarly treated for 25 weeks had decreased erythrocyte count and MCV at $0.3 mg/kg/day and decreased platelets and lymphocytes at $1 mg/kg/day, but no hematological effects were noted at 0.1 mg/kg/day (NTP 1983). No hematologic alterations were found in mice exposed to FireMaster FF-1 at dosages of #10 mg/kg/day for 6 months or #30 mg/kg/day for 30 days (Gupta et al. 1981; Luster et al. 1980).

Hematologic evaluation of swine treated with an unspecified PBB mixture for 16 weeks showed significantly decreased hemoglobin and hematocrit values in two of four animals exposed to 8 mg/kg/day at week 6, after which values returned to normal or near-normal within 2 weeks (Ku et al. 1978). Decreased PCV and serum protein developed in monkeys exposed to FireMaster FF-1 in dosages of $0.73 mg/kg/day for $25 weeks (two animals); additional hematologic effects observed in one monkey exposed to 18 mg/kg/day for 137 days were decreased erythrocyte and white blood cell counts (Allen et al. 1978; Lambrecht et al. 1978). No hematological changes were measured in cows treated with #0.65 mg/kg/day FireMaster BP-6 in capsules for 60 days, and observed for up to 140 days following the end of treatment (Moorhead et al. 1977). Similar treatment with 67 mg/kg/day did not cause abnormal hematologic indices in four of six cows; changes in the other two animals (e.g., leukocytosis, increased PCV) have uncertain toxicologic significance because the animals at this dose were sacrificed between days 33 and 66 because of impending death due to poor health.

Studies of hematologic effects of octabromobiphenyl mixture, performed only in rats, showed significantly decreased red blood cell count and PCV following 800 mg/kg/day for 30 days, but no hematological changes resulting from #1 mg/kg/day for 8 months (Norris et al. 1975a). In the only study of a decabromobiphenyl mixture, dietary administration of 100 mg/kg/day for 13 weeks caused no hematologic changes in rats (Millischer et al. 1980). Erythrocyte and leucocyte counts, differential leukocyte count, and hematocrit and hemoglobin levels were measured.

Polybrominated Diphenyl Ethers. No studies were located regarding hematological effects in humans after oral exposure to PBDEs.

OctaBDE caused red blood cell effects in intermediate-duration dietary studies in rats. Hematological changes included decreases in red blood cell count and packed cell volume following exposure to 800 mg/kg/day for 30 days (no effects at #80 mg/kg/day) (Norris et al. 1973, 1975a, 1975b) and reduced

erythrocytes, hematocrit, and hemoglobin following exposure to 750 mg/kg/day for 13 weeks (no effects at #70 mg/kg/day) (IRDC 1977).

DecaBDE and pentaBDE did not induce hematological effects in animals. In dietary studies with decaBDE, no hematological changes were found in rats exposed to #800 mg/kg/day for 30 days (Norris et al. 1973, 1975a, 1975b), #8,000 mg/kg/day for 13 weeks (NTP 1986), or #2,550 mg/kg/day for 103 weeks (NTP 1986), or in mice exposed to #9,500 mg/kg/day for 13 weeks or #7,780 mg/kg/day for 103 weeks (NTP 1986). There also were no hematological effects in rats exposed by diet to #1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaDBE) for 2 years (Kociba et al. 1975; Norris et al. 1975b) or #100 mg/kg/day of pentaBDE for 90 days (WIL Research Laboratories 1984).

Musculoskeletal Effects.

Polybrominated Biphenyls. Symptoms of musculoskeletal effects, described as "joint pain" and "swelling in joints," were frequently cited health complaints in two epidemiological studies of groups of Michigan residents who were likely to have ingested PBB-contaminated food (Anderson et al. 1978c; Landrigan et al. 1979). Although one study demonstrated a statistically significant difference between the prevalence rate for these types of symptoms in Michigan residents compared with nonexposed residents of Wisconsin farms (Anderson et al. 1978c), neither study demonstrated a positive association between serum PBB levels and the prevalence rates for symptoms of musculoskeletal effects.

There are no pathology data indicating that PBBs produce effects in musculoskeletal tissues of animals. No exposure-related histological changes in muscle or bone marrow were observed in rats that were administered a single 1,000 mg/kg dose of FireMaster FF-1 and observed for 2 years (Kimbrough et al. 1981). Rats and mice exposed to #30 mg/kg/day FireMaster FF-1 for 2 weeks showed no histological alterations in muscle or sternum (Gupta et al. 1981). In intermediate-and chronic-duration studies, rats and/or mice exposed to FireMaster FF-1 or FireMaster BP-6 dosages of #30 mg/kg/day by gavage for 30 days (Gupta et al. 1981), #10 mg/kg/day in the diet for 30 days (Akoso et al. 1982a; Sleight et al. 1978), #10 mg/kg/day by gavage for 25 weeks (NTP 1983), or #3.9 mg/kg/day in the diet for up to 105 weeks (NTP 1992) showed no histopathological changes in muscle or bone. A dosage of an unspecified PBB mixture as high as 50 mg/kg/day for 30 days produced no histopathological changes in rat muscle (Sleight and Sanger 1976). Excess porphyrins were detected in bone and/or teeth by fluorescence under ultraviolet light in some of the rat studies (Gupta and Moore 1979; NTP 1983), but

this appears to be a consequence of altered porphyrin metabolism (Hill 1985). No histological alterations were observed in sternebrae bone marrow of pregnant cows given FireMaster BP-6 in capsules for up to 60 days (Moorhead et al. 1977). Cows treated with 67 mg/kg/day were necropsied following sacrifice between days 33 and 66 because of impending death due to poor health, and those treated with nonlethal lower dosages of #0.65 mg/kg/day were examined 1 or 140 days following the end of treatment.

Polybrominated Diphenyl Ethers. No studies were located regarding musculoskeletal effects in humans after oral exposure to PBDEs.

Dietary studies with decaBDE found no histopathological changes in musculoskeletal tissues in rats exposed to #8,000 mg/kg/day for 13 weeks (NTP 1986), #1.0 mg/kg/day (77.4% containing 21.8% nonaBDE and 0.8% octaDBE) for 2 years (Kociba et al. 1975; Norris et al. 1975b), or #2,550 mg/kg/day for 103 weeks (NTP 1986), or in mice exposed to #9,500 mg/kg/day for 13 weeks or #7,780 mg/kg/day for 103 weeks (NTP 1986). A study of pentaBDE found no musculoskeletal changes in rats exposed dietary doses of #100 mg/kg/day for 90 days (WIL Research Laboratories 1984). No information was located on possible musculoskeletal effects of octaBDE.

Hepatic Effects.

Polybrominated Biphenyls. Results from several studies of humans exposed to PBBs do not demonstrate, in general, a conclusive association between adverse effects on the liver and oral exposure to PBBs. In a study in which serum was collected in 1974, 1977, 1978, and 1979 from 89, 240, 220, and 200 individuals, respectively, who were predominately residents of quarantined Michigan farms, no consistent statistically significant correlations were found between serum PBB levels and levels of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) or serum bilirubin (Kreiss et al. 1982). The prevalence rates of Michigan residents with abnormally high levels of SGPT (12.7% prevalence rate), SGOT (12.7%), or lactate dehydrogenase (8.6%) were statistically significantly higher than comparable rates for residents of Wisconsin farms (2.7, 2.0, and 3.3%) (Anderson et al. 1979). A contingency table analysis indicated that the prevalence of abnormal SGPT values in Michigan residents with serum PBB levels #1 ppb (8%) was lower than the prevalence rate for residents with serum PBB levels $1 ppb (14%), but correlation coefficients for serum PBB levels and serum liver enzyme levels were uniformly low (r<0.1) (Anderson et al. 1979). Physical examinations of Michigan residents (37 men and 9 women) with known exposure to PBBs and a history of incapacitating health care complaints revealed that 72% of the subjects displayed mildly enlarged livers, which were

associated with elevations in serum liver enzymes (SGOT and SGPT) predominately less than 2-fold above normal values (Stross et al. 1979). Mildly enlarged livers, confirmed by liver scanning, were observed only in 17 and 7% of 23 Michigan residents with known PBB exposure and incapacitating health complaints and 28 workers involved in the manufacture and distribution of PBBs, respectively; however, these subjects had histories of either substantial alcohol intake or exposure to multiple chemicals (Stross et al. 1981). Results of a caffeine breath test, discussed in Section 3.8.2, suggest that PBBs may have induced hepatic microsomal enzymes in exposed Michigan residents (Lambert et al. 1990).

Hepatic effects of PBBs are documented in various animal species although rats have been the species tested most extensively. The changes appear to be similar among species and reversible when mild. Characteristic hepatic effects include proliferation of the smooth endoplasmic reticulum, microsomal enzyme induction, increased serum levels of liver-associated enzymes indicative of possible hepatocellular damage, liver enlargement, hepatocyte vacuolation and fat deposition, fibrosis, and necrosis. PBBs also cause alterations in levels of cholesterol and other lipids in liver and serum, levels of vitamin A in liver and urine, and levels of porphyrins in liver, other tissues, and urine. These changes could be secondary to liver damage or due to direct effects on lipid, vitamin A, and porphyrin metabolism, which occurs primarily in the liver. Induction of microsomal enzymes by PBBs is a sensitive effect generally regarded as an adaptive response of the liver rather than as a manifestation of hepatotoxicity *per se* (Guzelian 1985). Although not necessarily adverse, induction of microsomal enzymes could alter the rate or pathways of metabolism of other xenobiotic or endogenous substances and increase activation of promutagens and procarcinogens or increase detoxification pathways. In addition, the induction of some microsomal enzyme activities is an indicator of exposure to PBBs and related compounds (Ah receptor agonists), which elicit a well known pattern of toxic responses (see Chapter 2). PBB-related liver enlargement is usually associated with hepatocyte enlargement and an increase in smooth endoplasmic reticulum and/or increased microsomal enzymatic activity; therefore, it is not considered an adverse effect unless accompanied by other biochemical changes and/or histological alterations.

Rats administered FireMaster FF-1 in a single 1,000 mg/kg dose and observed for 2–23 months posttreatment or a lethal dose of 1,000 mg/kg/day for 2 weeks developed enlarged livers with fatty and necrotic changes leading to fibrosis (Gupta and Moore 1979; Kimbrough et al. 1978b, 1981). Lower single doses of FireMaster FF-1 caused vacuolation and some biochemical changes (e.g., increased serum cholesterol and phospholipids, decreased serum retinol) at 500 mg/kg (Bernert et al. 1983; Kimbrough et

al. 1980), and hepatic porphyrin accumulation with no histologic changes at 200 mg/kg (Kimbrough et al. 1981). Repeated exposure to lower dosages of $3 mg/kg/day FireMaster FF-1 for 2 weeks (Gupta et al. 1981) or 5 mg/kg/day FireMaster BP-6 for 10 days (Raber and Carter 1986) caused hepatocyte enlargement and some fatty and single-cell necrotic changes in weanling and young rats. A limited amount of data suggest that octabromobiphenyl mixture-induced hepatic effects in rats are milder than for FireMaster mixtures at similar dosages. Fatty changes appear to be the most severe hepatic histopathologic effect of octabromobiphenyl observed following a single 1,000 mg/kg dose or doses of 3,000 mg/kg/day for 2 days and 6.53 mg/kg/day (but not 0.66 mg/kg/day) for 2 weeks (Lee et al. 1975a, 1975b; Waritz et al. 1977). In studies with mice, a single dose of 36 mg/kg FireMaster BP-6 increased liver weight (histology not evaluated) and had no consistent effects on disposition of injected ouabain or indocyanine green, indicating that hepatic function was not compromised (Cagen et al. 1977). Sporadic increases in the clearance of ouabain and indocyanine green were attributed to increased liver size. Exposure to 130 mg/kg/day FireMaster BP-6, for 11 days caused focal areas of coagulative necrosis (Corbett et al. 1975) and $3 mg/kg/day FireMaster FF-1 for 2 weeks caused scattered necrosis in mice (Gupta et al. 1981).

In intermediate-duration studies with rats, dosages $0.05 mg/kg/day FireMaster BP-6 for 20 days induced hepatic microsomal enzymes but histology was not evaluated (Babish et al. 1978). Dose-related hepatocyte swelling and vacuolation were induced by $0.1 mg/kg/day FireMaster BP-6 for 30 days (Akoso et al. 1982a), lipid accumulation, porphyrin levels, and atypical foci were increased by $0.3 mg/kg/day FireMaster FF-1 for 25 weeks (lethal dose) (NTP 1983), and bile duct hyperplasia was induced by 0.5 mg/kg/day FireMaster BP-6 for 82 days (Darjono et al. 1983). Rats exposed to higher, but not necessarily lethal, dosages of FireMaster FF-1 or FireMaster BP-6 for 1–3 months showed progression of these effects, including marked degenerative changes and porphyrin accumulation in these and other studies (Gupta and Moore 1979; Gupta et al. 1981; Kasza et al. 1978a; McCormack et al. 1978; Sleight and Sanger 1976; Sleight et al. 1978). In the only chronic study, incidences of hepatocellular hypertrophy, cytoplasmic vacuolation, atypical foci, and oval cell hyperplasia were increased in rats fed $0.5 mg/kg/day FireMaster FF-1 for up to 104 weeks (Chhabra et al. 1993; NTP 1992). Compared to this adult-only exposure, combined perinatal and adult exposure resulted in increased incidences of oval cell hyperplasia at 0.5 mg/kg/day and hypertrophy, cytoplasmic vacuolation, and bile duct fibrosis at 1.5 mg/kg/day. Studies of octabromobiphenyl mixture in rats have shown hepatic effects (e.g., hypertrophy and hyperplasia of centrilobular cells, vacuolation, and other fatty degenerative changes) at dosages $6.53 mg/kg/day for 4 weeks (Lee et al. 1975b; Norris et al. 1975a; Waritz et al. 1977), but normal liver histology at #1 mg/kg/day for 8 months (Norris et al. 1975a). A 13-week dietary study with

decabromobiphenyl mixture found that hepatic effects in rats, including vacuolization and distension of centrilobular hepatocytes often accompanied by slightly increased lipid, did not occur at dosages <100 mg/kg/day (Millischer et al. 1980). Information on hepatic effects of octabromobiphenyl mixture and decabromobiphenyl in species other than the rat was not located.

In mice, exposure to FireMaster FF-1 for 25 weeks increased liver weight, porphyrin content, and SGOT at $0.3 mg/kg/day and hepatocyte swelling occurred at $1 mg/kg/day (NTP 1983). Hepatic effects in mice exposed to $1.3 mg/kg/day FireMaster FF-1 for up to 105 weeks included hepatocyte hypertrophy, vacuolization, and necrosis; bile duct hyperplasia also developed (NTP 1992). Dosages $3 mg/kg/day for 4–6 weeks, but not 0.3 mg/kg/day, also induced hepatocyte necrosis and/or vacuolation in mice (Gupta et al. 1981; Loose et al. 1981; NTP 1983). Fatty changes and centrilobular necrosis developed in pregnant swine fed $1.25 mg/kg/day, but not 0.125 mg/kg/day, FireMaster BP-6 for 12 weeks during the second half of gestation through lactation (Werner and Sleight 1981). This adverse effect level cannot be corroborated in nonpregnant swine exposed to #8 mg/kg/day of unspecified PBBs for 16 weeks due to lack of liver histology evaluations, although relative liver weight increased at $1 mg/kg/day and no gross changes were observed (Ku et al. 1978). Guinea pigs appear to be particularly susceptible to hepatic effects of PBBs (unspecified) as indicated by ultrastructural vacuolation and formation of myelin bodies in hepatocytes following exposure to $0.04 mg/kg/day for 30 days; liver weights were increased at 0.4 mg/kg/day and histological vacuolation and severe centrilobular fatty change were observed at a lethal dose of 4 mg/kg/day (Sleight and Sanger 1976). Mink that ingested $0.24 mg/kg/day FireMaster FF-1 for #313 days showed increased liver weight and fatty infiltration (Aulerich and Ringer 1979; Ringer et al. 1981). In monkeys, lethal FireMaster FF-1 dosages $0.73 mg/kg/day for 25–50 weeks caused hepatocyte enlargement with increased lipid droplets, bile duct hyperplasia, increased SGPT, and decreased serum cholesterol (Allen et al. 1978; Lambrecht et al. 1978). Effects in six pregnant cows given 67 mg/kg/day of FireMaster BP-6 in capsules for up to 60 days included increased serum lactic dehydrogenase (LDH) and SGOT (Moorhead et al. 1977). Necropsy following sacrifice between days 33 and 66 because of impending death due to poor health showed increased liver weight and pathologic liver changes including friable appearance, glycogen depletion in hepatocytes, sinusoidal dilation, and scattered areas of early fatty degeneration. In general, the hepatic effects observed in cows are less pronounced than in other species at lethal doses. No adverse hepatic effects were observed in cows treated with #0.65 mg/kg/day and examined 1 or 140 days following the end of treatment.

Polybrominated Diphenyl Ethers. No studies were located regarding hepatic effects in humans after oral exposure to PBDEs.

No information was located on adverse hepatic effects of acute-duration oral exposure to PBDEs in animals. Intermediate- and chronic-duration studies in rodents indicate that the liver is a target of toxicity of PBDEs. Repeated dietary exposure to PBDEs typically caused liver enlargement with or without degenerative changes, and effects were generally dose-related in incidence and severity, more frequent and pronounced in males than females, and more severe with octaBDE and pentaBDE than decaBDE. Hepatic effects induced by DBDPO included increased liver weights at $80 mg/kg/day with centrilobular cytoplasmic enlargement and vacuolation at 800 mg/kg/day in male rats exposed for 30 days (Norris et al. 1973, 1975a, 1975b), degeneration and thrombosis in male rats exposed to 2,240 mg/kg/day for 103 weeks (NTP 1986), and centrilobular hypertrophy and granulomas in male mice exposed to $3,200 mg/kg/day for 103 weeks (NTP 1986). OctaBDE caused increased liver weight and histopathological changes such as hepatocellular enlargement and vacuolation in rats exposed to doses as low as 5–8 mg/kg/day (lowest tested doses) for 4–13 weeks (IRDC 1976, 1977; Norris et al. 1973, 1975a, 1975b). Hepatic effects in rats exposed to octaBDE for 13 weeks included increases in absolute and/or relative liver weight at $5-7 mg/kg/day and liver lesions in 40% of males at 5 mg/kg/day and 100% of both sexes at $50 mg/kg/day (IRDC 1977). The lesions were dose-related in severity as well as incidence and characterized by cytomegaly, change in hepatocytic cytoplasm to a finely granular, homogeneous type, and cytoplasmic vacuolation. At $600 mg/kg/day many of the livers had vacuolation of centrolobular hepatocytes and some had hepatocyte necrosis. Examinations performed at 8 weeks and 6 months postexposure showed that the liver effects persisted in the rats exposed to $50 mg/kg/day for 13 weeks (IRDC 1977).

PentaBDE induced liver effects in rats exposed to $9 mg/kg/day for 28 days (increased liver weight and enlargement of centrolobular and midzonal liver parenchymal cells) (IRDC 1976) and $2 mg/kg/day for 90 days (hepatocytomegaly) (WIL Research Laboratories 1984). The hepatomegaly in the 90-day study was dose-related with respect to severity (some affected hepatocytes at higher doses had vacuoles that likely contained lipid) and not completely reversible, as it was still evident in $10 mg/kg/day males and 100 mg/kg/day females at 24 weeks postexposure in lessened severity and incidence. Females exposed to 2 and 100 mg/kg/day pentaBDE for 90 days had an increased incidence of degeneration and necrosis of individual liver parenchymal cells at 24 weeks postexposure; the investigators concluded that this may represent the final loss of previously damaged cells and probably should be considered compound-related (WIL Research Laboratories 1984). The 2 mg/kg/day LOAEL for hepatic effects of pentaBDE was used as the basis for the intermediate-duration MRL for oral exposure as indicated in the footnote to Table 3-2 and discussed in Chapter 2 and Appendix A. Liver vitamin A concentrations were increased in rats and

mice exposed to pentaBDE by gavage in doses of 18 and 36 mg/kg/day, respectively, for 90 days (Hallgren et al. 2001).

Hepatic microsomal enzyme induction is a well-documented effect of PBDEs. Microsomal enzyme activity was induced in rats exposed by gavage to doses as low as 0.6 mg/kg/day of octaBDE and 0.4 mg/kg/day of pentaBDE for 90 days as indicated by increases in O-ethyl O-p-nitrophenyl phenylphosphonothioate (EPN) detoxification, *p*-nitroanisole demethylation, and cytochrome c reductase and cytochrome P-450 levels (Carlson 1980a). Some of these changes were persistent, lasting for 30-60 days after cessation of treatment, but not considered to be adverse due to the lack of any accompanying hepatic histological abnormalities. Rats that were treated with equimolar (0.1 mmol/kg/day) gavage doses of deca-, octa-, or pentaBDE (95.9, 76.6, or 56.4 mg/kg/day, respectively) for 14 days had octa- and pentaBDE-induced increases in liver weight and microsomal enzyme activity (e.g., increased EPN detoxification, *p*-nitroanisole demethylation, uridinediphosphate-glucuronyltransferase [UDPGT] activity, and benzo[a]pyrene hydroxylase activity); exposure to decaBDE only increased liver weight (Carlson 1980b). DecaBDE also had no effect on hepatic UDPGT, ethoxyresorufin-o-deethylase (EROD), or pentoxyresorufin-o-deethylase (PROD) activities in weanling rats that were treated with #100 mg/kg/day by gavage for 4 days (Zhou et al. 2001). Similar exposure to 0.3–300 mg/kg/day pentaBDE caused significantly increased EROD and PROD at $10 mg/kg/day and UDPGT at $30 mg/kg/day, and octaBDE induced PROD at $10 mg/kg/day and EROD and UDPGT at $30 mg/kg/day; neither of these PBDEs caused induction at #1 mg/kg/day.

Hepatic EROD, PROD, and methoxyresorufin-o-deethylase (MROD) were increased in mice exposed to $18 mg/kg/day (lowest tested dose) of pentaBDE by gavage for 14 days, although UDPGT was unchanged at #36 mg/kg/day (Fowles et al. 1994; Hallgren et al. 2001). Rats that were similarly treated with pentaBDE for 14 days had increased activities of EROD, MROD, and PROD at $18 mg/kg/day (lowest tested dose) and increased UDPGT at 36 mg/kg/day (Hallgren et al. 2001). PentaBDE also increased hepatic microsomal enzyme activity in maternally-exposed rats and their offspring (Zhou et al. 2002). Exposure to 1, 10, or 30 mg/kg/day by gavage from gestation day (Gd) 6 through postnatal day (Pnd) 21 caused significantly increased hepatic EROD and PROD at $10 mg/kg/day in dams (Gd 20 and Pnd 22) and offspring (Gd 20 and Pnds 4, 14, and 36), as well as increased UDPGT at 30 mg/kg/day in dams (Gd 20 and Pnd 22) and offspring (Gd 20 and Pnds 4 and 14).

Renal Effects.

Polybrominated Biphenyls. No statistically significant correlations were found between serum PBB levels and serum levels of blood urea nitrogen (BUN) or creatinine in a study of residents of quarantined Michigan farms after the 1973 PBB contamination episode (Kreiss et al. 1982). No other studies were located with information pertinent to renal effects in humans after oral exposure to PBBs.

Studies with animals have shown some renal effects following prolonged exposure to PBBs, but findings are generally inconsistent, and the functional significance is uncertain. No exposure-related histological changes in kidneys or bladder were observed in rats administered FireMaster FF-1 in a single dose of 200 or 1,000 mg/kg (Kimbrough et al. 1978b, 1981) and observed for 2–23 months posttreatment (Kimbrough et al. 1978a, 1981), or #30 mg/kg/day for 2 weeks (Gupta et al. 1981). Gross examination of rats exposed to 1,000 mg/kg/day for 2 weeks showed darkened kidneys (Gupta and Moore 1979). Other renal information was not reported, but the dosage was lethal. Urinalysis was normal in rats following exposure to #30 mg/kg/day for 2 weeks (Gupta et al. 1981); urinalysis was not evaluated in the other rat studies. Bladder histology, examined in some of the rat studies, was also reported to be normal (Gupta et al. 1981; Kimbrough et al. 1981). Kidney histology was not altered in rats exposed to #71 mg/kg/day octabromobiphenyl mixture for 2 weeks (Lee et al. 1975b; Waritz et al. 1977). Mice exposed to #30 mg/kg/day FireMaster FF-1 for 2 weeks showed no abnormal kidney or bladder histology or urinalysis findings (Gupta et al. 1981). Information on acute-duration renal effects in other species was not located.

In intermediate-duration studies with rats, dietary exposure to FireMaster BP-6 for 30 days produced no PBB-related alterations in urinalysis indices or BUN at 5 mg/kg/day (highest tested dose) or kidney histology at #10 mg/kg/day (Akoso et al. 1982a; Sleight et al. 1978). However, 5 mg/kg/day FireMaster BP-6 in the diet for 3 months caused progressive obsolescence of glomeruli in rats (Bowman's membrane was shrunken and glomerular tufts were shrunken, inactive, or had been largely replaced by scar tissue), although relative kidney weight, BUN, and renal function tests (clearance of inulin, *p*-aminohippurate, or fractional sodium excretion) were normal (McCormack et al. 1978). Also, *in vitro* accumulation of p-aminohippurate and N-methylnicotinamide, and ammoniagenesis and gluconeogenesis were not affected in renal cortical slices from these treated rats. Administration of FireMaster FF-1 by gavage for 25 weeks caused no renal effects at 0.1 mg/kg/day, but produced chronic progressive nephropathy at $1 mg/kg/day, and more serious histopathology at 10 mg/kg/day (NTP 1983). Renal pathology at the 10 mg/kg/day dosage included atrophy and edema of glomerular tufts with marked dilation of Bowman's

capsule and dilation of some renal tubules, with either serous fluid or proteinaceous casts in both cortical and medullary regions, and no changes in BUN (NTP 1983). Chronic administration of FireMaster FF-1 in the diet for up to 104 weeks, however, failed to produce any treatment-related histopathologic changes at dosages as high as 1.5 mg/kg/day (NTP 1992). The reason for the inconsistency between this finding and the results of the NTP (1983) study is unclear, but the different methods of oral treatment could be a factor.

Intermediate-duration gavage exposure to a higher FireMaster FF-1 dose of 30 mg/kg/day for 4.5 weeks caused dilation of Bowman's capsule with serous fluid in rats observed for . 60 days posttreatment (Gupta and Moore 1979); however, rats that were similarly treated (#30 mg/kg/day for 30 days) but observed longer (90 days posttreatment) had normal kidney histology, urinalysis values, and BUN (Gupta et al. 1981). Rats administered 50 mg/kg/day of an unspecified PBB mixture in the diet for 30 days with no posttreatment observation had increased BUN but no changes in urinalysis values or kidney histology (Sleight and Sanger 1976). In studies with octabromobiphenyl mixture in rats, dietary exposure to $8 mg/kg/day for 30 days caused hyaline degenerative cytoplasmic changes in kidneys with normal urinalysis values (Norris et al. 1975a). This finding is inconsistent with a report of normal kidney histology in rats exposed to #71 mg/kg/day octabromobiphenyl mixture in the diet for 4 weeks (urinalysis not constructed) (Lee et al. 1975b; Waritz et al. 1977); the reason for the discrepancy cannot be discerned from the reports. Kidney histology and urinalysis findings were also normal in rats administered #1 mg/kg/day octabromobiphenyl mixture for 8 months (Norris et al. 1975a). In the only study of a decabromobiphenyl mixture, urinalysis was normal in rats fed 100 mg/kg/day for 13 weeks (Millischer et al. 1980). Comprehensive histology evaluations were performed at this and lower dosages in this study, but the liver is the only tissue specifically mentioned as having been examined. Due to the total number tissues examined (21) and the route of exposure, it is probable that kidneys were examined but were not discussed because no histopathologic changes were found.

In gavage studies with mice, FireMaster FF-1 produced no renal histopathologic changes following exposure to #10 mg/kg/day for 25 weeks (BUN was normal) (NTP 1983) or #30 mg/kg/day for 30 days (normal BUN and urinalysis) (Gupta et al. 1981). Dietary exposure to 3.9 mg/kg/day FireMaster FF-1 for up to 105 weeks, however, caused an increased incidence of chronic progressive nephropathy in mice; this effect was not found at 1.3 mg/kg/day (NTP 1992). Kidney histological alterations were not reported in mink exposed to #2.4 mg/kg/day FireMaster FF-1 for 313 days (Aulerich and Ringer 1979; Ringer et al. 1981). Swine exposed to unspecified PBBs for 16 weeks had increased relative kidney weight at $1 mg/kg/day, but the adversity of this change is unclear since no gross renal pathology was observed

(#8 mg/kg/day) and histology was not evaluated (Ku et al. 1978). Monkeys that ingested 18 mg/kg/day FireMaster FF-1 for 137 days developed hyperplasia of the bladder epithelium, but histological changes in the kidneys were not reported (Allen et al. 1978). Urine alterations in six pregnant cows given 67 mg/kg/day of FireMaster BP-6 in capsules for up to 60 days included increased protein concentration and BUN, and decreased pH and specific gravity (Moorhead et al. 1977). Necropsy following sacrifice between days 33 and 66 because of impending death due to poor health showed enlarged, distended, and discolored kidneys, extreme dilation of the collecting ducts and convoluted tubules, degenerative changes in the tubular epithelium, and congestion with scattered microscopic hemorrhages in the medulla. The renal effects in cows appear to be more severe than those generally observed in other species at lethal doses. No urinalysis alterations or changes in kidney histology were observed in other cows treated with #0.65 mg/kg/day and examined 1 or 140 days following the end of treatment.

Polybrominated Diphenyl Ethers. No studies were located regarding renal effects in humans after oral exposure to PBDEs.

Studies of PBDEs in animals have mainly observed kidney changes following dietary exposure to octaBDE. Renal effects induced by octaBDE included hyaline degenerative cytoplasmic changes at $8 mg/kg/day and increased kidney weight at $80 mg/kg/day in rats exposed in the diet for 30 days (Norris et al. 1973, 1975a, 1975b), and noninflammatory kidney changes in male rats exposed to 600 mg/kg/day for 13 weeks (IRDC 1977). The incidence and severity of the kidney lesions in the 13-week study (tubule regeneration, intratubular casts, and cellular debris occurred in most 600 mg/kg/day males) suggested a compound-related effect (IRDC 1977). Another dietary study of octaBDE found no histopathological changes in the kidneys of rats exposed to #90 mg/kg/day for 90 days (IRDC 1976). Kidney pathology (hyaline degenerative cytoplasmic changes) was found in rats exposed to 800 mg/kg/day of decaBDE for 30 days (Norris et al. 1973, 1975a, 1975b), but not following exposure of rats to #90 mg/kg/day for 90 days (IRDC 1976), #8,000 mg/kg/day for 13 weeks (NTP 1986), #1.0 mg/kg/day (77.4% containing 21.8% nonaBDE and 0.8% octaDBE) for 2 years (Kociba et al. 1975; Norris et al. 1975b), or #2,550 mg/kg/day for 103 weeks (NTP 1986), or in mice exposed to #9,500 mg/kg/day for 13 weeks or #7,780 mg/kg/day for 103 weeks (NTP 1986). Studies of pentaBDE found no renal histopathology in rats exposed dietary doses of #90 mg/kg/day for 28 days (IRDC 1976) or #100 mg/kg/day for 90 days (WIL Research Laboratories 1984).

Endocrine Effects.

Polybrominated Biphenyls. No studies were located regarding endocrine effects in humans after oral exposure to PBBs.

Thyroid effects have been observed in animals treated with PBBs by gavage or diet in acute-, intermediate-, and chronic-duration studies. Characteristic changes include decreases in serum levels of serum thyroxine (T_4) and serum triiodothyronine (T_3) hormones, thyroid enlargement, and effects in the follicular cells including reduced size, hyperplasia with columnar appearance and papillary projections, and accumulation of colloid droplets. In the only acute study that investigated thyroid end points more sensitive than histology, rats administered an unspecified PBB mixture for 10 days showed serum T_4 levels (T_3 not evaluated) that were significantly reduced (p#0.05) at $3 mg/kg/day, but not at 1 mg/kg/day (Allen-Rowlands et al. 1981). The reduction in T_4 levels was both dose- and time-dependent as shown by 20-day results discussed below with intermediate-duration studies. Based on the NOAEL for decreased serum T_4, an acute oral MRL of 0.01 mg/kg/day was calculated as described in the footnote in Table 3-1. A single #286 mg/kg dose of an unspecified PBB mixture caused no change in 4-hour thyroidal ^{131}I uptake and incorporation into thyroglobulin in rats (Allen-Rowlands et al. 1981). No thyroid histological alterations were observed in rats in acute-duration studies with FireMaster FF-1, even with a single dose #1,000 mg/kg and up to 2 years posttreatment observation (Kimbrough et al. 1978b, 1981) or dosages of #1,000 mg/kg/day for 2 weeks (Gupta and Moore 1979; Gupta et al. 1981). The only information on thyroid effects of acute exposure to octabromobiphenyl mixture is a lack of histological changes in rats administered #71 mg/kg/day for 2 weeks (Lee et al. 1975b; Waritz et al. 1977). The only information on acute-duration thyroid effects of PBBs in species other than rat is the normal histologic integrity of the thyroid in mice at FireMaster FF-1 dosages of #30 mg/kg/day for 2 weeks (Gupta et al. 1981).

In intermediate-duration studies with rats, serum levels of T_3 or T_4 decreased at FireMaster dosages as low as 0.3 mg/kg/day FireMaster FF-1 for 25 weeks (NTP 1983), 0.45 mg/kg/day FireMaster BP-6 for 7 months (Byrne et al. 1987), 5 mg/kg/day FireMaster BP-6 for 30 days (Akoso et al. 1982b) or 1 mg/kg/day of an unspecified PBB mixture for 20 days (Allen-Rowlands et al. 1981). In the latter study, 8–11 rats were evaluated after exposure to 1, 3, or 6 mg/kg/day for 20 days. Other thyroid effects in these rats included significantly increased absolute thyroid weight at $3 mg/kg/day (not evaluated at 1 mg/kg/day), and increased plasma TSH levels, increased 5-hour thyroid uptake of ^{131}I and deceased incorporation of ^{131}I into monoiodotyrosine (MIT) at 6 mg/kg/day (Allen-Rowlands et al. 1981). No

effects on incorporation of ^{131}I into diiodotyrosine (DIT), T_3, or T_4 were observed. Serum T_4 levels were also reduced at $1 mg/kg/day in rats exposed for 20 days and evaluated after being placed on restricted food intake for $2 months following treatment (Allen-Rowlands et al. 1981). Rats administered 2.5 mg/kg/day of an unspecified hexabromobiphenyl mixture for 7 months showed no significant changes in serum T_3, but serum T_4 was not evaluated (Sepkovic and Byrne 1984). Thyroid ultrastructural changes were produced in rats by FireMaster BP-6 dosages as low as 0.05 mg/kg/day for 30–35 days (Akoso et al. 1982b; Kasza et al. 1978a), and histologic changes of the thyroid were observed at $5 mg/kg/day FireMaster BP-6 for 30 days (Sleight et al. 1978) and $30 mg/kg/day FireMaster FF-1 for 4.5 weeks (Gupta and Moore 1979). In the study that evaluated thyroid effects at the lowest dose, rats were administered estimated doses of 0.05, 0.5, or 5 mg/kg/day FireMaster BP-6 in the diet for 30 days (Akoso et al. 1982b). Effects were dose-dependent and included increased number and decreased size of follicles (especially at the peripheral location) at $0.05 mg/kg/day, follicles with epithelial tall columnar appearance and some papillary projections in the lumen at $0.5 mg/kg/day, and extensive follicular changes (hyperplasia and hypertrophy of follicular cells, prominent, and numerous papillary projections), increased relative thyroid weight, and decreased serum T_3 and T_4 at 5 mg/kg/day. Chronic exposure to #1.5 mg/kg/day FireMaster FF-1 for up to 104 weeks caused no thyroid histological alterations, but ultrastructure and serum thyroid hormones were not assayed (NTP 1992).

In the only intermediate-duration rat study of octabromobiphenyl mixture that assessed thyroid hormones, a dose of 2.5 mg/kg/day for 7 months produced no significant changes in serum T_3, but serum T_4 was not evaluated (Sepkovic and Byrne 1984). The histologic integrity of the thyroid was normal in rats fed octabromobiphenyl mixture at dosages as high as 1 mg/kg/day for 8 months (Norris et al. 1975a), 2.5 mg/kg/day for 7 months (Sepkovic and Byrne 1984), and 71 mg/kg/day for 4 weeks (Lee et al. 1975b; Waritz et al. 1977), although $8 mg/kg/day for 30 days induced dose-related thyroid hyperplasia (Norris et al. 1975a). An explanation for the discrepancy in the octabromobiphenyl mixture NOAELs of #71 mg/kg/day and LOAELs of $8 mg/kg/day is not apparent, particularly since treatment durations were similar, methods of treatment (diet) and animal strain and sex (male) were the same, and only the NOAEL study appears to have observed the animals (for 2–18 weeks) posttreatment.

Effects on the adrenal gland also have been observed in animals exposed to PBBs. As found for thyroid as discussed above, acute-duration exposure to FireMaster FF-1 produced no changes in rat adrenal histology following a single dose as high as 1,000 mg/kg (Gupta et al. 1981; Kimbrough et al. 1978b, 1981). Dosages of 1,000 mg/kg/day FireMaster FF-1 for 2 weeks caused gross adrenal damage (darkened glands) in rats, but #30 mg/kg/day caused no gross or histologic damage (Gupta and Moore 1979; Gupta

et al. 1981). The only information on acute-duration adrenal effects of PBBs in species other than rat is normal adrenal histology in mice at FireMaster FF-1 dosages of #30 mg/kg/day for 2 weeks (Gupta et al. 1981). No acute-duration studies of PBBs measure serum corticosteroid levels. In intermediate-duration studies, serum corticosterone B, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHS) decreased in rats fed $0.25 mg/kg/day FireMaster BP-6 for 5–7 months, but not 0.05 mg/kg/day (Byrne et al. 1988). Serum corticosterone levels and adrenal weight did not change in rats exposed to #6 mg/kg/day of an unspecified PBB mixture for a shorter duration of 20 days (other adrenal hormones were not evaluated) (Castracane et al. 1982). Adrenal histology was not evaluated in these studies, but no treatment-related alterations were observed in rats in other intermediate-duration studies with FireMaster BP-6 or FireMaster FF-1 (Akoso et al. 1982b; NTP 1983; Sleight and Sanger 1976; Sleight et al. 1978), except at lethal dosages (Gupta and Moore 1979), or in a chronic study with FireMaster FF-1 (NTP 1992). Necropsies of rats treated with 100–1,000 mg/kg/day FireMaster FF-1 for 4.5 weeks showed darkened adrenals (Gupta and Moore 1979). In the only rat study of octabromobiphenyl mixture that examined the adrenal gland, 2.5 mg/kg/day for 7 months produced no changes in relative adrenal weight; histology or serum corticosteroids were not evaluated (Sepkovic and Byrne 1984). Intermediate- or chronic-duration studies with FireMaster FF-1 in mice showed no adrenal histological effects at #3.9 mg/kg/day for up to 105 weeks (NTP 1992), #10 mg/kg/day for 25 weeks (NTP 1983), or #30 mg/kg/day for 30 days (Gupta et al. 1981).

Polybrominated Diphenyl Ethers. Plasma levels of 2,2',4,4'-tetraBDE and various other persistent organohalogen compounds (non-PBDEs), as well as hormone levels (free and total T_3 and T_4, thyroid stimulating hormone [TSH], free testosterone, follicle-stimulating hormone, lutenizing hormone, and prolactin), were analyzed in 110 men who consumed varying amounts of fatty fish (0–32 meals per month) from the Baltic Sea (Hagmar et al. 2001). There was a weak negative correlation between 2,2',4,4'-tetraBDE and plasma TSH after age adjustment, but 2,2',4,4'-tetraBDE could not explain more than 10% of the variance in TSH (r^2=0.10, $p<0.001$).

Hyperplasia of the thyroid has been observed in rats and mice following repeated dietary exposures to decaBDE. Thyroid follicular cell hyperplasia was increased in male B6C3F1 mice that were exposed to decaBDE for 103 weeks (NTP 1986). Incidences of the lesion were 2/50 (4%), 10/50 (20%), and 19/50 (38%) in the 0, 3,200, and 6,650 mg/kg/day dose groups of this study. Slight increases in follicular cell tumors that were considered to be equivocal evidence of thyroid carcinogenicity were also observed in the male mice (see Section 3.2.2.7, Cancer). No decaBDE-related histopathological changes in the thyroid were found after 103 weeks of exposure to #7,780 mg/kg/day in female mice, #2,240 mg/kg/day

in male Sprague-Dawley rats, or #2,550 mg/kg/day in female rats (NTP 1986). Dose-related increases in thyroid hyperplasia were reported for male Sprague-Dawley rats exposed to 80 and 800 mg/kg/day for 30 days (Norris et al. 1973, 1975b), although not in rats exposed to #90 mg/kg/day for 90 days, rats exposed to #8,000 mg/kg/day for 13 weeks, or mice exposed to #9,500 mg/kg/day for 13 weeks (IRDC 1976; NTP 1986). The occurrence of thyroid hyperplasia in the rats exposed to $80 mg/kg/day for 30 days could be related to the congener composition of the decaBDE mixture tested by Norris et al. (1973, 1975a, 1975b) (i.e., 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE, compared to $94% decaBDE typically used in other studies).

Thyroid hormone levels were determined in weanling (28-day-old) female Long-Evans that were treated by gavage for 4 days with technical decaBDE (DE-83R) or octaBDE (DE-79) in doses of 0.3, 1, 3, 10, 30, 60, or 100 mg/kg/day, or pentaBDE (DE-71) in doses of 0.3, 1, 3, 10, 30, 100, or 300 mg/kg/day (Zhou et al. 2001). The animals were sacrificed on the day after the last exposure and evaluated for changes in serum levels of total T_4, total T_3, and thyroid-stimulating hormone (TSH). DecaBDE caused no changes in levels of any of the thyroid hormones. OctaBDE induced a dose-related reduction in serum T_4 levels with statistically significant ($p<0.05$) decreases occurring at $10 mg/kg/day and a 70% maximum decrease compared to controls at the highest dose of 100 mg/kg/day. Serum total T_3 levels were significantly reduced at $60 mg/kg/day with a maximum reduction of 25% at 100 mg/kg/day. PentaBDE caused dose-related reductions in serum T_4 levels with significant decreases occurring at $30 mg/kg/day and an 80% maximum decrease compared to controls at the highest dose of 300 mg/kg/day. Serum total T_3 levels were significantly reduced at $100 mg/kg/day with a maximum reduction of 30% at 300 mg/kg/day. Neither octaBDE nor pentaBDE caused exposure-related changes in serum TSH concentrations. Benchmark dose (BMD) analysis of the octaBDE data found that the BMD and BMDL (95% lower confidence limit on the BMD) resulting in a 20% reduction in thyroid hormones (LED_{20}) were 9.25 and 5.29 mg/kg/day, respectively, for serum T_4 and 53.38 and 11.98 mg/kg/day, respectively, for serum T_3. For pentaBDE, the respective BMD and BMDL resulting in 20% reduced hormone levels were 12.74 and 6.95 mg/kg/day for serum T_4 and 32.94 and 8.56 mg/kg/day for serum T_3.

Serum levels of thyroid hormones were not evaluated in any other study of octaBDE. Dose-related increases in thyroid hyperplasia were observed in male Sprague-Dawley rats (incidences not reported) exposed to $8 mg/kg/day (lowest tested dose) in the diet for 30 days (Norris et al. 1973, 1975b). Thyroid hyperplasia was equivocally increased in male CD rats that were exposed to 90 mg/kg/day of octaBDE (unspecified mixture) in the diet for 28 days (IRDC 1976); incidences of slight or moderate hyperplasia were 0/5, 0/5, and 3/5 at 0, 9, and 90 mg/kg/day, respectively. CD rats that were exposed to octaBDE in

estimated dietary doses of 5, 50, or 600 mg/kg/day (males) or 7, 70, or 750 mg/kg/day (females) for 13 weeks had increased absolute and relative thyroid weights at $50/70 mg/kg/day (IRDC 1977). The thyroid weight increases were still observed at 8 weeks postexposure in the 600/750 mg/kg/day groups and were concluded to be likely compound-related. Most of the follicles in the thyroids of 4/35 males at 600 mg/kg/day and 1/35 females at 750 mg/kg/day had epithelium that was tall columnar rather than the normal cuboidal type. This effect was considered to be a very slight but probably compound-related histological change. The thyroid glands were considered within the range of normal morphology at 8 weeks postexposure in the 600/750 mg/kg/day rats as well as in the lower dose groups (IRDC 1977).

The 4-day study in weanling rats summarized above (Zhou et al. 2001) is not the only study of pentaBDE that found suppressed thyroid hormone levels. Serum T_4 levels were also reduced by pentaBDE in maternally-exposed rats and their offspring (Zhou et al. 2002). Long-Evans rats were administered 1, 10, or 30 mg/kg/day of pentaBDE (DE-71) in corn oil by gavage from Gd 6 through Pnd 21. Total concentrations of serum T_4 and T_3 were evaluated in dams on Gd 20 and Pnd 22 and offspring were evaluated on Gd 20 and Pnds 4, 14, 36, and 90. Serum T_4 was significantly ($p<0.05$) reduced compared to controls in dams at 30 mg/kg/day on Gd 20 and Pnd 22 (48 and 44% reduced, respectively), and in offspring at $10 mg/kg/day on Gd 20 ($15% reduced) and Pnds 4 and 14 (50 and 64% reduced at 10 and 30 mg/kg/day, respectively). The effect on serum T_4 concentrations in the offspring returned to control levels by Pnd 36. The NOAEL for the effect on serum T_4 levels (1 mg/kg/day) was used as the basis for the acute-duration MRL for oral exposure as indicated in the footnote to Table 3-2 and discussed in Chapter 2 and Appendix A. There were no exposure-related changes in serum T_3 levels in the dams or offspring, or any significant effects of treatment on litter size, sex ratio, or nonneurodevelopmental measures of offspring viability and growth as discussed in Section 3.2.2.6 (Developmental Effects). The BMD and BMDL resulting in a 20% reduction in serum T_4 levels were determined to be 2.36 and 0.94 mg/kg/day, respectively.

Serum total T_4 concentrations were significantly reduced in female C57BL/6J mice that were given a single gavage dose of pentaBDE (DE-71) as low as 0.8 mg/kg (lowest tested dose) (Fowles et al. 1994). Reductions in serum T_4 were found in four of five dose groups (i.e., 0.8, 4, 20, and 500 mg/kg, but not 100 mg/kg), but did not occur in a dose-dependent manner. This lack of dose-dependency might be explained by the number of animals per group, which was relatively small (n=6). Evaluation of mice exposed to 18, 36, or 72 mg/kg/day of pentaBDE by daily gavage for 14 days showed significantly reduced total and free T_4 levels at $18 mg/kg/day (Fowles et al. 1994). Serum T_3 and TSH levels and thyroid histology were not evaluated in the single-dose and 14-day mouse studies. Serum levels of total

and free T_4 were also significantly reduced in female C57BL/6J mice as well as female Sprague-Dawley rats that were similarly exposed to $18 mg/kg/day (lowest tested dose) of a different pentaBDE mixture (Bromkal 70-5 DE) for 14 days (Darnerud and Sinjari 1996; Hallgren et al. 2001). There were no exposure-related changes in TSH levels in the rats or mice and serum T_3 was not evaluated in either species. Serum measurements in rats and mice that were treated with 1, 6, or 18 mg/kg/day of 2,2',4,4'-tetraBDE for 14 days showed significantly reduced T_4 levels in both species at 18 mg/kg/day (Darnerud and Sinjari 1996; Hallgren and Darnerud 1998). Exposure to 18 mg/kg/day of 2,2',4,4'-tetraBDE did not affect TSH levels in the rats (not determined in mice).

End points assessed in a comprehensive 90-day feeding study of pentaBDE (DE-71) in male and female Sprague-Dawley rats included serum T_3 and T_4 levels (TSH not measured) and thyroid histology (WIL Research Laboratories 1984). Effects observed in both sexes included significantly reduced plasma T_4 levels at $10 mg/kg/day and increased follicular cell hyperplasia at 100 mg/kg/day. Incidences of follicular cell hyperplasia in the 0, 2, 10, and 100 mg/kg/day dose groups of this study were 0/10, 2/10, 2/10, and 5/10 in males and 0/10, 0/10, 1/10, and 4/10 in females. The thyroid hyperplasia was mild and transient as it was characterized as very slight in severity at all doses and was no longer observed at 24 weeks postexposure in any animals. Thyroid hyperplasia was equivocally increased in male CD rats that were exposed to 90 mg/kg/day of pentaBDE (unspecified mixture) in the diet for 28 days (IRDC 1976). Incidences of slight or moderate hyperplasia in the 0, 9, or 90 mg/kg/day dose groups of this study were 0/5, 1/5, and 3/5 males, respectively; no increases were seen in females.

Information on hormonal effects of PBDEs other than thyroid is limited to adrenal corticosterone data from a 14-day study of pentaBDE (DE-71). Measurements of serum corticosterone levels in female mice showed no clear chemical-related changes following exposure to 18, 36, or 72 mg/kg/day by daily gavage for 14 days (Fowles et al. 1994).

Dermal Effects.

Polybrominated Biphenyls. Limited human data from an epidemiological study provide suggestive evidence that oral exposure to PBBs may produce skin disorders in humans, but do not provide information regarding dose-response relationships. Symptoms of skin disorders (rashes, acne, increased sensitivity to the sun, darkening or thickening of the skin, discoloration or deformity of fingernails or toenails, slow healing of cuts) were reported with greater frequency in a group of 406 Michigan residents probably exposed to PBBs than in a group of 153 likely unexposed residents, but no association was

evident between serum PBB levels and prevalence of skin disorders (Anderson et al. 1978c). In a medical history survey study conducted in 1976, symptoms of skin disorders (peeling and scaling, erythema, hair loss, increased nail growth, increased sweating) experienced during the previous 3 years were reported at higher prevalence rates in a group of 321 Michigan residents from quarantined farms and in a group of 177 nonquarantined farm residents than in a group of 149 nonexposed Wisconsin residents (Chanda et al. 1982). Physical examination of the combined group of Michigan residents revealed alopecia in 4% of the subjects compared to no occurrence of alopecia in the control group.

PBBs produced characteristic dermal changes in certain species of animals following repeated exposures. No exposure-related histological changes were observed in the skin, salivary glands, or eyes of rats administered a single dose of 200 mg/kg FireMaster FF-1 and observed for 18–22 months (Kimbrough et al. 1981). Rats and mice exposed to #30 mg/kg/day FireMaster FF-1 for 2 weeks showed no histological alterations in pinnae, ear canals, or salivary glands, but examination of skin was not performed (Gupta et al. 1981). In intermediate- and chronic-duration studies, rats and/or mice exposed to FireMaster FF-1 or FireMaster BP-6 dosages of #30 mg/kg/day by gavage for 30 days (Gupta et al. 1981), #10 mg/kg/day in the diet for 30 days (Akoso et al. 1982a), #10 mg/kg/day by gavage for 25 weeks (NTP 1983), or #3.9 mg/kg/day in the diet for up to 105 weeks (Chhabra et al. 1993; NTP 1992) showed no histopathological changes in skin, pinnae, ear canals, or salivary glands. Xerophthalmia (extreme dryness of the conjunctiva, with keratinization of epithelium following chronic conjunctivitis) was observed in rats after 82 days of dietary exposure to 5 mg/kg/day FireMaster BP-6 (Darjono et al. 1983). Alopecia, loss of eyelashes, generalized subcutaneous edema, dry scaly skin, and periorbital edema developed in monkeys exposed to FireMaster FF-1 in dosages of $0.73 mg/kg/day for $25 weeks (two animals) or 18 mg/kg/day for 137 days (one animal) (Allen et al. 1978; Lambrecht et al. 1978). Histological examination, performed only in the monkey exposed to 18 mg/kg/day, showed atrophy and squamous metaplasia of sebaceous glands and keratinization of hair follicles (Allen et al. 1978). Dermatosis on the ventral surface was a clinical sign in two of four swine administered 8 mg/kg/day FireMaster FF-1 for 16 weeks (Ku et al. 1978). No additional information was reported on the dermatosis (a nonspecific term used to denote any cutaneous lesion or group of lesions), and histologic examinations were not completed.

Polybrominated Diphenyl Ethers. No studies were located regarding dermal effects in humans after oral exposure to PBDEs.

Histopathological examinations showed no dermal changes in rats following dietary exposure to #750 mg/kg/day of octaBDE for 13 weeks (IRDC 1977) or #100 mg/kg/day of pentaBDE for 90 days (WIL Research Laboratories 1984).

Ocular Effects.

Polybrominated Biphenyls. No studies were located regarding ocular effects in humans after oral exposure to PBBs.

Occasional eye discharge was observed in pregnant cows that were administered 67 mg/kg/day of FireMaster BP-6 in capsules for up to 60 days (Moorhead et al. 1977). Necropsy following sacrifice between days 33 and 66 because of impending death due to poor health showed hyperkeratosis of the eyelids and squamous metaplasia with keratin cysts in the tarsal glands in five of six animals. No ocular effects were observed in other cows treated with #0.65 mg/kg/day and examined 1 or 140 days following the end of treatment. Histological changes were not observed in the eyes of rats exposed to FireMaster FF-1 for 2 weeks (Gupta et al. 1981), or in rats and mice treated by gavage (NTP 1983) or fed FireMaster FF-1 for up to 105 weeks (Chhabra et al. 1993; NTP 1992).

Polybrominated Diphenyl Ethers. No studies were located regarding ocular effects in humans after oral exposure to PBDEs.

Histopathological examinations showed no ocular effects in rats following dietary exposure to #1.0 mg/kg/day of 77.4% decaBDE (containing 21.8% nonaBDE and 0.8% octaDBE) for 2 years (Kociba et al. 1975; Norris et al. 1975b), #750 mg/kg/day of octaBDE for 13 weeks (IRDC 1977), or #100 mg/kg/day of pentaBDE for 90 days (WIL Research Laboratories 1984).

Body Weight Effects.

Polybrominated Biphenyls. No studies were located regarding body weight effects in humans after oral exposure to PBBs.

Reduced body weight was observed in various species following acute oral administration of relatively high doses of PBBs; this effect is most evident with repeated exposure. In general, decreases in food and water intake are not sufficient to account for decreases in body weight. Effects on body weight can be

quite pronounced following intermediate- and chronic-duration exposure, constituting a wasting syndrome manifested by weight loss and depletion of body fat. In acute-duration studies with rats, a single 1,000 mg/kg dose of FireMaster FF-1 caused decreased weight gain during the following 2 years (Kimbrough et al. 1981), and a single 800 mg/kg dose of FireMaster BP-6 during pregnancy caused maternal weight loss (Beaudoin 1977). Single FireMaster doses of 400 (BP-6) or 500 (FF-1) mg/kg/day did not affect body weight in rats (Beaudoin 1977; Kimbrough et al. 1980). Administration of 1,000 mg/kg/day FireMaster FF-1 or 130 mg/kg/day FireMaster BP-6 for 2 weeks produced decreased weight gain or weight loss in rats and mice, respectively (Corbett et al. 1978; Fraker 1980; Fraker and Aust 1980; Gupta and Moore 1979), but 5 mg/kg/day FireMaster BP-6 for 10 days had no effect on body weight in rats (Raber and Carter 1986). A single #2,000 mg/kg dose or two daily 3,000 mg/kg doses of octabromobiphenyl mixture had no effect on body weight gain in rats observed for the following 14–28 days (Lee et al. 1975a; Norris et al. 1975a). No changes in body weight were produced in rats exposed to #71 mg/kg/day octabromobiphenyl mixture for 2 weeks (Lee et al. 1975b; Waritz et al. 1977). In intermediate-duration studies, decreased body weight gain and/or weight loss has been observed in rats at dosages as low as 3 mg/kg/day FireMaster FF-1 for 6 months (Luster et al. 1980; NTP 1983), 5 mg/kg/day FireMaster BP-6 for 1–3 months (McCormack et al. 1978; Sleight et al. 1978), and 30–50 mg/kg/day FireMaster FF-1 for 4.5–5 weeks (Gupta and Moore 1979; Sleight and Sanger 1976). FireMaster FF-1 dosages $100 mg/kg/day for 4.5 weeks (lethal doses) caused weight loss and emaciation in rats (Gupta and Moore 1979). Final body weights were decreased $11–28% in rats exposed to 0.5 or 1.5 mg/kg/day FireMaster FF-1 for up to 104 weeks (NTP 1992). No body weight changes were observed in rats fed a decabromobiphenyl mixture at dosages as high as 100 mg/kg/day for 13 weeks (Millischer et al. 1980).

In mice exposed to FireMaster FF-1, estimated dosages of 10 mg/kg/day for 25 weeks (NTP 1992) and 21.7 mg/kg/day for 6 weeks (Loose et al. 1981) decreased the rate of weight gain. Chronic exposure to #3.9 mg/kg/day FireMaster FF-1 for up to 105 weeks, however, did not produce adverse effects on mouse body weight (NTP 1992). Guinea pig, mink, and monkey seem to be particularly sensitive species, as indicated by pronounced weight loss in guinea pigs from ingestion of 4 mg/kg/day of unspecified PBBs for 30 days (Sleight and Sanger 1976), decreased weight gain in mink at FireMaster FF-1 dosages as low as 0.39 mg/kg/day with weight loss at 1.86 mg/kg/day (Aulerich and Ringer 1979; Ringer et al. 1981), and weight loss in monkeys at FireMaster FF-1 dosages as low as 0.73 mg/kg/day for 25–50 weeks (Allen et al. 1978; Lambrecht et al. 1978). Monkeys that ingested an estimated FireMaster FF-1 dosage of 0.012 mg/kg/day for 66 weeks lost weight (Lambrecht et al. 1978). Food intake and body weight gain were reduced in pregnant cows after 4 and 20 days administration of 67 mg/kg/day FireMaster BP-6 in

capsules (Moorhead et al. 1977). This dosage was lethal because death was impending between days 33 and 66 (treatment duration was 60 days). There were no effects on food intake or body weight in cows treated with #0.65 mg/kg/day and observed 1 or 140 days following the end of treatment.

Polybrominated Diphenyl Ethers. No studies were located regarding body weight effects in humans after oral exposure to PBDEs.

DecaBDE had no effect on body weight gain in rats and mice that were exposed to dietary doses of #16,000 and #19,000 mg/kg/day, respectively for 14 days, #8,000 and #9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986), or #2,550 and #7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986). Dietary ingestion of 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaDBE) similarly caused no body weight changes in rats exposed to #800 mg/kg/day for 30 days or #1.0 mg/kg/day for 2 years (Kociba et al. 1975; Norris et al. 1973, 1975a, 1975b).

OctaBDE did not affect body weight in rats exposed to dietary doses of #90 mg/kg/day for 28 days (IRDC 1976) or #800 mg/kg/day for 30 days (Norris et al. 1973, 1975a, 1975b), although exposure to $600 mg/kg/day for 13 weeks caused $12% decreases in weight gain (IRDC 1977). There were no pentaBDE-related body weight changes in rats exposed to #90 mg/kg/day for 28 days (IRDC 1976) or mice exposed to #72 mg/kg/day pentaBDE for 14 days (Fowles et al. 1994), although the rate of weight gain was reduced in rats exposed to #100 mg/kg/day pentaBDE for 90 days (WIL Research Laboratories 1984).

3.2.2.3 Immunological and Lymphoreticular Effects

Polybrominated Biphenyls. Numerous reports have been published regarding the immunological competence of individuals exposed to PBBs in the Michigan feed contamination episode. Due to the relatively high number of published reports and to the fact that often different groups of investigators appear to have examined the same cohort, only representative studies are discussed below.

Immunological parameters were compared between a group of 45 adult Michigan dairy farmers and their families who were exposed for periods ranging from 3 months to 4 years and two groups of control individuals not known to have been exposed to PBBs (Bekesi et al. 1978, 1979). In 27 of the 45 Michigan subjects, the peripheral blood lymphocytes responded within a normal range to phytohemagglutinin (PHA) and PWM mitogen-induced lymphoblastogenesis, but had reduced reactivity in mixed leukocyte cultures relative to controls. In the remaining 18 Michigan subjects, the response to PHA and PWM and the reactivity to mixed leukocyte cultures was significantly reduced ($p<0.00001$) relative to controls. Assays for membrane markers of peripheral blood lymphocytes showed significant reductions in markers in the Michigan subpopulation with abnormal lymphoblastogenesis. Both Michigan subpopulations had a significant increase in the number of lymphocytes without detectable surface markers, relative to controls. The number of markers for monocytes was not significantly different among the groups studied. There were no significant differences in serum PBB levels between the two Michigan subsets. No consistent correlation could be demonstrated between lymphocyte function and PBB plasma concentration.

Reexamination of a group of 40 Michigan farmers 5 years after the first examination (Bekesi et al. 1985; Roboz et al. 1985) showed that the number of T-lymphocytes and the lymphocyte response to stimulation with PHA were altered to the same extent reported 5 years earlier (Bekesi et al. 1978).

In a similar study, Michigan subjects were classified into three groups according to their serum PBB levels: high (>300 ppb), low (<1–11 ppb), and unexposed (controls) (Silva et al. 1979). The percentage of subjects that complained of recurrent infection was similar in the two exposed groups (about 20%). The total leukocyte count, percentage of lymphocytes, and percentage of subpopulations of T- and B-lymphocytes were similar among the three groups. Mean spontaneous lymphocyte transformation and lymphocyte mitogenic responsiveness to stimulation with three different mitogens were not significantly different among the three groups. Furthermore, there was no correlation between a poor mitogenic response and low numbers of T-lymphocytes (Silver et al. 1979).

It was also reported at this time that Michigan farm residents with the highest exposure to PBB had significantly elevated levels of IgM, IgA, and IgG relative to Wisconsin dairy farm residents (Bekesi et al. 1985). Cluster analysis of several immunological parameters performed for husbands and wives showed, according to the investigators, significant correlations for surface markers, lymphocyte functions, and IgG values (no correlation coefficient was >0.337). This finding was interpreted as supporting a common dietary source for the immune dysfunction rather than a genetic predisposition (Bekesi et al. 1985).

In yet another report, Michigan farmers reported a higher rate of infections (11%) than a group of chemical workers exposed to PBB (3%) (Stross et al. 1981), however, average PBB levels in serum, bile, and fat were higher in the chemical workers than in the farmers. When the patients were divided according to their PBB fat level into high, moderate, and low, there was an equal distribution of abnormal physical, laboratory, and diagnostic findings among the groups.

The immunological effects of the commercial PBB mixtures FireMaster FF-1 and FireMaster BP-6 have been examined in rats, mice, guinea pigs, dogs, and pigs, but in many cases, the most sensitive immunological end points were not examined. In all but two studies, the animals were exposed for an intermediate duration; most studies were conducted in rats, and many studies administered the PBBs by gavage (exceptions noted below). Identification of the most sensitive species is difficult due to the fact that not all studies examined the same end points, although limited data suggest that guinea pigs may be particularly sensitive. Immunological effects in animals, attributed to exposure to PBBs *in utero* or through lactation, are discussed in Section 3.2.2.6.

Limited data exist regarding immunological effects of PBBs in animals following acute oral exposure. No histopathological alterations were observed in the spleen and thymus of rats treated with a single dose of 1,000 mg/kg FireMaster FF-1 and observed for 2 years (Kimbrough et al. 1978b). A similar lack of effects in the thymus, spleen, and lymph nodes was reported in rats and mice treated for 2 weeks with up to 30 mg/kg/day FireMaster FF-1 (Gupta et al. 1981). However, mice treated with . 130 mg/kg FireMaster BP-6 in the diet for 14 days were incapable of mounting an antibody-mediated response following immunization with sheep red blood cells (SRBC) (Fraker 1980; Fraker and Aust 1980). This treatment also reduced absolute thymus weight by 88% and caused high lethality in mice.

Numerous intermediate-duration studies have examined the immunological effects of PBBs in rats. For example, treatment of rats with FireMaster FF-1 for 25 weeks significantly increased absolute and relative spleen weight at $1 mg/kg/day and significantly decreased absolute and relative thymus weight at

$0.3 mg/kg/day (NTP 1983). Nevertheless, no histopathological alterations were observed in these organs and in lymph nodes with doses of up to 10 mg/kg/day (NTP 1983). Similar results were reported in rats treated with 30 mg/kg/day FireMaster FF-1 for 4–5 weeks (Gupta and Moore 1979; Gupta et al. 1981), but a dose of 100 mg/kg/day caused thymic atrophy and necrosis of lymphoblasts (Gupta and Moore 1979). A much smaller dose, 0.5 mg/kg/day FireMaster BP-6 in the diet for 150 days, reportedly caused moderate lymphoid depletion in thymus and spleen (Rezabek et al. 1989). In the only chronic rat study, splenic fibrosis developed following exposure to 1.5 mg/kg/day, but not 0.5 mg/kg/day, FireMaster FF-1 in the diet for up to 104 weeks (NTP 1992). Treatment of rats for 5 weeks with 30 mg/kg/day FireMaster FF-1 significantly reduced the *in vitro* lymphocytic response to stimulation with two out of three mitogens and thymus and spleen weight (Luster et al. 1978). Relative thymus weight was reduced at 3 mg/kg/day; however, treatment with the test material did not alter the production of antibodies 4 days after immunization with SRBC. The same group of investigators reported significantly decreased lymphoproliferative responses to mitogens or allogenic cells in rats following treatment with 3 mg/kg/day FireMaster FF-1 for 6 months (Luster et al. 1980); a dose of 1 mg/kg/day was without effect. It must be mentioned, however, that in the studies conducted by Luster and co-workers, doses $3 mg/kg/day FireMaster, reduced body weight by $15% in the animals, suggesting that PBBs can affect the immune system, but only at dose levels that produce overt toxicity.

Mice treated for 30 days with FireMaster BP-6 in the diet at levels of approximately $1.3 mg/kg/day had a significantly reduced antibody-mediated response to SRBC ($p<0.001$) (Fraker 1980; Fraker and Aust 1980). Absolute thymus weight was significantly reduced ($p<0.01$) relative to controls with all dose levels tested (0.13, 1.3, 13 mg/kg/day). Delayed-type hypersensitivity was not altered by PBB treatment. Corticosterone levels in plasma were elevated in treated mice relative to controls, but not elevated enough to be responsible for the immunological findings. No histopathological effects were observed in the thymus, spleen, or lymph nodes of mice treated with 30 mg/kg/day FireMaster BP-6 for 4–5 weeks, but relative thymus weight was temporarily decreased (Gupta et al. 1981). Other studies in mice reported increased lethality ($p<0.05$) after bacterial inoculation in groups treated with 10 mg/kg/day FireMaster FF-1 for 6 months (Luster et al. 1980) and increased lethality ($p<0.05$) due to challenge with *Salmonella thyphosa* lipopolysaccharide after 3 or 6 weeks of dietary exposure to . 21.7 mg/kg/day FireMaster FF-1 (Loose et al. 1981). No histopathological changes were observed in the spleen, thymus, and lymph nodes of mice treated with up to 10 mg/kg/day FireMaster FF-1 for 25 weeks (NTP 1983), although 3.9 mg/kg/day for up to 105 weeks caused increased splenic hematopoiesis (NTP 1992).

Guinea pigs administered 0.4 mg/kg/day FireMaster BP-6 in the diet for 45 days exhibited a significant reduction ($p<0.01$) in tetanus-antitoxin titers following injection of tetanus toxoid (Vos and van Genderen 1973, 1974). A dose 5 times higher caused marked thymus atrophy, splenic effects (marked depletion of the follicles and periarteriolar lymphocyte sheaths), and lethality. Pregnant sows fed a diet that provided approximately 2.5 mg/kg/day FireMaster BP-6 for a total of 12 weeks (including part of gestation and lactation) showed a significantly reduced ($p<0.05$) lymphocyte response to stimulation with PHA and PWM mitogens relative to controls (Howard et al. 1980); a dose of 1.25 mg/kg/day was without effect. However, PBB treatment did not affect bactericidal activity of whole blood towards *Escherichia coli* and *Staphylococcus aureus*.

Two cows gavaged with daily doses of 67 mg/kg/day of an unspecified PBB mixture for 38 consecutive days showed minimal alterations in tests of humoral and cell immunity relative to a group of 54 unexposed animals (Kateley et al. 1982). The concentration of PBBs in tissues from these two cows reached 1,000 mg/kg, and they became moribund and were later sacrificed. A similar lack of significant immunological effects was reported in the same study for 58 cows from contaminated farms in Michigan that had PBB body burdens ranging from 0.02 to 24 mg/kg for at least 2 years (Kateley et al. 1982). Cows that received gavage doses of #0.65 mg/kg/day FireMaster PB-6 for 60 days showed no histopathologic alterations in the thymus or spleen (Moorhead et al. 1977). However, doses of 67 mg/kg induced thymic involution and atrophy, and were nearly lethal.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Polybrominated Diphenyl Ethers. No studies were located regarding immunological effects in humans after oral exposure to PBDEs. No effects on pokeweed mitogen-stimulated DNA proliferation or IgG immunoglobulin synthesis were found in human lymphocytes exposed to 2,2',4,4'-tetraBDE or 2,2',3,4,4'-pentaBDE *in vitro* (Fernlof et al. 1997).

Limited information is available on effects of acute-duration exposure to pentaBDE on immunologic function in animals. A single gavage dose of 0.8–500 mg/kg of pentaBDE (DE-71) did not effect the plaque-forming splenic cell (PFC) antibody response to injected SRBC in mice (Fowles et al. 1994). Mice that were given 18, 36, or 72 mg/kg/day doses of pentaBDE (DE-71) by gavage for 14 days had significantly reduced antibody response to SRBC (63% of control value, $p<0.02$) and decreased thymus weight at 72 mg/kg/day (Fowles et al. 1994). There were no exposure-related effects of the 14-day

exposure to #72 mg/kg/day on natural killer cell (NKC) activity to murine YAC-1 target cells; NKC activity was not evaluated in the single dose study. A 14-day study of another pentaBDE mixture (Bromkal 70-5 DE) was conducted in which mice and rats were administered 18 or 36 mg/kg/day by gavage and were evaluated for spleen and thymus weights, numbers of splenic and thymic lymphocyte subsets (CD4+, CD8+, and CD45R+ cells), and *in vitro* IgG immunoglobulin production in pokeweed mitogen-stimulated splenocytes (Darnerud and Thuvander 1998). The only exposure-related effect in either species was significantly reduced *in vitro* production of IgG in pokeweed-stimulated splenocyte cultures from the mice exposed to 36 mg/kg/day. Mice that were similarly tested with 18 mg/kg/day of the congener 2,2',4,4'-tetraBDE for 14 days had significantly reduced numbers of total splenocytes as well as CD4+, CD8+, and CD45R+ cells in spleen (Darnerud and Thuvander 1998). This was the only dose level of a single congener used in the mice. Rats were not evaluated.

Histopathological examinations of spleen, thymus, lymph node and/or bone marrow tissues showed no effects of repeated dietary administration in intermediate-duration studies in rats exposed to #8,000 mg/kg/day decaBDE for 13 weeks (NTP 1986), in mice exposed to #9,500 mg/kg/day decaBDE for 13 weeks, in rats exposed to #750 mg/kg/day octaBDE for 13 weeks (IRDC 1977), or in rats exposed to #100 mg/kg/day pentaBDE for 90 days (WIL Research Laboratories 1984). Chronic ingestion of decaBDE caused lesions in the spleen of rats exposed to $1,200 mg/kg/day (splenic hematopoiesis in males) or 2,240 mg/kg/day (splenic fibrosis and lymphoid hyperplasia in females) for 103 weeks (NTP 1986).

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Polybrominated Biphenyls. Neurological symptoms were reported frequently by Michigan residents during a 3–4-year period following the 1973 PBB contamination episode, but positive associations between serum PBB levels and frequency of neurological symptoms were not found in several studies. In an epidemiological study conducted by the U.S. Center for Disease Control and the Michigan Department of Public Health, fatigue was reported more frequently by several putatively exposed groups including 2,148 residents of farms quarantined for PBB contamination (36.4% prevalence rate), 1,421 recipients of food from contaminated farms (32.4%), 252 chemical workers involved in PBB manufacturing or distribution (22.0%), and 331 residents of farms with low levels of PBB contamination (41.4%), than by a small (60 persons) unexposed control group (15.8%); however, no positive association was apparent between serum levels of PBB and prevalence rates for any reported symptom (Landrigan et al. 1979). Neurological symptoms, including marked tiredness and decrements in the capacity for intellectual and physical work, also were reported with greater frequencies in groups of farmers and residents of Michigan likely to have consumed farm products contaminated with PBB, than in groups of unexposed Wisconsin farmers; however, serum PBB levels were not positively associated with prevalence rates for any symptom including neurological symptoms, nor with performance on neurobehavioral tests for a subset of this population (Anderson et al. 1978c, 1979; Valciukas et al. 1978, 1979). In a 1976 medical history questionnaire study of 342 Michigan children likely to have been exposed to PBBs and 72 unexposed children from Wisconsin, the number of subjectively reported symptoms of ill health, including several symptoms of neurological effects, did not increase with increasing serum PBB levels (assayed in 1976), but rather decreased; general neurological examinations did not reveal a pattern of abnormality among the Michigan children (Barr 1980). Subjectively reported symptoms of neurological effects including weakness, fatigue, difficulty in concentrating, and irritability were prevalent in a group of 23 farmers involved in the Michigan PBB contamination episode, but tests of intelligence, memory, and nerve conduction velocity failed to demonstrate abnormalities. In addition, a group of 28 workers involved in the manufacture or distribution of PBB displayed higher average serum PBB levels than the farmers (48 ppb versus 14 ppb), but did not report a prevalence of symptoms of neurological effects (Stross et al. 1981). In a study of 21 Michigan residents who consumed PBB-contaminated food and had lingering medical complaints and 21 volunteer control subjects with putative low-dose exposure to PBB, no positive association was observed between PBB levels in fat tissue and performance in a battery of neuropsychological tests (Brown and Nixon 1979). In general, the findings of the epidemiological and clinical studies of people exposed to PBBs in Michigan are inconclusive; they do not clearly demonstrate

or eliminate the possibility of an association between PBB oral exposure and the occurrence of neurological effects.

Limited data indicate that orally (gavage) administered PBBs can produce neurological effects in rats. FireMaster FF-1 at 10 mg/kg/day (3 days/week) for 8 weeks did not alter the performance of rats in tests of operant behavior, but decreased motor activity, grip strength, and startle responsiveness observed in rats following administration of #10 mg/kg/day for 6 months or 30 mg/kg/day for 4 weeks (Tilson and Cabe 1979). Motor activity changes were also observed in rats administered doses of FireMaster FF-1 as low as 1 mg/kg/day for 4 weeks (Geller et al. 1979). In this experiment, neither learning nor performance of a simple discrimination task was affected by 1, 3, or 6 mg/kg/day dosage levels, but increased motor activity was observed at 1 mg/kg/day. No changes were apparent at 3 mg/kg/day and decreased motor activity was apparent at 6 mg/kg/day, compared with controls. Weakness of the hind limb was noted in rats treated with 10 mg/kg/day FireMaster FF-1 for 6 months compared with control rats (Cabe and Tilson 1978). Histological examination of brain and/or spinal nerve tissue found no FireMaster FF-1-related alterations in rats or mice administered up to 10 mg/kg/day for 25 weeks (NTP 1983) or 3.9 mg/kg/day for up to 105 weeks (NTP 1992).

Neurodevelopmental effects were assessed in offspring of mice that were treated with 3 or 10 mg/kg/day doses of FireMaster (FF-1) in corn oil by gavage on every other day during gestation and until weaning of the offspring at 21 days of age (Tilson 1992). Acoustic startle response, negative geotaxis, motor activity, and body weight were measured in 8 pups/sex/dose at 30, 60, and 120 days of age. Tests for avoidance learning and neurochemistry were performed on one pup/sex/dose at 30 days of age and on the remaining animals at 120 days of age. Reductions in acoustic startle responsiveness and negative geotaxis latency were observed at 10 and $3 mg/kg/day, respectively, in both sexes at 30 and 60 days of age. Motor activity was decreased in 10 mg/kg/day females at 120 days of age. The learning tests showed increased avoidance response latencies at 30 and 120 days of age in both sexes at $3 mg/kg/day, but no effect on acquisition or retention. Neurochemical measurements included serotonin and metabolites, dopamine and metabolites, and norepinephrine in the cortex, hippocampus, and striation; the only effect observed was a decrease in dopamine concentration in the striation of both males and females at 120 days of age.

Postnatal neurodevelopmental effects were also evaluated in offspring of rats that received 0.2 or 2 mg/kg/day doses of FireMaster BP-6 dissolved in peanut butter from day 6 of gestation through day 24 postpartum and observed until postnatal day 60 (Henck et al. 1994). Multivariate analysis of variance of neurodevelopmental end points showed significant PBB-related effects for acquisition of forward

locomotion, cliff avoidance, cage emergence, and open-field activity in male and female offspring of the rats exposed to 2 mg/kg/day. The most prominent behavioral effects were delays in acquisition of forward locomotion and suppressed open-field activity. Other effects in the offspring included reduced crown-rump length and body weight at birth and reduced postnatal body weight as summarized in Section 3.2.2.6 (Developmental Effects).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Polybrominated Diphenyl Ethers. No studies were located regarding neurological effects in humans after oral exposure to PBDEs.

No information was located on neurological effects of oral exposure to commercial mixtures of PBDEs in animals. Behavioral tests of individual congeners in mice indicate that the developing nervous system is a potential target of PBDE toxicity. Neonatal male NMRI mice were treated with a single dose of 2,2',4,4'-tetraBDE (0.7 or 10.5 mg/kg) or 2,2',4,4',5-pentaBDE (0.8 or 12.0 mg/kg) in fat emulsion by gavage on Pnd 10 (Eriksson et al. 1998, 2001). Spontaneous behavior was tested at 2 and 4 months of age in all dose groups, and learning and memory ability (Morris swim maze performance) was tested at 5 months of age in the groups given the high dose of each congener. Measurements of locomotion, rearing, and total activity during three consecutive 20-minute periods in the spontaneous behavior test showed a disruption of habituation in mice exposed to both congeners. Habituation was defined as a decrease in the activity variables in response to the diminishing novelty of the test chamber over 60 minutes. During the first 20-minute period, at both 2 and 4 months, animals treated with 10.5 mg/kg 2,2',4,4'-tetraBDE and $0.8 mg/kg 2,2',4,4',5-pentaBDE were significantly less active than controls as shown by dose-related decreases in all three test variables. During the second period, the activities in all treated groups were comparable to controls at 2 and 4 months. During the third period, exposure to 10.5 mg/kg 2,2',4,4'-tetraBDE and $0.8 mg/kg 2,2',4,4',5-pentaBDE caused significantly more activity than controls at 2 and 4 months as shown by dose-related increases in test variables. The investigators noted that this nonhabituating behavior profile (i.e., decreased activity early in the test period and increased activity late in the test period) has also been reported in adult mice neonatally exposed to certain PCB congeners. The Morris water maze test evaluated cognitive abilities by providing visual cues to find and remember the location of a platform submerged in a pool of water. The decrease in time needed to locate the platform over a total of 20 trials in a 4-day acquisition period was used as a measure of learning ability. On day 5, the platform was relocated and the decrease in time needed to find the

relocated platform over five trials was used to assess relearning ability. The only exposure-related effect was found in the mice administered a single dose of 12.0 mg/kg 2,2',4,4',5-pentaBDE (that did not improve in finding the new location of the platform as did control animals and those in the 2,2',4,4'-tetraBDE group).

Spontaneous locomotion behavior was also evaluated in adult NMRI mice (4 months old) that were exposed as neonates on Pnds 3, 10, or 19 to a single oral dose of 8 mg/kg of 2,2',4,4'-tetraBDE (Eriksson et al. 1999). A non-habituating behavior profile similar to that observed in the Eriksson et al. (1998, 2001) studies was observed in the mice treated at either 3 or 10 days of age. There was no effect on spontaneous activity in the mice treated at 19 days of age, suggesting that there was a critical window for the induction of behavioral disturbances.

3.2.2.5 Reproductive Effects

Polybrominated Biphenyls. Analysis of semen from 41 male residents of Michigan who lived on PBB-contaminated farms or who had bought food directly from such farms and 11 males who were employed in a PBB manufacturing company revealed no abnormalities in the distribution of sperm counts, sperm motility, or sperm morphology, compared with an analysis of semen from 52 unexposed men (Rosenman et al. 1979). This study was conducted in 1977, . 4 years after initial contamination of Michigan's food supply, and would not have detected an earlier response that was subsequently reversed. PBBs were detected (detection limit of 0.2 ppb) in the serum of 1 of the 52 unexposed men and in all of the exposed men; however, individual or mean values for PBB levels were not reported.

No relationship was found between serum levels of PBBs and frequency and duration of lactation in a retrospective study of women exposed to PBBs during the Michigan contamination episode (Thomas et al. 2001). A group of 1,020 women with available initial serum PBB levels was identified from the Michigan Department of Community Health PBB registry. Among these participants, 446 had a live-born infant after their initial serum PBB level; characteristics of this cohort included mean age of 25.6±5.0 years, initial serum PBB level of 17.5±99.7 ppb, estimated serum PBB level at delivery of 9.4±61.9 ppb, estimated serum PCB level at delivery of 5.5±5.2 ppb, duration of breast-feeding as main source of nutrition of 2.6±3.3 months, and total duration of breast feeding of 4.1±5.3 months. The numbers of women who breast fed their first infant after the initial serum PBB level and had previously breast-fed were 293 (65.7%) and 49 (11.0%), respectively. Exposure was treated as a categorical variable by dividing the women into groups of low (reference) exposure (#1 ppb, n=260, serum levels at or below

the detection limit), moderate exposure (>1–#7 ppb, n=141), and high exposure (>7 ppb, n=45, levels above the 90th percentile). Three outcomes of interest were analyzed: (1) the decision to breast feed (yes/no), (2) the duration (months) of breast-feeding as the main source of nutrition, and (3) the total duration (months) of breast-feeding. None of the three outcomes was significantly associated with serum PBB levels, even after controlling for maternal age, previous history of breast-feeding, body mass index, maternal education, household income, history of smoking in the year before pregnancy, consumption of alcohol during the first trimester of pregnancy, history of thyroid disorder, gestational age of the infant, time to pregnancy, and year of birth.

Effects on reproductive organs and reproductive function have been observed in animals following oral exposure to PBBs. An increased incidence of uterine endometrial polyps was observed in rats, 2 years after they were administered a single gavage of 1,000 mg/kg dose FireMaster FF-1 (Kimbrough et al. 1981). Following weaning and two consecutive normal menstrual cycles in 6 months, serum progesterone was decreased in the same four females that showed this effect prebreeding. In a multiple-generation study in which only F_0 rats were fed $5 mg/kg/day FireMaster BP-6 in the diet from Gd 8 through postpartum day 28 (weaning), reproductive performance with respect to length of gestation or litter size was not affected in the F_1 or F_2 generations (McCormack et al. 1981). Implantation was completely blocked in two of five and two of three female rats that survived gavage administration of 28.6 or 57.1 mg/kg/day FireMaster BP-6, respectively, on alternate days between Gds 0 and 14 (Beaudoin 1979). Histological examination of reproductive organs in male and female rats and mice revealed no abnormalities following gavage treatment with doses up to 10 mg/kg/day FireMaster FF-1 for 25 weeks or 30 mg/kg/day for 4–5 weeks (Gupta and Moore 1979; Gupta et al. 1981; NTP 1983). Necrosis, hyperplasia, and metaplasia in the epithelial lining of the ductus deferens were observed in male rats that died following 100 mg/kg/day FireMaster FF-1 for 4–5 weeks (Gupta and Moore 1979). Treatment of male and female mink with diets providing up to 0.39 mg/kg/day FireMaster FF-1 for 6–7 months before breeding did not affect reproductive performance with respect to fertility or litter size (Aulerich and Ringer 1979; Ringer et al. 1981). In the only chronic study, histological examination of male and female reproductive organs showed increased cystic endometrial hyperplasia in rats exposed to 1.5 mg/kg/day FireMaster FF-1 for up to 104 weeks, but no changes were observed in mice exposed to #3.9 mg/kg/day for up to 105 weeks (NTP 1992). Following 6–7 months of exposure to 0.012 mg/kg/day FireMaster FF-1 in the diet, four of seven female monkeys displayed a lengthening of the menstrual cycle from 28 to 31 days and decreased serum progesterone; prior to the treatment, they had at least 2 years of normal cycles (Allen et al. 1979; Lambrecht et al. 1978). All seven of these monkeys conceived after one to four matings with control males (controls required one to three breedings), but two displayed prolonged

implantation bleeding and another two had fetuses that were aborted or stillborn (see Developmental Effects). Reduced spermatogenesis was observed in a male monkey that died after 25 weeks on a diet providing 0.73 mg/kg/day FireMaster FF-1 (Allen et al. 1978).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Polybrominated Diphenyl Ethers. No studies were located regarding reproductive effects in humans after oral exposure to PBDEs.

Information on effects of PBDEs on reproductive function is limited to negative findings in a one-generation study of decaBDE (FR-300 BA) in rats (Dow Chemical Co. 1975; Norris et al. 1975b). This commercial mixture was comprised of 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE and differs from current decaBDE formulations that contain $97% decaBDE. Male and female rats were exposed to 3, 30, or 100 mg/kg/day doses in the diet for 60 days before mating and subsequently during a 15-day period during which they were mated. Both sexes continued to receive the test diet throughout gestation and until the end of the 21-day lactation period. Parameters monitored included length of time between first day of cohabitation and parturition, numbers of live and dead newborn, number of live pups (Pnds 1, 7, 14, and 21), litter weight (Pnds 1, 7, and 14), and weanling weight (Pnd 21). Comprehensive histological examinations (adults and weanlings), skeletal examinations (weanlings), and cytogenetic evaluation of bone marrow (adults and weanlings) were also performed on Pnd 21. There were no exposure-related effects on reproductive parameters or any indications of maternal or neonatal toxicity.

No histopathological changes were observed in male or female reproductive tissues from rats that were exposed to decaBDE in dietary doses of #800 mg/kg/day for 30 days (Norris et al. 1973, 1975b), #8,000 mg/kg/day for 13 weeks (NTP 1986), #1.0 mg/kg/day (77.4% containing 21.8% nonaBDE and 0.8% octaDBE) for 2 years (Kociba et al. 1975; Norris et al. 1975b), or #2,550 mg/kg/day for 103 weeks (NTP 1986), or in mice exposed to #9,500 mg/kg/day for 13 weeks or #7,780 mg/kg/day for 103 weeks (NTP 1986); octaBDE in doses of #750 mg/kg/day for 13 weeks (IRDC 1977); or pentaBDE in doses of #100 mg/kg/day for 90 days (WIL Research Laboratories 1984).

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

3.2.2.6 Developmental Effects

Polybrominated Biphenyls. Examination of children (. 100 were identified) presumably exposed *in utero* or in early infancy during the peak of the Michigan PBB contamination episode and whose families lived on farms known to be contaminated with PBBs has not revealed any consistent or marked abnormalities in the children's physical and neuropsychological development. No significant abnormalities were found by physical and neurological examination of 33 of these exposed children when they had a mean age of 37.2 months, compared with a group of 20 age-matched, nonexposed control children (Weil et al. 1981). However, subjective interviews with parents suggested that more exposed children than control children had frequent upper respiratory illnesses such as colds, runny noses, and sore throats (Weil et al. 1981). PBBs were measured in the fat of the infants and in the blood of the mothers. Fat levels of PBBs in 27 of the children ranged from 0.01 to 20.96 ppm; half of the values were below 0.120 ppm, and five of the values were above 1.0 ppm. Maternal blood levels ranged from 0.001 to 0.845 ppm and seven mothers had levels that were not detectable (<0.001 ppm). Seagull (1983) administered 5 of 18 tests in a battery of childhood developmental tests (McCarthy Scales of Children's Abilities) to 19 of these exposed children when their ages ranged from . 2.5–4 years old and concluded that there was a statistically significant negative correlation for four of the five tests between PBB levels in fat tissue and developmental abilities. Mean fat concentrations of PBBs were 0.50 ppm (range, 0.10–0.74 ppm) and 4.218 ppm (range, 0.116–20.960 ppm) in the low and high exposure groups of this study. Schwartz and Rae (1983) later administered the full battery of neuropsychological developmental tests, as well as I.Q. tests, to the same group of children (minus one child whose family refused to participate in the follow-up study) when their ages ranged from approximately 4 to 6 years old. The exposed children's performances were within the normal range in all areas assessed. There were statistically significant negative correlations between PBB levels in adipose tissue (measured in the earlier study) and performance on some of the developmental tasks, but the tasks with significant correlations were not the same as those noted in the earlier study by Seagull (1983). The available studies, primarily due to the small data set and the inconsistency of the results, do not conclusively establish or eliminate the possibility that *in utero* and early infancy exposure to PBBs might adversely affect the development of human children. The information suggests that if the Michigan PBB contamination episode produced any effects on child development, they were subtle.

A comparison of 1966–1981 fetal mortality rates for Michigan counties with a high percentage of quarantined farms (6.8–20.4%) with those of Michigan counties with no quarantined farms did not conclusively establish differences in rates or trends after the 1973 contamination episode (Humble and

Speizer 1984). This study is difficult to interpret because the exposure status method was imprecise, the collected data included only spontaneous abortions occurring after 20 weeks of gestation (early trimester abortions were not counted), and the two populations displayed different pre-1973 trends for fetal mortality rates.

Results from animal studies indicate that *in utero* exposure to PBBs and exposure to PBBs through mothers' milk can produce embryolethal effects, structural abnormalities, growth retardation, liver effects, and neurological effects in offspring. Developmental toxicity has been observed in studies with hexabromobiphenyl and octabromobiphenyl commercial mixtures, but not with commercial decabromobiphenyl PBBs. Rats have been studied most extensively, but data are also available for mice, swine, minks, and monkeys.

Following gavage administration of 200 mg/kg FireMaster FF-1 to rats on gestation days 7 and 14, decreased pup survival to weaning, decreased body weight throughout the lives of offspring, and increased mortality in offspring after 2 years were observed (Groce and Kimbrough 1984). Single doses of 200 mg/kg FireMaster BP-6 administered to rats on one of several days during pregnancy caused increased fetal resorptions, and 400 or 800 mg/kg produced maternal toxicity (expressed as a decrease in body weight gain) and fetal malformations including cleft palate and diaphragmatic hernia (Beaudoin 1977). Increased fetal resorptions also were observed in rats receiving total doses of . 14.3 mg/kg/day FireMaster BP-6 by gavage on alternate days from days 0 through 14 of pregnancy (Beaudoin 1979). Body weight gain and levels of vitamin A in the liver were reduced in offspring of rats administered 5 mg/kg/day FireMaster BP-6 in the diet on gestation day 8 until weaning at 4 weeks postpartum (McCormack et al. 1982c). Additional effects in pups weaned onto the same treated diets as the dams included increased hepatic ALA synthetase activity (the rate-limiting enzyme in porphyrin synthesis) and increased urinary excretion of uro- and coproporphyrins at age 16 weeks. Dietary administration of FireMaster BP-6 in dosages of 42.9 mg/kg/day on Gds 7–15 or 50 mg/kg/day on Gds 7–20 produced decreased body weight, but no other developmental effects, in rat fetuses and pups monitored up to 60 days postpartum (Corbett et al. 1975; Harris et al. 1978b). Increased incidences of fetuses with extra ribs were found in rats fed diets providing $86 mg/kg/day of octabromobiphenyl mixture from gestation days 6 through 15 (Waritz et al. 1977); however, no embryotoxic, fetotoxic, or teratogenic effects occurred in rats following gavage administration of #1,000 mg/kg/day decabromobiphenyl mixture on Gds 6–15 (Millischer et al. 1980).

Effects in offspring of rats exposed to 0.5 mg/kg/day FireMaster FF-1 for 60 days before breeding until 8 weeks postpartum (4 weeks postweaning) and observed for up to the following 2 years included vacuolization and altered foci in the liver (Chhabra et al. 1993; NTP 1992). Pups of mice that were similarly perinatally exposed to 1.5 mg/kg/day FireMaster FF-1 developed liver cytomegaly and altered foci (Chhabra et al. 1993; NTP 1992). As discussed in Section 3.2.2.8 (Carcinogenic Effects), these mice also developed hepatocellular adenoma and carcinoma; combined perinatal and adult exposure induced higher incidences of liver tumors in mice than adult exposure alone (Chhabra et al. 1993; NTP 1992).

In a multiple-generation study, decreased pup survival to weaning, decreased body weight gain, delayed fur development, delayed eye and vaginal opening, and increased liver weight associated with hepatocyte swelling, vacuolization, and focal necrosis were observed in F_1 generation rats whose only exposure was from the mothers fed a diet providing 5 mg/kg/day FireMaster FF-1 from day 8 of pregnancy until weaning at 28 days postpartum; less severe liver responses were observed in the F_1 offspring of dams treated with 0.5 mg/kg/day (McCormack et al. 1981). Although survival of F_2 and F_3 generations was not affected by the 5 mg/kg/day treatment of the F_0 rat dams, F_2 offspring, but not F_3 offspring, displayed increased liver weights, liver enzyme induction, and hepatic histological alterations compared with controls (McCormack et al. 1981). Dietary administration of 2.5 mg/kg/day FireMaster BP-6 to rats from gestation day 0 through postpartum day 15 produced increased relative liver weights, decreased body weights, and decreased serum levels of the thyroid hormone, T_4, in 15-day-old offspring (Meserve et al. 1992). The pups had received direct stimulation of the pituitary by an injection of corticotropin-releasing factor or direct stimulation of the adrenals by an injection of adrenocorticotropic hormone. Provision of a diet containing 0.5 mg/kg/day FireMaster FF-1 to lactating rats for the 18 days following parturition increased liver weights and elevated levels of hepatic cytochrome P-450 and associated enzymic activities in both dams and pups; a diet providing 0.05 mg/kg/day produced no hepatic effects in dams, but induced hepatic enzymes in the pups (Moore et al. 1978). According to the investigators (Moore et al. 1978), the results could indicate that nursing pups are more sensitive than their dams to liver enzyme induction, or that due to the different kinetic parameters among the PBB congeners, the pups received a more potent PBB mixture than the dams. Yet, a third possibility is that the suckling pups received a higher dose of PBBs relative to their body weights due to bioconcentration of PBBs in breast milk (Dent 1978). Performance deficits in tests of operant behavior were observed in the 6-month-old offspring of rat dams given gavage doses of 0.2 or 2 mg/kg/day FireMaster BP-6 from day 6 of gestation until weaning (Henck and Rech 1986), but not in 75-day-old offspring of rat dams given gavage doses of 0.5 or 5 mg/kg/day for 4 weeks prior to mating (Geller et al. 1985). Effects found in offspring of rats exposed to 0.2 or 2 mg/kg/day doses of FireMaster BP-6 in the diet from day 6 of gestation through day 24 postpartum, and

observed through postnatal day 60, included reduced crown-rump length at birth at $0.2 mg/kg/day, reduced birth weight and postnatal body weight gain at 2 mg/kg/day, and supressed acquisition of forward locomotion, cliff avoidance, cage emergence, and open-field activity at 2 mg/kg/day (Henck et al. 1994).

Dietary administration of 50 mg/kg/day FireMaster BP-6 to mice from gestation days 7 through 18 produced decreased fetal body weight and fetal abnormalities including exencephaly, cleft palate, and hydronephrosis; 5 mg/kg/day did not produce significant developmental effects in this study (Corbett et al. 1975). Early postnatal deaths occurred among offspring of mice given 10 mg/kg/day FireMaster FF-1 on alternate days from gestation day 0 until litters were weaned (Luster et al. 1980). Immunological parameters were unaffected in surviving offspring whose mothers received up to 10 mg/kg/day doses, but decreased hematocrit levels were measured in offspring of mothers receiving doses $3 mg/kg/day (Luster et al. 1980). Performance deficits in tests of learning behavior were measured in offspring of female mice that received gavage doses of 3 or 10 mg/kg/day FireMaster FF-1 on alternate days from gestation day 0 through weaning at 21 days of age (Tilson 1992).

Decreased body weight at birth and at 4 weeks after birth were measured in mink kits whose parents were fed diets containing 0.155 mg/kg/day FireMaster FF-1 from 7–8 months prior to mating through 4 weeks postpartum (Aulerich and Ringer 1979; Ringer et al. 1981). Increased relative liver weight, fatty and necrotic hepatic changes, slight hyperplasia in the thyroid, and decreased serum levels of thyroid T_3 and T_4 hormones were observed in 4-week-old offspring of swine fed 2.5 mg/kg/day FireMaster BP-6 in the diet during the second half of gestation and during lactation; 1.25 mg/kg/day produced similar effects on the thyroid, but no necrosis in the liver of 4-week-old nursing pigs (Werner and Sleight 1981). Examination of several parameters of immune function in 4-week-old offspring of sows fed #2.5 mg/kg/day FireMaster BP-6 during gestation and lactation provided no conclusive evidence for immunosuppressive effects (Howard et al. 1980). An abortion and a stillbirth occurred among seven female monkeys that were fed 0.012 mg/kg/day FireMaster FF-1 in the diet for 7 months prior to conception and during pregnancy (Allen et al. 1979; Lambrecht et al. 1978). The surviving five infants had reduced birth weight and postnatal body weight gain, but no gross abnormalities. The incidence of dystocia (difficult birthing) was 50% increased among first- and second-generation offspring of cows treated with 0.65 mg/kg/day FireMaster BP-6 by gelatin capsule for 180 or 202 days during late pregnancy (Willett et al. 1982). The same dosage for 60 days caused a 21.6% increased incidence of dystocia, but this increase was not statistically significant (p=0.08). Stillbirths and preweaning deaths were not significantly increased, but all mortality was attributable to dystocia. Incidences of dystocia and calf mortality appeared to be related to higher birth weight, which in turn were correlated with

concentrations of PBBs in maternal blood and tissues. Growth and development were not affected in the surviving calves. Of six pregnant cows that were similarly treated with a maternolethal dosage (67 mg/kg/day) of FireMaster BP-6, three aborted after 30–38 days, and three retained dead fetuses (Moorhead et al. 1977).

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Polybrominated Diphenyl Ethers. No studies were located regarding developmental effects in humans after oral exposure to PBDEs.

Information on the developmental toxicity of PBDEs is available from studies of commerical mixtures of deca-, octa- and pentaBDE (Argus Research Laboratories 1985b; Breslin et al. 1989; Dow Chemical Co. 1975, 1985; Life Science Research Israel Ltd. 1987; Norris et al. 1975b; WIL Research Laboratories 1986). None of the BDE mixtures have been shown to be teratogenic in animals. Data on decaBDE indicate that it is fetotoxic in rats at high dose levels that are not maternally toxic. Developmental effects of decaBDE were investigated in rats that were exposed to doses of 10, 100, or 1,000 mg/kg/day by gavage on Gds 6–15 and examined on Gd 21 (Dow Chemical Co. 1985; Norris et al. 1975b). No treatment-related maternal toxicity was observed. The numbers of fetuses with subcutaneous edema and delayed ossification of normally developed skull bones were significantly increased at 1,000 mg/kg/day. Resorptions were significantly ($p<0.05$) increased at $10 mg/kg/day compared to controls as indicated by resorption/implantation site percentages [1% (3/288), 9% (12/141), 10% (13/135), and 4% (9/203)] and percentages of litters with resorptions [12% (3/25), 64% (9/14), 57% (8/14), and 39% (7/18)]. The resorptions were considered secondary to unusually low control values and unrelated to treatment because (1) the data do not follow a dose-response relationship across the three dose levels, and (2) the rates in the high dose group are comparable to historical control values. As discussed in Section 3.2.2.5 (Reproductive Effects), a one-generation study of decaBDE in rats found no effects of parental exposure to #100 mg/kg/day from 60 days before mating through the end of the lactation on numbers of live pups at birth and during the lactation period, body weights of pups at birth or weaning, or skeletal development or soft-tissue histology of pups at weaning (Dow Chemical Co. 1975; Norris et al. 1975b).

OctaBDE commercial mixtures caused skeletal ossification variations in rats and rabbits at maternally toxic levels and other indications of fetotoxicity at lower doses (Argus Research Laboratories 1985b; Life Science Research Israel Ltd. 1987). No maternal effects were observed in rats that were administered 2.5,

10, or 25 mg/kg/day doses of octaBDE (FR-1208) by gavage on Gds 6–15 (Life Science Research Israel Ltd. 1987). Fetal death, as measured by post-implantation loss, was somewhat elevated among litters from $10 mg/kg/day dams in comparison to controls. Post-implantation loss was significantly ($p<0.001$) higher than controls in both the 10 and 25 mg/kg/day groups when Freeman-Tukey arcsine transformed values were tested as normally distributing data (Student's t-test). The toxicological significance of this finding was unclear since under non-parametric assumptions (Mann-Whitney U-test), neither group was significantly different from controls, and post-implantation loss for all treated groups was within the range of laboratory historical control values. There were no indications of skeletal malformations of variations or delayed or retarded ossification in any treated group. Rats that were treated with 2.5, 10, or 25 mg/kg/day doses of a different octaBDE mixture (Saytex 111) by gavage on Gds 6–15 had significantly (p#0.01) increased resorptions (embryo/fetal deaths) at 25 mg/kg/day as shown by nonparametric analysis (Kruskal-Wallis test with Dunn's method of multiple comparisons) (Argus Research Laboratories 1985b). There was an average of 0.6, 1.2, 0.8, and 4.9 resorptions and 14.6, 14.7, 14.0, and 8.0% live fetuses per litter in the control to high dose groups. Average fetal body weights were also significantly reduced at 25 mg/kg/day.

Developmental toxicity testing of another octaBDE mixture (DE-79) in rats used gavage doses of 2.5, 10, 15, 25, or 50 mg/kg/day on Gds 6–15 (WIL Research Laboratories 1986). No exposure-related maternal or developmental effects were observed at #15 mg/kg/day. The only statistically significant ($p<0.05$) finding at 25 mg/kg/day was an increased serum bromide level. Effects observed at 50 mg/kg/day included significantly reduced mean maternal body weight gain during the posttreatment period (Gds 16–20) and fetotoxicity as indicated by increased postimplantation loss due to late resorptions (not significantly increased compared to control group but exceeded historical control range), 39% reduced mean fetal weight ($p<0.01$), skeletal variations (e.g., reduced ossification of the skull and various unossified bones) that were associated with the reduced fetal weights in this group, and single instances of malformations (fetal anasarca, bent limb bones, unilateral absence of 13th rib) commonly associated with maternal toxicity.

The developmental toxicity of a fourth octaBDE technical mixture (Saytex 111) was tested in rabbits exposed to doses of 2, 5, or 15 mg/kg/day on Gds 7–19 and examined on Gd 28 (Breslin et al. 1989). The 15 mg/kg/day group showed evidence of slight maternal toxicity as indicated by decreased body weight gain during Gds 7–20 and 7–28 (not statistically identified), reduced body weight on Gd 28 (7% less than controls, p#0.05), and significantly increased absolute and relative liver weights on Gd 28. Slight

fetotoxicity accompanied the maternal toxicity at 15 mg/kg/day as indicated by a significantly (p#0.05) increased incidence of delayed ossification of the sternebrae.

A developmental toxicity study of pentaBDE (Saytex 115) is available in which rats were administered 10, 100, or 200 mg/kg/day doses by gavage on Gds 6–15 and examined on Gd 20 (Argus Research Laboratories 1985a). The only exposure-related maternal effect was significantly (p#0.01) reduced body weight gain at $100 mg/kg/day during the dosing period. This effect was dose-dependent and increased in severity with continued dosing but recovered during the postdosage period when differences between exposed and control groups were no longer significant. Maternal body weight gain was 2.8, 20.1, and 29.9% less than controls during Gds 6–16 at 10, 100, and 200 mg/kg/day, respectively. There were no exposure-related indications of developmental toxicity. Average fetal body weight per litter was slightly but not significantly reduced at 200 mg/kg/day (2.6% less than controls, p>0.05).

Developmental toxicity was also evaluated in rats that were treated with 1, 10, or 30 mg/kg/day of pentaBDE (DE-71) in corn oil by gavage from Gd 6 through Pnd 21 (Zhou et al. 2002). Dams were sacrificed on Gd 20 and Pnd 22 and offspring were sacrificed on Gd 20 and Pnds 4, 14, 36, and 90. There were no exposure-related effects on maternal body weight gain, litter size, sex ratio, or offspring viability and growth as assessed by numbers of pups at birth and on Pnds 4–21, body weight of pups on Pnds 4–90, and eye opening status on Pnds 11–18. Serum measurements of thyroid T_3 and T_4 hormone levels showed that serum T_4 was significantly reduced in dams at 30 mg/kg/day (Gd 20 and Pnd 22) and offspring at $10 mg/kg/day (Gd 20 and Pnds 4 and 14) as detailed in Endocrine Effects in Section 3.2.2.2.

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

3.2.2.7 Cancer

Polybrominated Biphenyls. No epidemiological studies were located that provided evidence for an association between exposure to PBBs and the occurrence of cancer in humans, although one case report is available concerning gastrointestinal cancer in a Michigan dairy farmer with known exposure to PBBs and other chemicals.

The Michigan Department of Public Health, the U.S. Center for Disease Control, the National Institutes of Health, the Food and Drug Administration, and the EPA established a cohort of Michigan residents with varying levels of PBB exposure to determine the short- and long-term effects (especially cancer) of exposure to PBBs (Landrigan et al. 1979). The epidemiological and clinical data collected during the first 4 years after the Michigan PBB contamination episode indicated that cancer was not a prevalent "symptom" among the cohort at that time. Prevalence rates for cancer in exposed groups ranged from 0.4 to 0.6% compared with 0% in a small control group comprised of residents of farms with low PBB contamination (Landrigan et al. 1979). When the cohort was divided into seven groups based on serum PBB levels, no trend with concentration was apparent, but the incidence of cancer was the highest in the group with the highest serum PBB levels. Subsequent follow-up examinations of this cohort have not been reported.

In studies conducted by the Environmental Science Laboratory of the Mount Sinai School of Medicine, mean plasma levels of carcinoembryonic antigen (CEA), which has been used as a screening tool for tumor recurrence after cancer therapy, were found to be slightly higher in 1976 in a population of 611 Michigan residents who likely ingested PBB-contaminated food than mean levels in a nonexposed population of Wisconsin farm residents, but the difference was not statistically significant (Anderson et al. 1978b). Cancer was not listed as a condition in the report of results of a symptomatology survey completed by this cohort (Anderson et al. 1979). Reports of follow-up examinations of this cohort have not been reported.

A relationship between serum PBBs and risk of breast cancer was suggested in a nested case-control study of 1,925 women enrolled in the Michigan Department of Public Health registry for persons exposed to PBBs (Henderson et al. 1995). Study participants had lived on or received food from a farm quarantined by the Michigan Department of Agriculture, were recruited from July 1976 to December 1977, and followed up annually from 1978 through 1993. Twenty women who developed breast cancer were age- and race-matched to 290 controls. Median serum PBB concentrations were similar in the

cancer cases (3 ppb, range 0.5–16 ppb) and controls (2 ppb, range 0.5–419 ppb). Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for increasing serum PBB levels categorized into tertiles (<2 ppb, 2–3 ppb, $4 ppb) and a dichotomous variable (<2 ppb, $2 ppb). The estimated risk for breast cancer was slightly elevated for women with serum PBB levels of 2–3 ppb (OR=3.5, 95% CI=0.9–13) and $4 ppb (OR=3.1, 95% CI=0.8–12) when compared with the reference group (<2 ppb), or when the dichotomous variable was used in the analysis (OR=3.3, 95% CI=0.9-11.4). The results were essentially the same when the data were adjusted for available risk factors (body mass index and family history of cancer), or when matched sets of cases and controls were stratified into two groups based on date of diagnosis ($10 years after exposure). The results of this study are inconclusive due to the small number of cases, apparent lack of statistically significant increases (p values were not reported, but confidence intervals were broad with lower limits less than unity, indicating that it is difficult to exclude chance as an explanation for the findings), and lack of information on important breast cancer risk factors (e.g., exposure to other organochlorine chemicals and estrogen receptor status).

Another study of the Michigan PBB registry evaluated associations between levels of serum PBBs and risks of various site-specific cancers (Hoque et al. 1998). Primary cancers (195 malignancies) were identified in 187 persons among 3,899 registrants enrolled in 1976 and followed through 1993. Controls were 696 randomly selected cancer-free individuals who were frequency matched to cases by age (in 5-year strata) and sex in a 4:1 ratio (except above age 70 years when, due to lower numbers, all eligible controls were used). PBB levels in the cases were measured at the time of registry enrollment. Serum PBB concentration ranges was categorized into four groups (not detectable–3 ppb, 4–20 ppb, 21–50 ppb, >50 ppb) defined by the median and the 90th and 95th percentiles. Conditional logistic regression was used to calculate univariate and multivariate (adjusted) ORs by cancer site for the three highest serum PBB categories compared to the reference (#3 ppb) group. The multivariate ORs were adjusted for family history of cancer, smoking status, alcohol use, age, serum PCB level, and sex. Digestive system cancer (12 cases) and lymphoma (not otherwise specified) (8 cases) showed increasing dose-response relationships for risk as PBB concentrations increased. Digestive system cancer was a grouping that comprised of the following sites: liver (five cases), stomach (five cases), esophagus (one case) and pancreas (one case). Adjusted ORs for digestive system cancer were 1.00 (reference), 8.23 (95% CI=1.27–53.3), 12.3 (0.80–191), and 22.9 (1.34–392) for the #3, 4–20, 21–50, and >50 ppb categories, respectively. The corresponding adjusted ORs for PBB level and lymphoma risk were 1.00, 3.85 (0.32–46.2), 19.6 (1.52–253), and 48.9 (4.09–585). The lymphoma ORs were incompletely adjusted due to missing data for serum PCB level and family cancer history in the reference category. Increased

risks were also observed for breast cancer in the 4–20 ppb category (nine cases, adjusted OR=2.41, 95% CI=0.92–6.30), cancer at an unknown site in the 4–20 ppb category (four cases, adjusted OR=31.0, 95% CI=1.40–685), and leukemia in the 21–50 ppb category (one case, adjusted OR=4.49, 95% CI=0.92–6.30). The associations found in this study should be viewed as suggestive and preliminary due to the small numbers of cases. The 2.4-fold increased risk of breast cancer for PBB levels between 4 and 20 ppb is consistent with the 3-fold increased risk for breast cancer observed for PBB levels >2 ppb in the Henderson et al. (1995) study of the same cohort summarized above.

A Michigan dairy farmer, who had a history of health complaints after 1976, developed malignant cancer of the esophageal and stomach wall in 1986; the man subsequently died in 1988 (Sherman 1991). Samples of adipose tissue, collected in 1976 and 1987, revealed PBB concentrations of 0.83 and 0.85 ppm, respectively. Also detected in the fat tissue collected in 1987 were polychlorinated biphenyl (PCB) at 3.57 ppm and chlordane residues at concentrations ranging from 0.018 to 0.039 ppm.

FireMaster FF-1 has induced liver tumors and/or neoplastic nodules in rats and mice following single or repeated administration by gavage in oil vehicle, as well as following chronic dietary administration. In female Sherman rats given a single 1,000 mg/kg dose and observed for 2 years, incidences of hepatocellular carcinomas and liver neoplastic nodules were 41.4% (24/58) and 72.4% (42/58), respectively (Kimbrough et al. 1981). In an earlier study using the same treatment (single 1,000 mg/kg dose), groups of five Sherman rats of each sex were examined at 2, 6, 10, and 14 months following treatment (Kimbrough et al. 1978b). Neoplastic nodules were found in the livers of 22.5% (9/40) of the treated rats observed for at least 10 months (4/5, 2/5, and 3/5 in the 10-month females, 14-month males, and 14-month females, respectively). Liver tumors were not found, but this could be related to the relatively small number of animals (20/sex) and/or short duration of observation (#14 months). Liver neoplastic nodules without tumors also developed in 31.2% (5/16) of Sherman rats treated with a lower single dose (200 mg/kg) and observed for 18–22 months (Kimbrough et al. 1981). No liver tumors or neoplastic nodules developed in untreated control groups in any of these single dose studies, and treatment-related tumors in sites other than liver were not observed. When administered to pregnant rats once on gestation day 7, a dose of 200 mg/kg induced both hepatocellular carcinomas and liver neoplastic nodules in offspring that were observed for 2 years (Groce and Kimbrough 1984). The incidences of tumors in male offspring (9.6% [4/41] versus 0% [0/42] in controls) and nodules in female offspring (17.6% [9/51) versus 4.2% [2/48]) increased significantly (p#0.055). Treatment-related tumors were not observed in nonhepatic tissues of the offspring.

Hepatocellular carcinomas and liver neoplastic nodules also increased in female Sherman rats gavaged with 100 mg/kg FireMaster FF-1 twice a week for two 3-week periods (12 total doses) separated by . 10 weeks (Kimbrough et al. 1981). Following observation for 2 years, the incidence of carcinomas was 60.7% (17/28 versus 0/25 in controls) and incidence of nodules was 85.7% (24/28 versus 1/25). In repeated dose studies performed by NTP (1983), FireMaster FF-1 was administered via gavage to Fischer-344/N rats and B6C3F1 mice of both sexes at dosages of 0, 0.1, 0.3, 1, 3, or 10 mg/kg/day on 5 consecutive days per week for 25 weeks. Both rats and mice were observed for life (up to 23 and 24 months posttreatment, respectively). Incidences of hepatocellular carcinoma were dose-related and significantly ($p<0.01$) increased in male rats at $3 mg/kg/day (0/33 [controls], 2/39, 0/40, 1/33, 7/33, and 7/31 [high-dose]) and female rats at 10 mg/kg/day (7/20 versus 0/20 in controls). The incidence of cholangiocarcinoma was significantly ($p<0.01$) increased in female rats at 10 mg/kg/day (7/20 versus 0/20) and almost significant ($p=0.06$) in males at 10 mg/kg/day (2/31 versus 0/33). Liver neoplastic nodules were dose-related and significantly ($p<0.01$) increased in female rats at $3 mg/kg/day. No clear treatment-related effects on incidences of hepatic neoplastic nodules in males, or bile duct hyperplasia, myelomonocytic (mononuclear cell) leukemia, or foci of pancreas-like tissue in the liver in either sex were observed. In mice, incidences of hepatocellular carcinoma significantly ($p<0.01$) increased at 10 mg/kg/day in males (21/22 versus 12/25 in controls) and females (7/8 versus 0/13). Metastasis to lung also significantly ($p<0.05$) increased in female mice at 10 mg/kg/day. No treatment-related effects on hepatocellular adenomas or hepatoblastomas were observed. Thyroid follicular cell adenoma tended to increase in treated female mice, but data are inconclusive due to low incidences and small numbers of animals.

The carcinogenicity of FireMaster FF-1 was additionally evaluated in Fischer-344/N rats and B6C3F1 mice of both sexes that received adult exposure only, perinatal exposure only, or combined perinatal and adult exposure (NTP 1992). The adult-only exposure involved dietary administration of PBBs (F_1 diets) to . 8-week-old animals for up to 104 weeks (rats) or 105 weeks (mice). Perinatal-only exposure involved dietary treatment of dams (F_0 diets) for 60 days prior to breeding and throughout gestation and lactation until pups were 8 weeks old. The pups were administered the same treatment as the dams from weaning at week 4 until age 8 weeks, and were subsequently administered the same or different dietary treatments (F_1 diets) for up to 104 weeks (rats) or 105 weeks (mice). This study was designed to compare the carcinogenicity of PBBs given in a conventional bioassay protocol (i.e., the adult-only exposure) with that of PBBs given in a combined perinatal and adult exposure regimen.

Eight F_0:F_1 doses (estimated) were tested in rats among one unexposed control group (0:0 mg/kg/day), two adult-only exposure groups (0:0.5 and 0:1.5 mg/kg/day), one perinatal-only exposure group (0.5:0 mg/kg/day), and four combined perinatal and adult exposure groups (0.05:0.15, 0.15:0.5, 0.5:0.5, and 0.5:1.5 mg/kg/day) (Chhabra et al. 1993; NTP 1992). Incidences of hepatocellular tumors were increased in adult-only exposed rats of both sexes. In males ingesting 0:0, 0:0.5, and 0:1.5 mg/kg/day, incidences of adenoma were 1 of 50, 10 of 49, and 38 of 50; of carcinoma, 0 of 50, 2 of 49, and 19 of 50; and of adenoma or carcinoma (combined), 1 of 50, 12 of 49, and 41 of 50, respectively. In females, incidences of adenoma were 0 of 50, 10 of 50, and 38 of 50; of carcinoma, 0 of 50, 2 of 50, and 4 of 50; and of adenoma or carcinoma (combined), 0 of 50, 12 of 50, and 39 of 50, respectively. These increases in liver tumor incidences were statistically significant (p#0.002) except for carcinoma in 0:0.5 mg/kg/day males and females and 0:1.5 mg/kg/day females (p>0.05). Combined perinatal and adult exposure significantly enhanced the development of liver tumors in female rats, as shown by comparisons with females receiving adult exposure only. Compared to the 0:0.5 mg/kg/day female adult-only exposed group, incidences of hepatocellular adenoma were 22 of 50 (p=0.01) and 35 of 50 (p<0.001); of carcinoma, 1 of 50 (p=0.05) and 8 of 50 (p=0.048); and of hepatocellular adenoma or carcinoma (combined), 22 of 50 (p=0.03) and 39 of 50 (p<0.001) in the 0.15:0.5 and 0.5:0.5 mg/kg/day groups, respectively. Compared to the 0:1.5 mg/kg/day female adult-only exposed group, incidences of hepatocellular adenoma, carcinoma, and hepatocellular adenoma or carcinoma (combined) were 45 of 50 (p=0.049), 22 of 50 (p<0.001), and 47 of 50 (p=0.016), respectively, in the 0.5:1.5 mg/kg/day group. This enhancing influence of perinatal exposure did not occur in the males. Perinatal-only exposure did not cause significantly increased incidences of liver or other tumors in rats of either sex.

Increased incidences of mononuclear cell leukemia occurred in adult-only exposed rats but were not clearly related to treatment (Chhabra et al. 1993; NTP 1992). The incidences of this leukemia in the 0:0, 0:0.5, and 0:1.5 mg/kg/day groups were 25 of 50, 33 of 50, and 31 of 50, respectively, in males and 14 of 50, 22 of 50, and 23 of 50, respectively, in females; the incidences in the 0:0.5 mg/kg/day males and 0:1.5 mg/kg/day females were significantly (p#0.05) increased. Comparison of the combined perinatal and adult exposure groups with the adult-only exposed groups showed no significant enhancement; however, comparison with the unexposed control (0:0 mg/kg/day) incidences showed a consistent increase in the incidence of this neoplasm at higher doses. In the 0.15:0.5 and 0.5:0.5 mg/kg/day groups, the incidences of leukemia were 41 of 50 (p#0.01) and 37 of 50 (p#0.01) in males and 17 of 50 (p>0.05) and 27 of 50 (p#0.01) in females. In the 0.5:1.5 mg/kg/day groups, the incidences were 37 of 50 (p#0.01) in males and 25 of 50 (p#0.05) in females. The incidences in some of these groups fall outside the NTP historical control range. The incidences in males were as high as 82% and exceeded the upper historical

control range of 62%. In females, the incidences were as high as 54% and exceeded the overall upper historical control range of 52% and the laboratory upper historical control range of 28%. A combined (life table) analysis of data from all eight experimental groups indicates that significant increases in the incidence of the leukemia are associated with increasing F_1 concentrations (p#0.05 in males; p#0.01 in females). For males, there was also a marginally significant (p#0.05) increase associated with F_0 exposure.

Eight F_0:F_1 doses were also tested in the mice among one unexposed control group (0:0 mg/kg/day), two adult-only exposure groups (0:1.3 and 0:3.9 mg/kg/day), one perinatal-only exposure group (3.9:0 mg/kg/day), and four combined perinatal and adult exposure groups (0.39:0.39, 1.3:1.3, 3.9:1.3, and 3.9:3.9 mg/kg/day) (NTP 1992). As in the rats, hepatocellular tumors were significantly ($p<0.001$) increased in adult-only exposed mice of both sexes. In males ingesting 0:0, 0:1.3, and 0:3.9 mg/kg/day, incidences of adenoma were 9 of 50, 48 of 49, and 42 of 50; of carcinoma, 8 of 50, 30 of 49, and 36 of 50; and of adenoma or carcinoma (combined), 16 of 50, 48 of 49, and 48 of 50, respectively. In adult-only exposed females, incidences of adenoma were 4 of 50, 39 of 50, and 46 of 48, carcinoma were 1 of 50, 28 of 50, and 41 of 48, and adenoma or carcinoma (combined) were 5 of 50, 42 of 50, and 47 of 48, respectively. Combined perinatal and adult exposure resulted in increased incidences of liver neoplasms in some treated groups. However, because adult-only exposure to 1.3 or 3.9 mg/kg/day resulted in such high incidences of liver neoplasms (84–98%), the possible enhancing effect of combined perinatal and adult exposure could not be adequately assessed in either sex. Compared to 0:1.3 mg/kg/day adult-only exposure, combined perinatal and adult exposure to 3.9:1.3 mg/kg/day caused significantly increased incidences of carcinoma in males (40 of 50, $p=0.01$) and females (44 of 50; $p<0.001$), adenoma in females (47 of 50, $p=0.005$) and adenoma or carcinoma (combined) in females (50 of 50, $p<0.001$). Compared to 0:3.9 mg/kg/day adult-only exposure, combined perinatal and adult exposure to 3.9:3.9 mg/kg/day caused significantly increased adenoma incidence in males (48 of 50; $p=0.007$) and decreased adenoma incidence in females (41 of 47; $p=0.022$). Perinatal-only exposure also caused significantly increased incidences of liver neoplasms in mice of both sexes. Comparison of the 0:0 and 3.0:0 mg/kg/day groups showed hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) incidences of 31 of 50 ($p<0.001$), 17 of 50 ($p=0.033$), and 40 of 50 ($p<0.001$) in males and 19 of 50 ($p<0.001$), 7 of 50 ($p=0.213$), and 21 of 50 ($p<0.001$) in females. Combined perinatal and adult exposure to 3.9:1.3 mg/kg/day also caused a significant ($p=0.029$) increase in the incidence of thyroid follicular cell adenoma in male mice (5 of 48) compared to adult-only exposure to 0:1.3 mg/kg/day (0 of 49). This incidence of thyroid adenoma exceeds the historical control range of 0–4% in untreated males in NTP

studies, but the effect was not seen in the higher dose groups (0:3.9 or 3.9:3.9 mg/kg/day). Perinatal-only exposure did not induce thyroid or other nonhepatic tumors in mice of either sex.

The existing evidence conclusively demonstrates that the liver is the main target of PBB carcinogenicity in animals. Results of a chronic study (Chhabra et al. 1993; NTP 1992) suggest that male rats are more sensitive than female rats (based on a higher carcinoma/adenoma ratio), and that mice are more sensitive than rats (based on earlier occurrence of hepatocellular adenomas, higher combined incidence of all liver neoplasms, and higher liver concentrations of PBBs). Based on findings in male rats and mice of both sexes in this study, there is some evidence that combined perinatal and adult dietary exposure to FireMaster FF-1 enhanced the susceptibility of hepatocellular neoplasms in animals receiving adult exposure.

The Cancer Effect Levels (CELs) for FireMaster FF-1 reported in Kimbrough et al. (1981), Groce and Kimbrough (1984), and NTP (1983, 1992) are recorded in Table 3-2 and plotted in Figure 3-2.

There are data indicating that FireMaster BP-6 has tumor promoting activity in rats and hamsters. In standardized liver tumor promotion assays, development of enzyme-altered hepatic foci (putative preneoplastic lesions) was assessed in rats that were 70% hepatectomized, initiated with a subcarcinogenic intraperitoneal dose of diethylnitrosamine 24 hours after the partial hepatectomy, and promoted with orally administered FireMaster BP-6 beginning 30 days later. Various promotion protocols caused significantly increased numbers of enzyme-altered hepatic foci with gamma-glutamyl transpeptidase (GGT) activity, including two gavage doses of 65 mg/kg on adjacent days (6.5 mg/kg was not effective) (Rezabek et al. 1987), estimated dietary dosages of 0.5 or 5 mg/kg for 180 days (Jensen et al. 1982), and estimated dietary dosages of 0.5 mg/kg/day for 140 days or 5 mg/kg for 15 days (Jensen et al. 1984). In a similar assay with rats that were not hepatectomized, a single gavage dose of 100 mg/kg FireMaster BP-6 administered 7–10 days after initiation with dimethylnitrosamine (NDMA) or N-nitrosopyrrolidine (NPYR) promoted development of hepatic enzyme-altered foci (Rangga-Tabbu and Sleight 1992). A statistically significant increased number of tracheal papillomas (but not number of animals with papillomas) developed in a group of hamsters given a single subcutaneous initiating dose of diethylnitrosamine and fed an estimated dietary dosage of 8.3 mg/kg/day FireMaster BP-6 for 140 days (Wasito and Sleight 1989).

Individual PBB congeners have been examined for tumor promoting activity in rats that were partially hepatectomized and initiated with diethylnitrosamine (DENA). Numbers of hepatic GGT-altered foci

and/or neoplastic nodules were increased following promotion with 3,3',4,4'-tetrabromobiphenyl (. 0.25 mg/kg/day in the diet for 180 days or 8 weekly intraperitoneal injections of . 7 mg/kg), 2,2',4,4',5,5'-hexabromobiphenyl (. 0.5 mg/kg/day in the diet for 180 days) or 3,3',4,4',5,5'-hexa-bromobiphenyl (. 0.05 mg/kg/day in the diet for 140 days) (Buchmann et al. 1991; Dixon et al. 1988; Jensen et al. 1982, 1983). Dietary exposure to . 5 mg/kg/day of 2,2',4,4',5,5'-hexabromobiphenyl for 480 days similarly promoted hepatic development of altered foci and neoplastic nodules in rats, whereas . 0.05 mg/kg/day of 3,3',4,4',5,5'-hexabromobiphenyl did not, although an apparent synergistic effect was observed when these two congeners were fed together (Jensen and Sleight 1986). Additional information on structure-promotion relationships for PBBs is discussed in Section 3.5.2.

The tumor initiating potential of PBBs is not well characterized. Numbers of GGT-altered foci were significantly increased in partially hepatectomized rats that were administered a single 1–10 mg/kg oral dose of 3,3',4,4'-tetrabromobiphenyl followed by phenobarbital in the diet for 180 days (Dixon et al. 1988), indicating that PBBs may have initiating activity in hepatocarcinogenesis. The potential for liver tumor initiation by PBBs appears to be weak compared to their potent promoting activity (Buchmann et al. 1991; Dixon et al. 1988; Jensen et al. 1984).

Polybrominated Diphenyl Ethers. There was no clear association between risk of non-Hodgkin's lymphoma (NHL) and exposure to 2,2'4,4'-tetraBDE in a case-control study of 77 Swedish men and women who were recruited in 1995–1997 and ranged in age from 28 to 85 years (Hardell et al. 1998; Lindstrom et al. 1998). Adipose tissue levels of 2,2'4,4'-tetraBDE (used as a marker for total PBDE exposure) were compared in 19 patients with NHL, 23 patients with malignant melanoma, 8 patients with other cancers or *in situ* changes, and 27 persons with no cancer diagnosis. The highest concentrations were seen in the patients with NHL. The mean concentration of 2,2'4,4'-tetraBDE was 13.0 ng/g (ppb) lipid (range 1.0–98.2 ppb) in the 19 NHL patients and 5.1 ppb (range 0.6–27.5 ppb) in the 27 persons without known malignancies. Logistic regression, adjusted for age, gender, sum of PCBs, and sum of chlordanes, was performed on cases and controls in three concentration groups (<2.05, 2.05–<5.43, and $5.43 ppb). A nonsignificantly elevated risk with a suggestive dose-response was found for NHL in the two highest concentration groups compared with the lowest group; the ORs and 95% CIs were 1.9 (0.3–14) and 3.8 (0.7–26) in the middle and high groups, respectively. Although the risk was highest in the group with the highest concentration of 2,2'4,4'-tetraBDE (p=0.09 for trend), there was no significant difference between cases and controls (p=0.14). The results for patients with malignant melanoma did not differ from controls.

Information on carcinogenic effects of PBDEs in animals is limited to results of chronic bioassays of decaBDE mixtures in rats and mice (Kociba et al. 1975; Norris et al. 1975b; NTP 1986). As summarized below, these studies provide limited evidence for the carcinogenicity of decaBDE in animals. No carcinogenicity studies of octaBDE or pentaBDE were located in the available literature.

The National Toxicology Program evaluated the carcinogenicity of commercial grade decaBDE (94-97% pure, no detected brominated dioxins or furans) in Sprague-Dawley rats (50/sex/dose) and B6C3F1 mice (50/sex/dose) that were exposed in the diet for 103 weeks and observed for an additional 0–1 weeks (NTP 1986). Comprehensive gross and histological examinations were performed on all animals in all dose groups including those that were moribund or died during the study. Reported estimated dose levels in the rats were 1,120 and 2,240 mg/kg/day in males and 1,200 and 2,550 mg/kg/day in females. Incidences of liver neoplastic nodules in low- and high-dose male rats (7/50 and 15/49, respectively) and high-dose female rats (9/50) were significantly greater than in controls (1/50 in both males and females) (p#0.03, Fisher Exact test) and showed positive dose-related trends (p<0.001, Cochran-Armitage trend test). Incidences of hepatocellular carcinoma alone (1/50, control males; 1/50, low-dose males; 1/49, high-dose males; 0/50, control females; 2/49, low-dose females; and 0/50, high-dose females) were not significantly increased in the treated rat groups compared to controls. The increased incidences of neoplastic nodules were considered as some evidence of compound carcinogenicity in both sexes. A dose-related trend for mononuclear cell leukemia was observed in treated male rats but was not considered to be biologically significant because of a high incidence in control animals.

Reported estimated doses in the mice were 3,200 and 6,650 mg/kg/day in males and 3,760 and 7,780 mg/kg/day in females (NTP 1986). Hepatocellular adenoma or carcinoma (combined) occurred at significantly increased incidences in low-dose male mice (22/50, p=0.002) and high-dose male mice (18/50, p=0.019) in comparison to controls (8/50) and showed a positive dose-related trend (p=0.021). Incidences of hepatocellular carcinoma alone were not significantly increased in either the low- or high-dose male mice. Slightly elevated incidences of thyroid gland follicular cell adenoma or carcinoma (combined) were additionally observed in exposed male mice but the increases were not statistically significant (control, 0/50; low dose, 4/50; high dose, 3/50). Incidences of follicular cell hyperplasia were significantly increased in male mice as summarized in the subsection on Endocrine Effects in Section 3.2.2.2. No significantly increased incidences of neoplastic lesions were observed in the female mice. NTP (1986) concluded that the significant increase in liver tumors and equivocal increase in thyroid tumors represented equivocal evidence of carcinogenicity in male mice. The evidence of carcinogenicity in the male mice was considered limited by an early loss of control animals. Losses of

control male mice were significant during the first year of the study but were subsequently comparable to the dosed mice; the early losses were presumed to be due to fighting among animals in both control and treatment groups.

The carcinogenicity of decaBDE was also evaluated in Sprague-Dawley rats (25/sex/dose) that were exposed to dietary doses of 0, 0.01, 0.1, or 1.0 mg/kg/day for approximately 2 years (702 days for males, 735 days for females) (Kociba et al. 1975; Norris et al. 1975b). The commercial mixture was comprised of 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE and therefore differs from typical decaBDE formulations containing $97% decaBDE. Comprehensive histological examinations showed no exposure-related neoplastic effects. The ability of this study to detect carcinogenic changes is limited by the very low dose levels in comparison to those tested in the NTP (1986) bioassay.

The Cancer Effect Levels (CELs) for decaBDE in the NTP (1986) study are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.3 Dermal Exposure

A few studies have examined groups of chemical workers involved in the manufacture and distribution of PBBs and/or PBDEs (Bahn et al. 1980; Brown et al. 1981; Chanda et al. 1982; Landrigan et al. 1979; Rosenman et al. 1979; Stross et al. 1981). Although the route of exposure (inhalation relative to dermal) of these workers has not been well defined, they appear to have had a high potential for dermal exposure (Anderson et al. 1978d). Results from these studies are discussed in this section, as well as in Section 3.2.1.

3.2.3.1 Death

Polybrominated Biphenyls. No reports of death in humans after dermal exposure to PBBs were located in the available literature.

No deaths were observed over a 14-day period among a group of four rabbits exposed to up to 10,000 mg/kg of body weight of a commercial octabromobiphenyl mixture by application to abraded and occluded dorsal trunk skin (Waritz et al. 1977). The bromobiphenyl was applied as a 35% (w/v) paste in corn oil. The same group of investigators reported that four of four rabbits died over a 14-day period after application of 5,000 mg/kg of a commercial hexabromobiphenyl mixture in the same vehicle as the octabromobiphenyl mixture. A dose of 10,000 mg/kg applied for 24 hours killed two of four rabbits. The cause of death was not reported. A commercial mixture of decabromobiphenyl in corn oil was not lethal in rats that were observed for 14 days following application of a single dose as high as 5,000 mg/kg to covered intact skin (Millischer et al. 1980). The octabromobiphenyl LOAEL of 5,000 mg/kg is reported in Table 3-2. It is unclear whether the different lethality rates observed among the hexa-, octa-, and decabromobiphenyl mixtures reflect differences in lethal potency or in absorption rates or both.

Table 3-3. Levels of Significant Exposure to PBBs and PBDEs - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE						
Death						
Rabbit (NZW)	24 hr			5000	(4/4 died)	Waritz et al. 1977 (HBB)
Systemic						
Rabbit (Albino)	once	Derm	658			Millischer et al. 1980 (DBB)
Rabbit (NZW)	5 d 1x/d	Derm		0.19	(hyperkeratosis)	Needham et al. 1982 (FF-1)
Rabbit (NS)	2 wk 5 d/wk 1x/d	Hepatic		1	(increased liver weight)	Waritz et al. 1977 (OBB)
		Derm	1			
		Bd Wt	1			
Rabbit (NZW)	24 hr	Hepatic	100 M	1000	(increased liver weight; necrotic foci)	Waritz et al. 1977 (HBB)
		Bd Wt	1000 M	5000	(11% weight loss)	

Table 3-3. Levels of Significant Exposure to PBBs and PBDEs - Dermal (continued)

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE						
Systemic						
Gn pig (Albino Hartley)	3 wk 3x/wk	Derm	62 M			Waritz et al. 1977 (OBB)

Bd Wt = body weight; d = days; Derm = dermal; hr = hour(s); M = male; wk = week(s); x = time(s)

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Polybrominated Diphenyl Ethers. No reports of death in humans after dermal exposure to PBDEs were located in the available literature.

No deaths occurred in rabbits that were observed for 14 days following a single #2,000 mg/kg dermal dose of decaBDE, octaBDE or pentaBDE (IRDC 1974, 1975a, 1975b). The PBDEs were applied to clipped intact skin, covered with an occlusive barrier, and washed from the treatment site 24 hours later.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or renal effects in humans or animals after dermal exposure to PBBs.

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to PBDEs.

Systemic effects that have been observed in humans and animals following dermal exposure to PBBs and PBDEs are described below. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 3-3.

Hepatic Effects.

Polybrominated Biphenyls. No studies were located regarding hepatic effects in humans after dermal exposure to PBBs.

No significant changes in relative or absolute liver weight or gross pathological effects were reported in groups of four rabbits after application of a single dose of up to 10,000 mg/kg of octabromobiphenyl mixture in corn oil to abraded and occluded dorsal skin over a 24-hour period (Waritz et al. 1977). It was unclear if histopathological examinations were performed. Using the same protocol in rabbits, these investigators reported a significant increase ($p<0.01$) in relative and absolute liver weight, distinct lobular markings, and necrotic foci with doses $1,000 mg/kg of a commercial hexachlorobiphenyl mixture. A dose of 100 mg/kg was without effect. A significant increase ($p<0.01$) in relative liver weight was reported in rabbits after application of 1 mg/kg/day of a commercial mixture of octabromobiphenyl in corn oil to the intact and occluded shaved dorsal skin on 5 days/week for 2 weeks (Waritz et al. 1977). Histopathological examinations were not performed. A relatively low dose (0.0013 mg/kg) of FireMaster

BP-6 dissolved in benzene/decame (1:9) applied once a day for 5 days to the ear of three rabbits caused no histopathological effects in the liver (Hass et al. 1978).

No studies were located regarding hepatic effects following intermediate or chronic dermal exposure to PBBs.

Endocrine Effects.

Polybrominated Biphenyls. Hypothyroidism was diagnosed in 4 of 35 men who were occupationally exposed to unspecified PBBs and/or decaBDE (Bahn et al. 1980). The cohort consisted of workers (mean age 35.9 years) who had been employed at a production plant for at least 6 weeks during a 52-month period during which PBBs and decaBDE were the only chemicals manufactured and who had volunteered for a comprehensive medical evaluation performed 3 months after the end of the 52-month period. There was no further description of exposure, and it was assumed to have occurred by both inhalation and dermal routes. As detailed in Section 3.2.1.2, the results of this study suggest that occupational exposure to PBBs, decaBDE, and/or bromine affected the thyroid, but the mixed chemical exposure and a lack of data on serum or tissue levels of the chemicals preclude attributing effects solely to any particular congener or mixture of congeners.

No studies were located regarding endocrine effects in animals after dermal exposure to PBBs.

Polybrominated Diphenyl Ethers. There is suggestive evidence of hypothyroidism in a small group of workers who were occupationally exposed to decaBDE as well as PBBs (Bahn et al. 1980) as summarized above and detailed in Section 3.2.1.2.

No studies were located regarding endocrine effects in animals after dermal exposure to PBDEs.

Dermal Effects.

Polybrominated Biphenyls. As discussed in Section 3.2.1.2, results from a medical history survey study of workers in a PBB manufacturing plant and a nonexposed group of Wisconsin farm residents indicated an association between occupational exposure to PBBs and the occurrence of acne (Chanda et al. 1982). The survey covered a period of 3 years of potential exposure, but exposure levels were not reported. No adverse dermal effects were observed on the arms or legs of subjects after a 6-day application of polymer

fibers containing commercial octabromobiphenyl mixture under an occlusive covering; no additional information was reported (Waritz et al. 1977).

Several studies examined the acute dermal effects of commercial PBB mixtures in rabbits. Application of 0.19 mg/kg FireMaster FF-1 for 5 days, in toluene vehicle, to the inner surface of the left ear of two rabbits (right ear served as control) induced moderate hyperkeratosis, which included marked dilation of the hair follicles, with moderate proliferation of the epithelium and partial atrophy of the sebaceous glands (Needham et al. 1982). There was also evidence of excess keratin and debris in the subjacent hair follicles. Application of either a dry or water-moistened formulation of octabromobiphenyl mixture (amount not reported) for 24 hours did not adversely affect intact skin in rabbits, but slight erythema and edema were observed in abraded skin (Norris et al. 1975a). Repeated applications over a 2-week period of the dry octabromobiphenyl mixture formulation (amount not reported) to occluded intact or abraded skin caused no skin response, but the water-moistened formulation caused slight and transient erythema (Norris et al. 1975a). None of these studies reported the number of animals used. Rough skin with mild erythema was observed in occluded intact shaved dorsal skin of a group of rabbits after repeated applications of a dose of 1 mg/kg/day octabromobiphenyl mixture in corn oil over a 2-week period (Waritz et al. 1977). Application of a commercial decabromobiphenyl mixture in olive oil to covered intact or abraded skin for 4 hours, in an amount equivalent to 658 mg/kg, caused very slight erythema with or without edema in rabbits (Millischer et al. 1980).

Limited information is available regarding intermediate-duration dermal effects of PBBs in animals. A 10% chloroform solution of an unspecified commercial formulation of octabromobiphenyl did not induce bromacne when applied to the ear of rabbits for 30 days (Norris et al. 1975a). Only slight erythema and exfoliation was observed. Doses of 62 mg/kg of octabromobiphenyl mixture were not sensitizing when applied to the intact or abraded skin of guinea pigs over a 3-week period (Waritz et al. 1977).

No studies were located regarding dermal effects in animals after chronic application of PBBs.

Polybrominated Diphenyl Ethers. A human sensitization study was conducted in which 77.4% decaBDE (containing 21.8% nonaBDE and 0.8% octaBDE) as a 5% suspension in petrolatum was applied via patch, 3 times a week for 3 weeks, to 50 subjects (Norris et al. 1975a). No skin sensitization responses occurred during the sensitizing period or on challenge 2 weeks following the last application. No additional information was reported regarding the design and results of this study.

There was no evidence of primary irritation in intact skin of rabbits that were dermally exposed to decaBDE (500 mg as dry solid was applied to clipped skin and occluded for 24 hours) (IRCD 1974). Similar application of 77.4% decaBDE (containing 21.8% nonaBDE and 0.8% octaBDE) (dry solid, amount not reported), octaBDE (500 mg as dry solid), or pentaBDE (0.5 mL as a viscous liquid) was also non-irritating to intact rabbit skin (IRCD 1975a, 1975b; Norris et al. 1975a). Similar application of solid 77.4% decaBDE (21.8% nonaBDE and 0.8% octaBDE) or octaBDE to abraded skin caused a slight erythematous and edematous response in rabbits (Norris et al. 1975a). OctaBDE moistened with water caused no response on intact skin and a moderate erythematous and slight edematous response on abraded skin after 24 hours of occluded contact in rabbits (Norris et al. 1975a).

Repeated applications of solid 77.4% decaBDE (21.8% nonaBDE and 0.8% octaBDE) or octaBDE to intact skin (5 days/week for 2 weeks) or abraded skin (3 days) was non-irritating to rabbits (Norris et al. 1975a). Similar repeated applications of octaBDE moistened with water caused a slight erythematous response on intact skin and a moderate erythematous and slight edematous response on abraded skin. All skin sites returned to normal appearance following cessation of exposure.

OctaBDE and pentaBDE were non-sensitizing in maximization tests in guinea pigs (Microbiological Associates Inc. 1996). The induction doses consisted of three pairs of interscapular region intradermal injections of (1) a 50:50 solution of Freund's adjuvant and corn oil, (2) 2.5% octaBDE or 5% pentaBDE solutions in corn oil, and (3) 2.5% octaBDE or 5% pentaBDE in the 50:50 corn oil/Freund's adjuvant solution. Control groups received the same regimen without PBDEs. After 7 days, the PBDE-treated animals received topical applications of neat octaBDE or pentaBDE on the previously treated interscapular sites. Two weeks later, the animals were challenged with topical doses of neat octaBDE or pentaBDE on the left flank. Subsequent examination of the test sites at 24, 48, 72, 96, or 120 hours after the challenge dose showed no erythema or edema responses in any of the animals, indicating that the PBDEs did not cause delayed contact hypersensitivity.

A 10% chloroform solution of 77.4% decaBDE (containing 21.8% nonaBDE and 0.8% octaBDE) or octaBDE did not induce bromacne when applied to the ear of rabbits for 30 days (Norris et al. 1975b). A slight erythematous response and slight exfoliation were the only observed effects. No additional information was reported on the design and results of this acnegenesis study.

Ocular Effects.

Polybrominated Biphenyls. No studies were located regarding ocular effects in animals after dermal exposure to PBBs.

Transient irritation of the conjunctival membranes was observed after a single instillation of an unreported amount of dry solid octabromobiphenyl mixture to the eye in rabbits, but the cornea, iris, and lens were unaffected (Norris et al. 1975a). Commercial grade decabromobiphenyl did not cause eye irritation in rabbits when 0.05 mg in olive oil was instilled for 30 seconds followed by rinsing, but application of an unspecified amount of dry powder without rinsing was slightly irritating (Millischer et al. 1980). Mild conjunctival redness and swelling and a copious discharge was reported after application of 100 mg of an unspecified commercial PBB powder mixture (either hexa- or octabromobiphenyl) for 20 seconds into the conjunctival sac of two rabbits (Waritz et al. 1977). These effects disappeared within 4 hours in both washed (with tap water) and unwashed eyes. The iris and cornea were unaffected.

Polybrominated Diphenyl Ethers. No studies were located regarding ocular effects in animals after dermal exposure to PBDEs.

Ocular effects were investigated in rats that had 100 mg decaBDE (solid), 100 mg octaBDE (solid), or 0.1 mL pentaBDE (viscous liquid) instilled into the conjunctival sac (ICRD 1974, 1975a, 1975b). The eyes were examined for irritation after 24, 48, and 72 hours and 7 days and corneal injury after 72 hours. There were no exposure-related effects with decaBDE or octaBDE, although pentaBDE caused slight evidence of corneal damage in one of six rats (IRDC 1975b).

Body Weight Effects.

Polybrominated Biphenyls. No studies were located regarding body weight effects in humans after dermal exposure to PBBs.

No treatment-related effects on body weight were reported in rabbits given a dose of 1 mg/kg/day of a commercial mixture of octabromobiphenyl in corn oil via application to the intact shaved dorsal skin for 2 weeks (Waritz et al. 1977). No significant effect on final body weight was reported in groups of four rabbits after application of a single dose of up to 10,000 mg/kg of octabromobiphenyl mixture in corn oil to the abraded and occluded dorsal skin over a 24-hour period (Waritz et al. 1977). The observation

period was 14 days. In a similar study with a commercial mixture of hexabromobiphenyl, rabbits treated with 1,000 mg/kg showed no weight gain over 14 days. Doses of 5,000 and 10,000 mg/kg induced an 11% and 20% weight loss, respectively, whereas, a dose of 100 mg/kg was without effect (Waritz et al. 1977).

Polybrominated Diphenyl Ethers. No studies were located regarding body weight effects in humans after dermal exposure to PBDEs.

There were no adverse effects on body weight in rabbits that were observed for 14 days following a single #2,000 mg/kg dermal dose of decaBDE, octaBDE, or pentaBDE (IRDC 1974, 1975a, 1975b). The PBDEs were applied to clipped intact skin, covered with an occlusive barrier, and washed from the treatment site after 24 hours.

3.2.3.3 Immunological and Lymphoreticular Effects

Polybrominated Biphenyls. Several immunological parameters were evaluated in a group of 28 workers from the Michigan Chemical Company who were involved in the manufacturing and distribution of PBBs including FireMaster FF-1 (Stross et al. 1981). It is assumed that the main route of exposure was dermal, but inhalation and/or oral exposure cannot be ruled out. The subjects had worked directly with PBBs during the previous 5 years. Immunological studies included determination of immunoglobulin levels, skin testing, and lymphocyte transformation studies. No abnormalities in lymphocyte number or function could be determined when compared to an unexposed group. One of three blastogenic responses (PWM) was significantly reduced ($p<0.01$) relative to controls, but was within the normal range for the laboratory. No specific information was provided regarding the skin testing and immunoglobulin levels.

No studies were located regarding immunological effects in animals after dermal exposure to PBBs.

Polybrominated Diphenyl Ethers. No studies were located regarding immunological effects in humans or animals after dermal exposure to PBDEs.

3.2.3.4 Neurological Effects

Polybrominated Biphenyls. Twenty-five workers at a PBB manufacturing plant displayed mean scores on tests of memory and learning that were typical for people of their age, educational, occupational, and cultural backgrounds, even though they displayed an elevated mean PBB concentration in adipose tissue (9.33 ppm compared with 3.94 ppm for farm residents) (Brown et al. 1981). Workers with the highest concentrations of PBB in adipose tissue showed no evidence of memory dysfunction in these tests. Because 15/25 "directly handled PBBs or performed maintenance work in the area where PBBs were manufactured," it is likely that at least part of the exposure was by the dermal route.

No studies were located regarding neurological effects in animals after dermal exposure to PBBs.

Polybrominated Diphenyl Ethers. No studies were located regarding neurological effects in humans or animals after dermal exposure to PBDEs.

3.2.3.5 Reproductive Effects

Polybrominated Biphenyls. Eleven workers in a PBB manufacturing company in Michigan displayed no differences in the distribution of sperm counts, motility, or morphology compared with a control group of 52 unexposed men (Rosenman et al. 1979). PBBs were detected in the serum of all exposed subjects and in only one unexposed subject, but mean or individual serum PBB values were not reported.

No studies were located regarding reproductive effects in animals after dermal exposure to PBBs.

Polybrominated Diphenyl Ethers. No studies were located regarding reproductive effects in humans or animals after dermal exposure to PBDEs.

3.2.3.6 Developmental Effects

Polybrominated Biphenyls. No studies were located regarding developmental effects in humans or animals after dermal exposure to PBBs.

Polybrominated Diphenyl Ethers. No studies were located regarding developmental effects in humans or animals after dermal exposure to PBDEs.

3.2.3.7 Cancer

Polybrominated Biphenyls. No studies were located regarding cancer in humans after dermal exposure to PBBs.

An unspecified PBB mixture (purity not reported) was not tumorigenic when applied to the shaved dorsal skin of female CD-1 mice at a dose of 3.3 mg/kg twice weekly for 30 weeks; no tissues other than skin were examined (Berry et al. 1978, 1979). This same treatment did not promote the development of skin tumors in mice pretreated with a single application of a tumor initiator, dimethylbenzanthracene (DMBA), 1 week prior to PBB exposure (Berry et al. 1978, 1979). The results of these studies must be interpreted with caution, since a dose-response study was not done (i.e., only one dose level was tested, and the doses may have been too low). Toxic doses of FireMaster FF-1 promoted development of skin tumors in female HRS/J hairless mice (Poland et al. 1982). A single dermal application of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) initiator, followed by twice weekly applications of FireMaster FF-1 at 66.7 mg/kg for 5 weeks and then 33.3 mg/kg for 15 weeks, resulted in a 60% (9/15) incidence of papillomas compared to 0% (0/23) in MNNG-only controls. Toxic effects included mortality, which caused the dose reduction after 5 weeks, and severe hepatomegaly and hepatic porphyria.

Polybrominated Diphenyl Ethers. No studies were located regarding cancer in humans or animals after dermal exposure to PBDEs.

3.3 GENOTOXICITY

Polybrominated Biphenyls. No studies were located regarding genotoxic effects in humans following inhalation, oral, or dermal exposure to PBBs.

In vivo genotoxicity studies of PBBs in animals are summarized in Table 3-4. Administration of single oral doses between 50 and 1,000 mg of FireMaster FF-1/kg (purity not reported) by gavage in corn oil to male and female B6C3F1 mice and male Fischer-344 rats did not induce unscheduled deoxyribonucleic acid (DNA) synthesis in hepatocytes (Mirsalis et al. 1985, 1989). However, doses $200 mg/kg significantly increased hepatic cell proliferation in mice, but not in rats. The increase in cell proliferation without a change in unscheduled DNA synthesis suggests that PBBs acted as a promoter rather than directly causing DNA damage (initiator). A commercial mixture of decabromobiphenyl did not induce gene mutation in *Salmonella typhimurium* bacteria that were intraperitoneally injected into male CFLP mice in a host-mediated assay (Millischer et al. 1980). This decabromobiphenyl mixture also did not induce micronuclei in bone marrow erythrocytes of mice (Millischer et al. 1980). The mice in the host-mediated assay and micronucleus test were orally treated (method not specified) with total doses of 5,000, 10,000, or 20,000 mg/kg, administered in two equal doses 24 hours apart.

In vitro studies indicate that PBBs are not directly genotoxic. As summarized in Table 3-5, PBBs did not exhibit mutagenic activity when tested in the prokaryotic organisms *S. typhimurium* (Haworth et al. 1983; Millischer et al. 1980; NTP 1983) and *E. coli* (Rossman et al. 1991) with or without activation systems in the limited number of studies available. *In vitro* testing in eukaryotic cells resulted in negative genotoxic responses in hamster cells (Galloway et al. 1987; Kavanagh et al. 1985; Williams et al. 1984), rat liver cells (Kavanagh et al. 1985; Williams et al. 1984), mouse liver and lymphoma cells (Myhr and Caspary 1991; Williams et al. 1984), and human fibroblasts (Williams et al. 1984).

An *in vitro* study with a ^{14}C-PBB mixture containing 12 major components found only traces of radioactivity bound to rat liver microsomal macromolecules (Dannan et al. 1978a). Binding, however, was dependent upon the type of microsomes used to activate the PBB mixture. Microsomes isolated from animals pretreated with methylcholanthrene (MC) bound twice the amount of radioactivity compared with controls, whereas activation with phenobarbital (PB) or PBB bound 5 times more radioactivity than control microsomes. Also, the authors showed that no radioactivity was covalently bound to DNA following incubation with ^{14}C-PBB. The type of microsomes used or the presence or

Table 3-4. Genotoxicity of PBBs and PBDEs *In Vivo*

Species (test system)	End point	Results	Reference
PBBs			
Mammalian cells:			
Rat hepatocytes	Unscheduled DNA synthesis	–	Mirsalis et al. 1989 (FF-1)
Mouse hepatocytes	Unscheduled DNA synthesis	–	Mirsalis et al. 1985, 1989 (FF-1)
Host-mediated assays:			
Salmonella typhimurium (mouse hosted-mediated)	Gene mutation	–	Millischer et al. 1980 (DBB)
Micronucleus test:			
Mouse bone marrow erythrocytes	Chromosome aberration (micronuclei)	–	Millischer et al. 1980 (DBB)
PBDEs			
Cytogenicity:			
Rat bone marrow cells (one-generation reproduction study)	Chromosome aberration	–	Norris et al. 1973, 1975 (77.4% decaBDE, 21.8% nonaBDE)

– = negative result; DBB = decabromobiphenyl commericial mixture; decaBDE = decabromodiphenyl ether; DNA = deoxyribonucleic acid; FF-1 = FireMaster FF-1; nonaBDE = nonabromodiphenyl ether; PBBs = polybrominated biphenyls; PBDEs = polybrominated diphenyl ethers

Table 3-5. Genotoxicity of PBBs and PBDEs *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
PBBs				
Prokaryotic organisms:				
Salmonella typhimurium (plate incorporation)	Gene mutation	–	–	NTP 1983 (FF-1)
S. typhimurium (plate incorporation)	Gene mutation	–	–	Haworth et al. 1983 (HBB)
S. typhimurium (plate incorporation)	Gene mutation	–	–	Millischer et al. 1980 (DBB)
Escherichia coli (culture)	Gene mutation	–	–	Rossman et al. 1991 (PBB)
Eukaryotic organisms				
Mammalian cells:				
Chinese hamster CHO cells (cell culture)	Chromosomal aberration	–	–	Galloway et al. 1987 (HBB)
Chinese hamster CHO cells (cell culture)	Sister chromatid exchange			Galloway et al. 1987 (HBB)
Chinese hamster V79 cells (cell culture)	Gene mutation	–	–	Kavanagh et al. 1985 (BP-6)
Chinese hamster V79 cells (cell culture)	Gene mutation	No data	–	Kavanagh et al. 1985 (2,4,5-HBB)
Chinese hamster V79 cells (cell culture)	Gene mutation	No data	–	Kavanagh et al. 1985 (3,4,5-HBB)
Chinese hamster V79 cells (cell culture)	Gene mutation	–	–	Kavanagh et al. 1985 (3,4-TBB)
Rat liver cells WB (cell culture)	Gene mutation	No data	–	Kavanagh et al. 1985 (2,4,5-HBB)
Rat liver cells WB (cell culture)	Gene mutation	No data	–	Kavanagh et al. 1985 (3,4,5-HBB)
Mouse lymphoma cells L5178Y (cell culture)	Gene mutation	–	–	Myhr and Caspary 1991 (FF-1)
Rat liver cells (cell culture)	DNA repair	No data	–	Williams et al. 1984 (FF-1)
Mouse liver cells (cell culture)	DNA repair	No data	–	Williams et al. 1984 (FF-1)
Hamster liver cells (cell culture)	DNA repair	No data	–	Williams et al. 1984 (FF-1)
Rat liver cells (cell culture)	Gene mutation	No data	–	Williams et al. 1984 (FF-1)
Human fibroblast D-550 (cell culture)	Gene mutation	–	No data	Williams et al. 1984 (FF-1)

Table 3-5. Genotoxicity of PBBs and PBDEs *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
PBDEs				
Prokaryotic organisms: *Salmonella typhimurium* (plate incorporation)	Gene mutation	–	–	NTP 1986 (decaBDE)
Mammalian cells: Mouse lymphoma L5178Y cells (cell culture)	Gene mutation	–	–	NTP 1986 (decaBDE)
Chinese hamster Sp5/V79cells (cell culture)	Gene recombination	no data	-	Helleday et al. 1999 (2,2',4,4'-tetraBDE)
Chinese hamster SPD8/V79cells (cell culture)	Gene recombination	no data	%	Helleday et al. 1999 (2,2',4,4'-tetraBDE)
Chinese hamster Sp5/V79 cells (cell culture)	Gene recombination	no data	%	Helleday et al. 1999 (3,4-diBDE)
Chinese hamster SPD8/V79 cells (cell culture)	Gene recombination	no data	%	Helleday et al. 1999 (3,4-diBDE)
Chinese hamster Sp5/V79 cells (cell culture)	Gene recombination	no data	%	Helleday et al. 1999 (2-monoBDE)
Chinese hamster SPD8/V79 cells (cell culture)	Gene recombination	no data	%	Helleday et al. 1999 (2-monoBDE)
Chinese hamster ovary cells (cell culture)	Sister chromatid exchange	–	–	NTP 1986 (decaBDE)
Chinese hamster ovary cells (cell culture)	Chromosomal aberrations	–	–	NTP 1986 (decaBDE)

– = negative result; 2,2',4,4'-tetraBDE = 2,2',4,4'-tetrabromodiphenyl ether; 2,4,5-HBB = 2,2',4,4',5,5'-hexabromobiphenyl; 2-monoBDE = 2-bromodiphenyl ether; 3,4,5-HBB = 3,3',4,4',5,5'-hexabromobiphenyl; 3,4-diBDE = 3,4-dibromodiphenyl ether; 3,4-TBB = 3,3',4,4'-tetrabromobiphenyl; BDE = brominated diphenyl ethers; BP-6 = FireMaster BP-6; DBB = decabromobiphenyl commercial mixture; decaBDE = decabromobiphenyl ether; DNA = deoxyribonucleic acid; FF-1 = FireMaster FF-1; HBB = hexabromobiphenyl (unspecified); PBB = unspecified mixture; PBBs = polybrominated biphenyls; PBDEs = polybrominatedd diphenyl ethers

absence of nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) in the incubation mixture made no difference.

Although it appears that PBBs are not mutagenic, due to their enzyme induction properties, they may potentiate the genotoxic activity of other compounds by activation to reactive intermediates.

Polybrominated Diphenyl Ethers. No studies were located regarding genotoxic effects in humans following inhalation, oral, or dermal exposure to PBDEs.
A limited amount of information has been published on the genotoxicity of PBDEs in animals *in vivo* or in prokaryotic and eukaryotic cells *in vitro* as summarized in Tables 3-4 and 3-5, respectively. Cytogenetic examination of bone marrow cells showed no increase in aberrations in maternal and neonatal rats following maternal oral exposure to #100 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for 90 days prior to mating and during mating, gestation, and lactation (Norris et al. 1973, 1975a). *In vitro* assays found that decaBDE did not induce gene mutations in bacterial cells (*S. typhimurium TA98, TA100, TA1535,* or *TA1537*) or mammalian cells (mouse lymphoma L5178Y cells), and did not induce sister chromatid exchange or chromosomal aberrations in Chinese hamster ovary cells (NTP 1986). *In vitro* exposure to the congeners 2,2',4,4'-tetraBDE, 3,4-diBDE, and 2-monoBDE caused increased recombinogenic activity at the HGPRT locus in Chinese hamster SPD8 and Sp5 V79 cells (Helleday et al. 1999).

3.4 TOXICOKINETICS

Data regarding the toxicokinetics of PBBs in humans are limited to information derived from cases of accidental ingestion of food contaminated with PBBs and cases of occupational exposure by the inhalation and dermal routes. These data provide qualitative evidence that PBBs are absorbed in humans by the inhalation, oral, and dermal routes. Limited quantitative data in animals indicate that some PBB congeners are well absorbed after oral exposure. Dermal absorption data for animals are insufficient for estimating absorption rates, and no inhalation absorption data were located. In blood, 80% of PBBs, are bound to protein and 20% are associated with lipids. The distribution pattern of PBBs did not differ significantly between humans and animals and among animal species. Due to their lipophilic nature, PBBs, especially the highly brominated congeners, tend to accumulate in lipid-rich tissues. Greater relative amounts of PBBs are usually found in the liver, adipose, skin, and breast milk. Certain components of PBB mixtures are metabolized by the microsomal monooxygenase system catalyzed by cytochrome P-450 of the type induced by phenobarbital. The rate of metabolism of some PBB congeners

depends on the bromine substitution pattern. PBB congeners of low bromine content are transformed into hydroxylated derivatives that are predominately eliminated in the urine. Highly brominated congeners are either retained or excreted unchanged in the feces. The exact mechanism of PBB toxicity is not known. It has been suggested, however, that the mechanism for some congeners is related to the enhancement of gene expression triggered by initial binding to the same cytosolic receptor (Ah) involved in PCB and polychlorinated dioxin toxicity.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Polybrominated Biphenyls. No studies were located regarding absorption of PBBs in humans after inhalation exposure. However, absorption of PBBs by inhalation (and by dermal contact) in humans can be inferred by the relatively high levels of PBB residues detected in adipose tissue and serum of workers involved in PBB manufacturing (Brown et al. 1981; Landrigan et al. 1979; Stross et al. 1981).

No studies were located regarding quantitative absorption of PBBs in animals after inhalation exposure to PBBs. However, increased bromine concentrations were found in the liver and adipose tissue of rats exposed continuously to a commercial mixture of octabromobiphenyl for 15 weeks, suggesting that absorption had occurred (Waritz et al. 1977).

Polybrominated Diphenyl Ethers. No studies were located regarding absorption of PBDEs in humans or animals after inhalation exposure.

3.4.1.2 Oral Exposure

Polybrominated Biphenyls. Quantitative oral absorption data in humans were not located, but reports of increased levels of PBB residues in tissues and serum of individuals accidentally exposed to contaminated food indicate that gastrointestinal absorption of PBBs had occurred (Eyster et al. 1983; Humphrey and Hayner 1975; Landrigan et al. 1979; Miceli et al. 1985; Wolff et al. 1982).

Absorption of PBBs from the gastrointestinal tract in animals can be inferred from the numerous reports of adverse effects (Section 3.2.2) and increased residue levels in tissues following oral administration of these compounds (Section 3.4.2.2); however, few quantitative data exist. By comparing the amount of

radioactivity in the feces of rats administered a single oral dose of 1 mg ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl/kg with that monitored after a single intravenous injection of the compound, it was estimated that . 93% of the oral dose was absorbed over a 24-hour period (Matthews et al. 1977). Data obtained from similar experiments later confirmed these results (Tuey and Matthews 1980). It was also demonstrated that absorption of the hexabromobiphenyl congener was independent of the dose, since $90% was absorbed over a dose range of 1–30 mg/kg (Matthews et al. 1977). In contrast with the high absorption rate for the hexabromobiphenyl congener, octabromobiphenyl (45.2% octa, 47% nona, 5.7% deca, 1.8% hepta) appeared to be less well absorbed by rats after administration of a single dose of 1 mg/kg (Norris et al. 1975a). Within the first 24 hours after dosing, 61.9% of the dose was found in the feces. This indicates that at least 38.1% of the dose was absorbed, but absorption may have been higher, since biliary excretion may have occurred.

Polybrominated Diphenyl Ethers. No information was located regarding absorption of PBDEs in humans following oral exposure. Limited information regarding absorption in animals has been inferred from data on elimination and excretion. Results from these studies suggest that decaBDE is poorly absorbed in rats. For example, 24 hours following administration of a single gavage dose of ^{14}C-decaBDE (commercial mixture), approximately 91% of decaBDE-derived radioactivity was found in the feces (Norris et al. 1975b). In the same time period, approximately 62% of a dose of octaBDE was detected in the feces, suggesting that octaBDE is more efficiently absorbed than decaBDE. Studies conducted with reagent-grade decaBDE provided similar results (El Dareer et al. 1987). The less brominated 2,2',4,4'-tetraBDE was much more efficiently absorbed by rats and mice since only 5 and 7% of a single dose was found in the feces 24 hours after dosing (Örn and Klasson-Wehler 1998).

3.4.1.3 Dermal Exposure

Polybrominated Biphenyls. No studies were located regarding absorption of PBBs in humans or animals after dermal exposure to PBBs. However, absorption of PBBs through the skin in humans can be inferred by the relatively high levels of PBB residues detected in the adipose tissue and serum of workers involved in the manufacturing of these chemicals (Brown et al. 1981; Landrigan et al. 1979; Stross et al. 1981). It is assumed that dermal route predominates, but inhalation and/or oral exposure cannot be ruled out.

Similarly, dermal absorption in rabbits can be inferred from reports of lethality and liver effects observed after application of a commercial mixture of hexabromobiphenyl to abraded and occluded dorsal skin (Waritz et al. 1977).

Polybrominated Diphenyl Ethers. No information was located regarding dermal absorption of PBDEs in humans. The only information regarding dermal absorption in animals is that from a study of absorption in an *in vitro* preparation (Hughes et al. 2001). In that study, ^{14}C-decaBDE dissolved in tetrahydrofuran was applied to dorsal skin (three dose levels) excised from adult hairless female mice and fractions of receptor fluid were collected over a 24-hour period. Transfer of radioactivity to the receptor fluid was minimal, only 0.07 to 0.34% of the applied radioactivity. Two to 20% of the radioactivity was found in the skin, and the lowest dose applied had the highest percentage of the dose in the skin. Washing the skin with solvent 24 hours after application removed 77–92% of the applied dose. In this study, decaDBE did not easily penetrate the skin, but inferences to dermal absorption in humans based on these limited results may not be appropriate.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Polybrominated Biphenyls. No studies were located regarding distribution of PBBs in humans after inhalation exposure.

Limited information was located regarding distribution of PBBs in animals after inhalation exposure. Increased bromide concentrations were observed in the liver and adipose tissue of rats exposed continuously to vapors of a commercial octabromobiphenyl mixture (33% octa, 60% nona, 6% deca, 1% hepta) (3.5 pg octabromobiphenyl/L air at equilibrium) for 15 weeks (Waritz et al. 1977). Relative to controls, the concentration of bromide in liver and fat was increased by 39 and 100%, respectively; bromide concentration in skeletal muscle was not affected by treatment. No further details were provided.

Polybrominated Diphenyl Ethers. No information was located regarding distribution of PBDEs in humans following inhalation exposure.

The distribution of bromine was examined in tissues of rats after inhalation exposure octaBDE (IRDC 1978). Groups of rats were exposed to 0, 1.2, 12, 120, or 1,200 mg/m^3 of dusts of octaBDE 8 hours/day for 14 days. At necropsy, sections of the lungs, adipose tissue, and liver were collected for bromine analysis using a neutron activation technique. The results showed concentrations of bromine in the lungs and adipose tissue significantly higher in all groups relative to controls; the amounts of bromine detected

were concentration-related. In the liver, the concentration of bromine was also elevated in all groups relative to controls except in the 1.2 mg/m^3 exposure group; the increases in the liver were not as marked as in the lungs or in adipose tissue.

3.4.2.2 Oral Exposure

Polybrominated Biphenyls. Numerous reports have been published regarding levels of PBBs in serum, adipose tissue, breast milk, placenta, and cord serum of humans exposed to PBBs via the diet (Anderson et al. 1978d; Eyster et al. 1983; Landrigan et al. 1979; Stross et al. 1979, 1981; Wolff et al. 1979a, 1982). By using paired sampling, several significant correlations were determined (Eyster et al. 1983). For example, in parturient women from Michigan, statistically significant correlations were found between PBB levels in maternal serum and placenta, cord serum, breast milk, and adipose; and between PBB levels in adipose tissue and breast milk. In addition, there was a significant correlation between PBB levels in serum and feces and between serum and biliary fluid samples in farmers and chemical workers in Michigan. In groups of pregnant, nonpregnant, and male chemical workers the serum to adipose tissue PBB concentration ratios ranged from 1:140 to 1:160, but in male farmers, this ratio was 1:325–329 (Eyster et al. 1983). The latter value is consistent with other reports regarding Michigan populations (Landrigan et al. 1979; Wolff et al. 1982). It is unclear why the partitioning ratios between male chemical workers and farmers should differ. The investigators noted that the group of farmers was much larger and might represent a better sample, as well as the possibilities that the farmers may have been more physically active or, for a variety of reasons, may have had lower total serum lipids (the amount of serum lipid might have affected the serum concentration of PBBs). PBB levels in body tissues and fluids are further discussed in Section 6.4.

Analysis of postmortem tissue samples from 15 subjects in the Grand Rapids, Michigan area indicated that renal fat had the highest single PBB concentration (1.65 μg/g wet weight) and the highest mean concentration (0.475 μg/g) (Miceli et al. 1985). In regards to adipose, PBB concentrations in different tissues, could be divided into three range groups: high (ratios of 0.45–0.56, adrenal, atheromatous aorta, and thymus), medium (ratios of 0.1–0.28, pancreas, liver, and left ventricle), and low (ratios of 0.02–0.09, kidney, lung, brain, skeletal muscle, thyroid, and nonatheromatous aorta).

As with the structurally related PCBs (ATSDR 2000), PBBs are rapidly (minutes to hours) cleared from the blood and initially accumulate mainly in the liver, lungs, and muscle (Domino et al. 1982; Matthews et al. 1977). Due to their high affinity for lipid-rich tissues, PBBs are subsequently redistributed to

adipose and skin for storage or metabolism in the liver, and a dynamic equilibrium of PBB concentrations is established among all tissues for each PBB homolog (Tuey and Matthews 1980).

In rats treated by gavage with one or four daily doses of ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl, initial concentrations of radioactivity were highest in muscle, liver, and adipose tissue, but later redistribution to adipose tissue (4–7 days after the last dosing) resulted in lower concentrations in liver and muscle (Matthews et al. 1977). In rats dosed daily with ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl over a 30-day period, tissue concentrations on day 31 were (in increasing order): blood, muscle, liver, skin, and adipose and were in general agreement with those predicted by a physiological compartment model (Tuey and Matthews 1980). When the model was scaled to nonlactating humans as discussed in Section 3.4.5 (Physiologically Based Pharmacokinetic/Pharmacodynamic Models), human intake of 9.8 g of the congener over a 230-day period would result in peak concentrations of 720 and 2.1 ppm in fat and blood, respectively, 5 years after the onset of exposure. The model also predicted that the body burden after 5 years would be 5.2 g and the half-life 6.5 years. This half-life is shorter than the 12 years (median, range 4–97 years) calculated for hexabromobiphenyl in a Michigan cohort (Lambert et al. 1990) (see Section 3.8.1).

In rats fed diets containing octabromobiphenyl mixture for several weeks, adipose tissue and liver accumulated much more bromine than did skeletal muscle (Lee et al. 1975b). For example, after 2 weeks of treatment, adipose of rats dosed with 50 mg/kg/day had 200 times more bromine than did adipose of control rats; the liver of these rats had 100 times more bromine than the livers of controls. Feeding a PBB-free diet for 2 weeks decreased PBB levels in liver and muscle, but not in fat. Eighteen weeks after exposure, the concentration of bromine in the adipose tissue of rats dosed with 50 mg/kg/day continued to increase to . 840 times that of controls. Similar results were reported by Norris et al. (1975a, 1975b). These investigators also reported that 16 days after a single dose of octabromobiphenyl mixture in rats, PBB residues were present in the adrenals, adipose tissue, heart, and skin at levels ranging from 0.14 to 0.25% of the administered dose; the liver, pancreas, and spleen contained lesser amounts.

The distribution and elimination of PBBs from tissues were examined in rats over a period of 112 days after a single oral dose of FireMaster FF-1 (Domino et al. 1982). Elimination from blood was best described by a three-compartment model, and an elimination half-life from whole blood of 145 days was estimated. Relative to the three compartments (C1, C2, and C3): C1 consisted of heart, kidney, spleen, and whole blood; C2 included liver, lung, cerebrum, cerebellum, and testes; and C3 included subcutaneous fat. PBB residues in C1 rose quickly, peaked within 5 hours of dosing and then fell rapidly;

a half-life of 3.62 hours was estimated. PBB peaked in C2 at 12 hours and then decreased; the half-life was 17.6 hours. In C3, levels of PBB peaked only after 1 week and remained elevated for several weeks; the estimated half-life was 31.1 days. Tissues with PBBs in order of increasing concentration were: blood, spleen, kidney, and heart in C1, and testes, cerebrum, cerebellum, lung, and liver in C2. Simulations of different body fat proportions showed that reduction in body fat decreased the half-life of the chemical considerably. According to the investigators (Domino et al. 1982), tissues within C1 and C2 may be at greater risk of toxicity during the subacute phase of PBB ingestion. In their view, this could explain the fact that blood PBB levels in Michigan families were not positively correlated with toxic symptoms of exposure to PBBs (see Section 3.2).

In mink treated with FireMaster FF-1 in the diet for up to 11 months, the concentration of PBB residues in adipose tissue were higher than in brain and skeletal muscle at all times (Aulerich and Ringer 1979; Ringer et al. 1981). The source of the PBBs (FireMaster FF-1 versus food contaminated with PBBs) did not seem to have a significant influence on the qualitative or quantitative distribution of residues in tissues. Sows fed FireMaster BP-6 in the diet for 12 weeks also accumulated PBBs in adipose tissue; on a fat basis, the highest concentration of PBBs was found in the liver, followed by adipose, kidney, and brain (Werner and Sleight 1981). Distribution studies in guinea pigs after a single dose of FireMaster FF-1 showed preferential accumulation of residues in liver, kidneys, and lungs 2 days after dosing (Ecobichon et al. 1983). This was followed by a slow decrease in these organs, but levels in adipose tissue reached a maximum between 7 and 14 days after dosing and then decreased.

Several studies have examined the distribution of PBB residues in offspring after maternal exposure to PBBs during gestation and/or lactation. In 4-week-old pigs exposed *in utero* and via lactation to FireMaster BP-6, PBBs accumulated preferentially in adipose tissue and liver on a wet tissue basis. Over a wide range of doses, however, adipose had at least two times the PBB concentration compared to the liver (Werner and Sleight 1981). PBB levels in tissues of sows were comparable to those measured in tissues of 4-week-old pigs. On a fat basis, the liver had the highest concentration of PBBs in both sows and the young. In pigs exposed only *in utero*, PBB levels in liver and adipose were similar and considerably lower than in tissues of sows or 4-week-old pigs, suggesting that far more PBBs are transferred through lactation than through the placenta. A similar conclusion was reached in rat studies (McCormack and Hook 1982; Rickert et al. 1978). In contrast, PBB levels in liver and body fat of guinea pigs exposed briefly through lactation were considerably lower than the tissue levels acquired transplacentally in a 2-day period (Ecobichon et al. 1983). A biological half-life of 22 days in tissues of dams and pups was estimated in that study (Ecobichon et al. 1983).

Polybrominated Diphenyl Ethers. In male rats administered a single gavage dose of 1 mg/kg of a ^{14}C-labeled commercial octaBDE mixture, radioactivity could be detected on day 1 in all tissues taken from the rats (Norris et al. 1975b). Similar findings were reported for rats treated with a commercial decaBDE mixture, although the levels of radioactivity found in the tissues were lower than in the rats treated with octaBDE (Norris et al. 1975b). On day 16 after dosing, the adrenals, adipose tissue, heart, and skin of the octaBDE-dosed rats had 0.14–0.25% of the administered dose per gram of tissue; lesser amounts were detected in the liver, pancreas, and spleen. In contrast, on day 16 after dosing, only the adrenals and spleen from decaBDE-treated rats contained radioactivity. These findings are consistent with the poor absorption and rapid fecal elimination shown by the decaBDE compound.

Norris et al. (1975b) also examined the bromine content of tissues from rats administered either octaBDE or decaBDE (1 mg/kg/day) in the diet for 90 days followed by an additional 90-day period on a control diet. During the recovery period, interim sacrifices were conducted on days 0, 10, 30, and 60. On recovery day 0, kidney and serum from rats treated with either mixture had the same amounts of bromine as their respective controls. However, adipose tissue of octaBDE- and decaBDE-treated rats had approximately 90- and 4-fold more bromine per gram of tissue than their respective controls. These levels remained practically unchanged over the 90-day recovery period. In the liver, the bromine content from decaBDE-treated rats was elevated on day 0 of recovery, but decreased and stabilized near control values after day 10 of the recovery period. Bromine in liver from octaBDE-treated rats was increased approximately 8-fold relative to controls on day 0 and decreased gradually to about half that amount by day 90 of recovery.

In a study of rats treated for 180 days with decaBDE or octaBDE in the diet, bromine in the liver from decaBDE-dosed rats was slightly higher than in control rats throughout the study period, whereas octaBDE-treated rats showed a gradual and significant increase in liver bromine levels reaching about 7 times those of controls by the 180th day (Norris et al. 1975b). Analysis of adipose tissue showed an even more pronounced accumulation of bromine in octaBDE-dosed rats and practically no accumulation in decaBDE-dosed rats. No significant accumulation of bromine was seen in serum, kidney, skeletal muscle, or kidneys.

Studies conducted with analytical-grade decaBDE also showed poor absorption of the compound. Twenty-four hours after feeding rats ^{14}C-decaBDE most of the radiolabel (82–86%) was recovered in the feces and gut contents (El Dareer et al. 1987). No tissue sampled had more than 0.5% of the administered dose. In general, the highest amounts were found in the liver, and rats fed a lower dose retained more

label in the tissues than rats fed a higher dose. The latter suggests that the percent of the dose retained decreases as the amount of decaBDE in the diet increases.

Administration of a single gavage dose of ^{14}C-2,2',4,4'-5-pentaBDE to rats resulted in preferential deposition of label in the carcass (38%), adipose tissue (38.%), and blood (1.4%) 72 hours after dosing (Hakk et al. 1999). No other tissue had more than 1% of the radioactivity at 72 hours. Fractionation of the carcass showed that the majority of the label was in the skin. When deposition was expressed as concentration, the lipid-rich tissues such as adipose tissue, skin, and adrenals contained the highest concentration of radioactivity.

Analysis of tissues from rats 5 days after administration of a single gavage dose of ^{14}C-2,2',4,4'-tetraBDE showed that adipose tissue had an approximately 70 times higher concentration of label than other tissues on a fresh weight basis and 3.5-fold higher on a lipid weight basis (Örn and Klasson-Wehler 1998). The lungs had the second highest concentration of radiolabel with approximately twice that in the liver and kidneys. In mice treated in the same fashion, adipose tissues also had the highest concentration of radioactivity, 10-fold higher than other tissues on a fresh weight basis. On a lipid weight basis, adipose tissue had a concentration of ^{14}C similar to liver and twice that in lung and kidney.

Treatment of pregnant rats by gavage with decaBDE on Gds 6–15 resulted in no significant increase in bromine content in the liver of fetuses on gestation day 21 relative to controls (Norris et al. 1975b). However, placental transfer cannot be totally ruled out since no other fetal tissue was examined.

3.4.2.3 Dermal Exposure

Polybrominated Biphenyls. No studies were located regarding distribution of PBBs in humans after dermal exposure.

Increased liver weight and necrosis were observed in rabbits after application of an unspecified hexabromobiphenyl mixture to the skin, suggesting that PBBs or metabolites reached that organ (Waritz et al. 1977). No further information was available.

Polybrominated Diphenyl Ethers. No studies were located regarding distribution of PBDEs in humans or animals after dermal exposure.

3.4.2.4 Other Routes of Exposure

Polybrominated Biphenyls. In general, the distribution pattern of PBBs after parenteral administration is similar to that obtained after oral exposure. In rats, immediately after intravenous injection of ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl adipose, skin, muscle, liver, and blood contained . 29, 20, 40, 10, and 1.5% of the dose, respectively (Matthews et al. 1977). Seven to 42 days postdosing, most of the residue in liver and muscle was redistributed to adipose tissue. The percent of the dose remaining in liver and muscle on day 42 was 0.8 and 3.5%, respectively. The concentration of radioactivity in skin remained relatively constant over a 42-day period. In a similar study in rats, the adipose/blood equilibrium distribution rate was found to be much higher than for any other tissue examined, and 4 days after dosing, adipose tissue contained $60% of the body burden (Tuey and Matthews 1980).

The elimination half-times from blood and several tissues were determined in rats administered a single intraperitoneal dose of 10 mg/kg FireMaster BP-6 (Miceli and Marks 1981). Elimination from serum followed first-order kinetics, and a half-time of 23.1 weeks was calculated over a 36-week period after dosing. Adrenal and adipose tissue had the highest PBB concentrations at week 6, and these levels were maintained throughout the 36-week observation period. Concentrations of PBBs were also elevated in the liver, lungs, and pituitary at week 6, whereas PBB levels in brain, kidney, and spleen were several-fold lower. Elimination half-times from adrenal, brain, fat, liver, lung, and spleen were 43.3, 63.0, 69.3, 11.5, 11.2, and 9.0 weeks, respectively. Elimination from heart, kidney, and pituitary did not appear to follow first-order kinetics; thus, elimination half-times from these tissues were not calculated. The concentration of PBB in adipose tissue was at least 4 times higher than in any other tissue, and unlike other tissues,

continued to increase, reaching a maximum at week 12 postdosing. The adipose/serum ratio of PBB concentration increased from 222 at 6 weeks to 722 at 36 weeks, reflecting the much more rapid elimination of PBB from serum than from adipose tissue. The investigators estimated that, given the elimination half-time from fat of 69 weeks, >1 μg/g of PBB would remain in fat by the time the rats reached 2 years of age, the end of their lifespans.

The distribution of PBB residues was also examined in pregnant mink and ferrets after injection of a mixture of 2,2'4,4',5,5'-hexabromobiphenyl and 2,2',3,4,4',5,5'-heptabromobiphenyl (Bleavins et al. 1980). Two hours after a single injection in the jugular vein on gestation day 37, the liver, kidney, and adipose tissue of ferret dams had 1.625, 0.108, and 0.124% of the dose/g tissue, respectively. PBB levels in fetal tissues did not exceed 0.013% of the dose (liver). In mink, PBB levels in maternal liver, kidney, and adipose tissue were 1.622, 0.087, and 0.031% of the dose/g tissue, respectively. Fetal liver had the highest amount of PBBs, 0.005% of the dose. In a different experimental series, the investigators (Bleavins et al. 1980) also showed that the dam's milk was the major route of offspring exposure since PBB levels, on a per gram or per kit basis, were significantly higher in 2-week-old kits than in newborn kits. The ratio of the 2-week PBB concentration to the birth concentration was 3.94/g and 36.66/kit. On a per kit basis, treated newborn kits accumulated 0.80% of the maternal dose through *in utero* exposure.

Polybrominated Diphenyl Ethers. No relevant information was located regarding distribution of PBDEs following exposure by non-natural routes of administration.

3.4.3 Metabolism

Polybrominated Biphenyls. Information regarding the metabolism of PBBs in humans is limited. Chromatographic analysis of serum samples from Michigan dairy farmers and from Michigan Chemical Corporation employees revealed some differences in peak profile between these two groups and between these two groups and the peak profile of FireMaster BP-6 (Wolff and Aubrey 1978; Wolff et al. 1979a). Farmers had a lower concentration of two pentabromobiphenyls relative to chemical workers and FireMaster BP-6. Both farmers and workers had a significant reduction in the amount of 2,2',3,4,4',5,5'-heptabromobiphenyl relative to FireMaster BP-6. Other minor differences between the groups were also apparent. The differences in peak profiles between farmers and chemical workers were attributed to different routes of exposure. Farmers had predominantly dietary exposure to PBBs which, according to the authors (Wolff and Aubrey 1978), could have undergone partial metabolism in the animal food source (see below). It should be noted that chemical transformation of the PBBs due to

cooking of meat or pasteurization of milk should not be expected since the temperatures reached during these processes is probably not high enough. As discussed in Chapter 4, temperatures must exceed .500 EC for structural alterations of PBBs to occur. Nevertheless, a significant reduction (36–52%) in the concentration of PBBs in pressure-cooked meat relative to raw meat (due to loss of fat) has been reported (Zabik et al. 1978). The decreased heptabromobiphenyl peak in farmers and workers relative to FireMaster BP-6 may reflect poor absorption of this congener since it is not expected to be metabolized readily (Wolff and Aubrey 1978; Wolff et al. 1979a).

Human exposure to PBBs in the Michigan contamination episode occurred primarily through consumption of contaminated meat and dairy products. The limited information available regarding the metabolism of PBBs in dairy cattle is insufficient to ascertain whether humans ingested PBBs or metabolic products of PBBs. In a controlled study, cows fed single or repeated doses of FireMaster BP-6 excreted 50% of the dose in the feces as parent compound (Willet and Durst 1978). Tissues, feces, or urine were not analyzed for metabolites. Results of studies in rats, and also *in vitro* studies (see below), have shown that highly brominated PBB congeners, such as the major components of FireMaster BP-6, undergo little or no metabolic transformation. Based on the existing information, it seems reasonable to assume that in the Michigan contamination episode, humans consumed mainly unchanged penta-, hexa-, and heptabromobiphenyls.

The *in vivo* metabolism of some PBB congeners and of commercial PBB mixtures has been investigated in a limited number of animal studies. For example, in pigs, intraperitoneal injection of 4-bromobiphenyl yielded three urinary metabolites: 4'-bromo-4-biphenylol (3% of the dose), bromobiphenylol (traces), and 4'-bromobiphenylol (0.5% of the dose) (Kohli and Safe 1976). 4,4'-Dibromobiphenyl yielded four urinary metabolites: 4,4'-dibromo-3-biphenylol (5% of the dose), 3,4'-dibromo-4-biphenylol (1% of the dose), 4'-bromo-3-methoxy-4-biphenylol (1% of the dose), and traces of a dibromomethoxybiphenyl. The authors suggested these results indicate that metabolism of the 4,4'-congener occurs through the formation of an arene oxide. The major urinary metabolite of FireMaster BP-6 was a pentabromobiphenylol (1% of the dose), which could have resulted from direct hydroxylation of the minor pentabromobiphenylol isomers in FireMaster BP-6 or by debromination/hydroxylation of the major congener, 2,2',4,4',5,5'-hexabromobiphenyl.

In rabbits, metabolism of 2-bromobiphenyl yielded two polar metabolites, one metabolite was identified as 2'-bromo-4-biphenylol (1% of the dose), and the other metabolite (traces) was also a monohydroxylated derivative, but the position of the hydroxyl group was not determined (Kohli et al.

1978). 3-Bromobiphenyl produced a major metabolite (4% of the dose) identified as either 3-bromo-4-biphenylol or 5-bromo-2-biphenylol; a minor dihydroxylated metabolite was also detected. 4-Bromobiphenyl yielded two metabolites: 4'-bromo-4-biphenylol (2% of the dose) and 4'-bromo-3,4-biphenyldiol (1.5% of the dose). Experiments with tritiated 4-bromobiphenyl suggest that the metabolism of this congener involves the formation of an arene oxide.

Similar results have been reported in rats (Sparling et al. 1980). 4'-Bromo-4-biphenylol was the major metabolite of 4-bromobiphenyl. 2-Bromobiphenyl was metabolized to 2-bromo-4,4'-biphenyldiol and 2-bromo-4',5-biphenyldiol; 2-bromo-5-biphenylol was a minor metabolite. 3-Bromobiphenyl also yielded diols as major metabolites: 3-bromo-4,4'-biphenyldiol and an unknown diol. The main conclusions of this experiment were: the major site of hydroxylation is at the *para* position of the unsubstituted phenyl ring, and also at the *para* position of the ring for the 2- and 3-brominated congeners; substitutions in positions 2 and 3 tend to direct hydroxylation to position *para* and *ortho* (minor) to the substituents; and the 2- and 3-hydroxylated products are subsequently dehydroxylated, whereas the 4'-hydroxy congener is not.

In contrast to the lower brominated congeners, no major metabolites were identified in the urine or feces of rats treated with a single intraperitoneal dose of 2,2'4,4'5,5'-hexabromobiphenyl, suggesting that this congener is stable and persistent (Safe et al. 1978). Analyses of the feces of dogs administered FireMaster BP-6 orally revealed the presence of a metabolite identified as 6-hydroxy-2,2',4,4',5,5'-hexabromobiphenyl (Gardner et al. 1979). This metabolite was not found in the liver, but the parent compound was identified. Since hydroxylation in position 6 of highly substituted congeners is unlikely, it was postulated that the metabolite found in the feces was formed by microbial metabolism of the PBB in the intestinal tract. The *in vitro* metabolism of 2,2',4,4',5,5'-hexabromobiphenyl with liver microsomes of rats induced with either 2,2',4,4',5,5'-hexabromobiphenyl or FireMaster BP-6 produced three major metabolic fractions: lipophilic ether soluble polar metabolites, trichloroacetic acid (TCA) soluble conjugates, and macromolecular adducts (Purdy and Safe 1980).

The NADPH-dependent metabolism of a PBB mixture was studied *in vitro* with liver microsomes of rats induced with PB, PBB, or 3-MC (Dannan et al. 1978a). Of the 12 major components of the mixture, only 2,2',4,5,5'-pentabromobiphenyl and a hexabromobiphenyl were metabolized by microsomes from PB- or PBB-treated rats. Of seven structurally identified PBB components, only 2,2',4,5,5'-pentabromobiphenyl had a bromine-free *para* position. Although 2,2',4,5,5'-pentabromobiphenyl, 2,3',4,4',5-pentabromobiphenyl, and 2,2',3,4,4',5'-hexabromobiphenyl have two adjacent unsubstituted carbons, only

2,2',4,5,5'-pentabromobiphenyl was metabolized. No significant metabolism occurred when the PBB mixture was incubated with microsomes of control rats or MC-induced rats. When 2,2'- and 4,4'-dibromobiphenyl were incubated with liver microsomes of PB-treated rats, only the 2,2'-congener was metabolized. These results suggest that the presence of a free *para* position is required for the metabolism of brominated biphenyls and that the bromine content of the molecule is less important in determining metabolism than the position of bromines on the biphenyl nucleus.

A more recent study with hepatic microsomes of induced rats showed that MC pretreatment increased the NADPH-dependent metabolism of PBB congeners (di-, tri-, and tetrabrominated), which had adjacent unsubstituted *ortho* and *meta* positions on at least one ring (Mills et al. 1985). Some penta- and hexabromobiphenyls that have adjacent unsubstituted *ortho* and *meta* positions were not metabolized, suggesting that further bromination prevents metabolism. Pretreatment with PB increased the microsomal metabolism of congeners that have adjacent unsubstituted *meta* and *para* positions on at least one ring. It was concluded that the rates of metabolism of PBB congeners depends on the position of the bromines and the form of the cytochrome P-450 induced. The ability to metabolize PBBs also depends on the species. For example, hepatic microsomes isolated from rats have a greater potential to metabolize PBBs than hepatic microsomes isolated from pigeons (Borlakoglu and Wilkins 1993).

Polybrominated Diphenyl Ethers. Three main metabolic peaks were identified in the feces from rats fed reagent-grade decaBDE for 8 days (El Dareer et al. 1987). Of the total decaBDE-derived radioactivity recovered in the feces, 1.5–27.9% constituted metabolites. Since absorption of decaBDE is minimal, El Dareer et al. (1987) suggested that metabolism apparently took place in the gastrointestinal tract. In parallel experiments in rats injected ^{14}C-decaBDE intravenously, feces and gut contents contained 74% of the administered radioactivity 72 hours after the injection, and 63% of the excreted material was metabolites. In rats dosed intravenously with ^{14}C-decaBDE and with biliary cannulas, 7.17% of the dose appeared in the bile, and <1% of this amount was unchanged decaBDE. Only one metabolite was detected. The structure of the metabolites detected in these experiments was not defined.

Analysis of fecal extracts of rats administered a single gavage dose of ^{14}C-2,2',4,4',5-pentaBDE showed, after methylation, the presence of two monomethoxy pentaBDE metabolites and two de-brominated monomethoxy tetraaBDE metabolites (Hakk et al. 1999); however, the precise structure of these metabolites could not be determined. Less than 10% of the radiolabel was found in these metabolites and >90% was present as parent compound. In rats with cannulated biliary ducts, the investigators identified two monohydroxypentaBDE metabolites and two dihydroxypentaBDE metabolites. No glucuronide or

sulfate conjugates were found in the bile. There was some evidence suggesting the presence of a thio-substituted pentaBDE possibly formed through the mercapturic acid pathway.

Five metabolites were detected in the feces of rats and mice collected over a 5-day period after administration of a single dose of ^{14}C-2,2',4,4'-tetraBDE (Örn and Klasson-Wehler 1998). Although the precise structure was not identified, the data suggested that the metabolites were hydroxylated derivatives of tetraBDE. An additional metabolite, possibly a methyl thio-substituted tetraBDE, was also detected in the feces. Yet, at least 85% of the radioactivity in the feces corresponded to the parent compound. A water-soluble metabolite was detected in urine from mice, but could not be isolated. Unchanged tetraBDE was also the major compound in all tissues analyzed, but minor amounts of hydroxylated tetraBDE metabolites were detected.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion of PBBs or PBDEs in humans or animals after inhalation exposure.

3.4.4.2 Oral Exposure

Polybrominated Biphenyls. No studies were located that provide information on percentage of ingested PBBs excreted by humans. However, PBBs in biliary fluid of a group of farmers and chemical workers ranged from undetected to 70 µg/L, and the correlation between serum PBB levels and levels in bile was statistically significant (Eyster et al. 1983). Similarly, PBB levels in feces ranged from undetected to 862 µg/kg, and the correlation between serum PBB levels and fecal levels was also statistically significant (Eyster et al. 1983).

Serum half-life values have been estimated using human data from the Michigan PBB cohort (Lambert et al. 1990; Michels Blanck et al. 2000b; Rosen et al. 1995). A median half-life of 12.0 years (95% CI 4–97 years) was estimated based on two serum measurements from 15 women ($20 years of age) with an initial serum PBB level of $5 ppb (Lambert et al. 1990). An analysis of 51 women ($18.8 years of age) and 112 men ($18.1 years of age) with at least two measurements 1 year apart and an initial PBB level of $20 ppb found a median half-life of 13.0 years (95% CI 6.3–infinite years) and 10.0 years (95% CI 6.7–20.0 years), respectively (Rosen et al. 1995). Based on a median half-life of 10.8 years (95% CI 9.2–14.7 years) for the entire group (163 persons, median PBB level 45.5 ppb), it was estimated that it will take more than 60 years for their PBB levels to fall below a detection limit of 1 ppb.

Determinants of PBB serum decay were investigated in 380 Michigan women ($16 years of age) who had an initial PBB level of at least 2 ppb and at least two measurements taken when they were not pregnant (Michels Blanck et al. 2000b). The mean initial PBB level was 20.9 ppb (standard deviation 78.7), and the mean time between the first and last measurement was 4.2 years (range 16.0–75.2 years). A total of 109 women (29%) did not have a reduction in serum PBBs over time. Assuming that PBBs reached equilibrium in the body before substantial amounts were eliminated and before the first serum measurements were taken, the entire body was modeled as a single compartment for PBBs with exponential decay. The median PBB half-life in the entire group was 13.5 years (95% CI 10.5–23.2 years). Subject-specific decay rate estimates were regressed on predictor variables including initial age, body mass index (BMI), smoking history, breast-feeding duration, and parity. The serum PBB decay rate was slower, resulting in a longer half-life, with higher initial PBB levels; women with initial PBB levels of <10 and >10 ppb had median half-lives of 12.9 and 28.7 years, respectively. The PBB decay rate was also slower (p=0.03) in women with an initial BMI above the median (BMI$23). Increasing number of pregnancies between the first and last measurement was also associated with slower decay, but the effect was of borderline statistical significance (p=0.06). Breast feeding as either a

continuous variable or as categorized by tertiles of duration (<3, 3–9, or >9 months), age, and smoking were not associated with serum PBB decay.

Lactation constitutes the most important route of excretion of PBB in lactating women. Numerous studies reported PBB levels in breast milk from Michigan women (Brilliant et al. 1978; Eyster et al. 1983; Humphrey and Hayner 1975; Jacobson et al. 1984; Landrigan et al. 1979). PBB levels in breast milk on a lipid basis ranged from undetected to 92,667 µg/kg, with a median of 250 µg/kg, in a group of parturient women from Michigan (Eyster et al. 1983). Regression analysis of the data revealed that on a lipid basis, PBBs are 107–119 times more concentrated in milk than in serum. Also, adipose PBB levels are 1.1–1.5 times higher than the breast milk levels when milk levels were $100 µg/kg.

The importance of PBB transfer through lactation in experimental animals is discussed in Section 3.4.2.2.

There is limited information regarding excretion of PBBs in experimental animals. Rats dosed once with ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl excreted 7.9% of the dose in the feces within the first 24 hours; urinary excretion data were not provided (Matthews et al. 1977). It was estimated that <10% of the administered dose would ever be excreted. These results are consistent with those of other investigators who report that this congener is stable and persistent (Safe et al. 1978). In rats gavaged with ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl for 22 days, between 10 and 20% of the daily dose was excreted daily in the feces; this value was predominantly due to elimination of unabsorbed PBB (Tuey and Matthews 1980). In monkeys, the main route of excretion of hexabromobiphenyl residues was also in the feces (Rozman et al. 1982). Between 60 and 70% of the administered dose was excreted in the feces in the first 11 days after dosing; urinary excretion was minimal. The difference between the absorption rate reported by Matthews et al. (1977) and that reported by Rozman et al. (1982) can probably be accounted for by differences in the experimental designs.

Rats treated with a single gavage dose of ^{14}C-octabromobiphenyl excreted <1% of the administered dose in urine and expired air over a 16-day period (Norris et al. 1975a). Within the first 24 hours after dosing, 61.9% of the dose was present in the feces. The proportion that represents unabsorbed PBB is not known. By day 16, 74% of the administered dose had been recovered in the feces.

Polybrominated Diphenyl Ethers. Elimination half-lives for components of a commercial pentaBDE mixture (Bromkal 70) from perirenal fat of rats were estimated to be between 19 and 111 days (von Meyerinck et al. 1990). The rats were administered a single gavage dose of 300 mg/kg of the mixture and

analyses of perirenal fat were conducted for up to 70 days after dosing. Analysis of the mixture, revealed at least seven components: one tetraBDE, three pentaBDEs, and three hexaBDEs, but the stereochemistry of the individual compounds was not ascertained. In general, the elimination half-lives increased as the degree of bromination increased. Also, no significant differences were observed between male and female rats with the exception of the tetraBDE, which exhibited a significantly higher elimination half-life in female rats.

In rats treated by gavage with a single 1 mg/kg dose of commercial ^{14}C-decaBDE or octaBDE mixtures, most of the excreted radioactivity measured over a 16-day period was in the feces and <1% of the label was detected in the urine and expired air (Norris et al. 1975b). No significant differences in excretion patterns were observed between males and females, but the excretion rate of decaBDE was very different than that of octaBDE. Approximately 91% of the decaBDE-derived radioactivity was found in the feces in the first 24 hours and almost all radioactivity (>99%) was accounted for by day 2 after dosing. In contrast, approximately 62% of the administered radioactivity derived from octaBDE was detected in the feces after the first 24 hours, after which time, an additional 11% of the label was slowly eliminated over the next 15 days. At the end of the study period, 26.4% of the octaBDE-derived radioactivity had not been recovered in the excreta. The investigators estimated an elimination half-life of <24 hours for decaBDE; octaBDE had an initial phase half-life of <24 hours and a second phase half-life of >16 days. A more recent study with ^{14}C-decaBDE in rats found that >9% of the dose was excreted in the bile over a 72-hour period following dosing compared to #0.02% in the urine (Hakk et al. 2000).

In an acute feeding study in rats fed analytical-grade decaBDE for 12 days and ^{14}C-decaBDE on day 8, recovery of radioactivity in the feces on days 9–12 ranged from 91.3 to 101% of the amount ingested (El Dareer et al. 1987).

The feces was the major route of elimination of 2,2',4,4',5-pentaBDE in rats administered a single dose of the ^{14}C-labeled compound (Hakk et al. 1999). Over a 72-hour period, <1% of the administered dose was recovered in the urine and approximately 42% in the feces. In rats with cannulated bile ducts, <0.4% was detected in the urine and about 87% in the feces over the same period of time.

Rats given a single gavage dose of 14.6 mg/kg of ^{14}C-2,2',4,4'-tetraBDE excreted 14% of the dose in the feces and <0.5% in the urine over a five day period (Örn and Klasson-Wehler 1998). Mice treated in the same manner excreted 20% of the dose in the feces and 33% in the urine over the same time period. The amount of non-absorbed material in the feces on day 1 was approximately 5 and 7% of the dose in rats

and mice, respectively, suggesting efficient absorption in both species (Örn and Klasson-Wehler 1998). The results also suggest that mice have a more efficient metabolism and excretion of tetraBDE than rats.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of PBBs or PBDEs in humans or animals after dermal exposure.

3.4.4.4 Other Routes of Exposure

Polybrominated Biphenyls. Rats given a single intravenous dose of ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl excreted a cumulative 0.96, 3.3, and 6.6% of the dose in the feces 1, 7, and 42 days after dosing, respectively (Matthews et al. 1977). Only traces (0.1% of the dose) were excreted in the urine. Two decay components were calculated from excretion data; an initial decay rate of 1.05% of the dose/day and a later rate of 0.15% of the dose/day. Biliary excretion accounted for 0.68% of the dose between 0 and 4 hours after dosing. Analysis of bile and feces showed that at least 95% of the radioactivity corresponded to the parent compound. Moreover, in rats, . 35% of the radioactivity excreted in the bile during the first week after a single dosing was reabsorbed (Tuey and Matthews 1980).

Parenteral administration of mono- and dibromobiphenyls to rats, rabbits, and pigs suggests that the urine is an important route of excretion for polar metabolites (Kohli and Safe 1976; Kohli et al. 1978; Sparling et al. 1980). However, cumulative urinary excretion did not account for more than 5% of the administered doses. Data regarding fecal excretion were not provided.

Polybrominated Diphenyl Ethers. No relevant information was located regarding elimination of PBDEs following exposure by non-natural routes of administration.

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 in risk assessment 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.

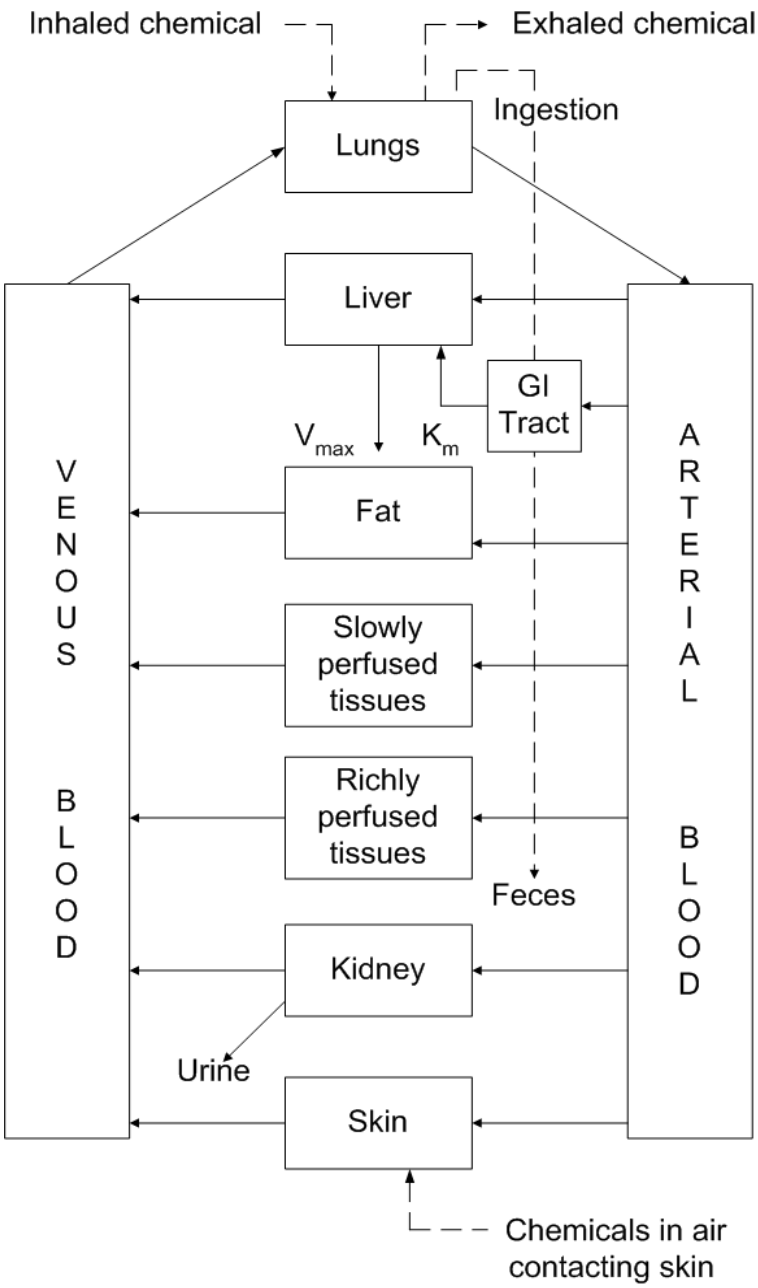
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for

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. PBPK models also provide a basis for extrapolating better toxicity values for use in human risk assessment. Figure 3-3 shows a conceptualized representation of a PBPK model.

Polybrominated Biphenyls. A PBPK model that incorporates tissue volume, affinity for PBBs, and rate of perfusion was developed to describe the distribution and body burden of the major component of FireMaster PBB mixtures, 2,2',4,4',5,5'-hexabromobiphenyl, in the rat (Tuey and Matthews 1980). The modeling methods are an extension of those used to predict the disposition of PCBs (Matthews et al. 1977). The model predicts that at equilibrium, changes in the PBB concentration or changes in tissue volume of any tissue will lead to a corresponding change in all tissues. For example, if the concentration of a PBB congener in the liver is reduced by metabolism or excretion, then the concentration of that PBB congener in all tissues will be reduced proportionally. Congeners that cannot be readily metabolized (as is the case for 2,2',4,4',5,5'-hexabromobiphenyl) 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 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. In rats orally dosed daily with ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl over a 30-day period, tissue concentrations on day 31 were (in increasing order): blood, muscle, liver, skin, and adipose, and were in general agreement with those predicted by the PBPK model. When the model was scaled to nonlactating humans by adjusting for tissue volume, blood flow, and clearance and rate constant parameters, human intake of 9.8 g of the congener from milk consumption over a 230-day period would result in peak concentrations of 720 and 2.1 ppm in fat and blood, respectively. The model also predicted that the body burden after 5 years would be 5.2 g and the half-life 6.5 years. The half-life of 6.5 years predicted using the rat-based PBPK model is shorter than half-life values estimated using human sera

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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 via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

data from the Michigan PBB cohort (Lambert et al. 1990; Michels Blanck et al. 2000b; Rosen et al. 1995), as discussed in Section 3.4.4 (Elimination and Excretion).

Polybrominated Diphenyl Ethers. No PBPK/PD models were located for PBDEs.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Polybrominated Biphenyls. The mechanism by which PBBs enter the blood stream from the lungs, skin, or gastrointestinal tract is not known and little information is available on how PBBs are distributed in the body. The available data indicate that the absorption mechanism is likely passive diffusion. Results from studies of Michigan subjects showed that in the blood stream, 80% of the PBBs was bound to protein and 20% was associated with lipids (Greaves et al. 1984). Of the fraction bound to protein, 73% was bound to apolipoprotein B and the remaining percent was bound to apolipoprotein A. In an *in vitro* model, shown to be representative of environmentally contaminated blood, the distribution of PBBs among plasma, erythrocytes, mononucleocytes, and polymorphonucleocytes was 89:9:<1:<1, respectively (Roboz et al. 1985).

In an *in vitro* study in an adipocyte cell line (3T3L1 cells), >75% of the 2,2',4,4',5,5'-hexabromobiphenyl taken up by the cells was associated with subcellular fractions that contained 85% of the cellular triglyceride, with only 20% of the compound found in the microsomal plasma-membrane fraction (Kraus and Bernstein 1986). This study also found that inhibition of respiration by cyanide at a concentration that completely inhibited oxygen consumption did not affect uptake of 2,2',4,4',5,5'-hexabromobiphenyl, supporting the assumption that because of their lipophilic nature, PBBs penetrate membranes by passive diffusion.

Polybrominated Diphenyl Ethers. No studies were located regarding pharmacokinetic mechanisms for PBDEs.

3.5.2 Mechanisms of Toxicity

PBBs and PBDEs share some toxicological properties with other structurally similar compounds, particularly PCBs, chlorinated dibenzo-*p*-dioxins (CDDs), and chlorinated dibenzofurans (CDFs) (Agency for Toxic Substances and Disease Registry 1994, 1998, 2000). However, for PBDEs, the introduction of the ether bridge makes the classification of congeners as either "dioxin-like" or "nondioxin-like" less unequivocal. Studies of structure-induction properties, structure-affinity binding properties, and structure-toxicity (with polychlorinated diphenyl ethers [PCDEs]) properties suggest that some *ortho* substituted PBDE (or PCDE) congeners can exhibit stronger affinity for the Ah receptor and exhibit stronger dioxin-type toxicity than their corresponding non-*ortho* substituted analogs (Chen et al. 2001; Howie et al. 1990). For example, 3,3',4,4'-tetraCDE was less immunotoxic and a less potent inducer of EROD and aryl hydrocarbon hydroxylase (AHH) than 2,3',4,4',5-pentaCDE (Howie et al. 1990). This is contrary to what would have been expected for the corresponding PCB or PBB congeners. This has been attributed to the greater distance between the two biphenyl rings in PBDE or PCDE congeners, relative to PCBs or PBBs. In other words, introduction of *ortho* substitutions into PBDEs or PCDEs does not create a spatial impediment for the two phenyl rings to assume a semi-flat position respect to each other as it does for PCBs or PBBs. This has implications not only for dioxin-type toxicities, but also for nondioxin-type toxicities. For example, studies have shown that mono- and diortho-substituted PCBs exhibit neurotoxic properties and structure-activity relationships for various neurological end points have been established (see Agency for Toxic Substances and Disease Registry 2000 for details). Although structure-activity relationships have not yet been fully examined for PBBs or PBDEs, it is reasonable to speculate that mono- and diortho-substituted PBDEs may not necessarily follow the neurotoxic potency rankings constructed with mono- and diortho-substituted PCBs.

There are also geometrical differences in PCBs, PBBs, and PBDEs due to the higher atomic weight and considerably larger molecular volume of bromine compare to chorine (Hardy 2000, 2002). These differences contribute to dissimilar physical/chemical properties that can influence the relative bioavailability, absorption, tissue accumulation, receptor interactions, and toxicities of the chemicals. For example, a comparison of a series of isosteric 3,3',4,4'-tetrahalobiphenyls in rats showed that relative toxicity (growth rate and thymic atrophy), Ah receptor binding affinity, and AHH and EROD induction potencies increased with increasing bromine substitution (Andres et al. 1983). Possible explanations for this effect included the increased polarizability of bromine versus chlorine and differences in the electronic, hydrophobic, and hydrogen bonding characteristics of bromine and chlorine (Andres et al. 1983).

Polybrominated Biphenyls. The mechanism of toxicity for PBBs has been extensively studied, but is not completely understood (Akoso et al. 1982a, 1982b; Andres et al. 1983; Dannan et al. 1982a, 1982b; Goldstein et al. 1979; Parkinson et al. 1983; Render et al. 1982; Robertson et al. 1982; Safe 1984). Many PBBs, PCBs, chlorinated dibenzo-*p*-dioxins (CDDs), chlorinated dibenzofurans (CDFs), and other structurally related halogenated aromatic hydrocarbons are believed to share a common mechanism of action strongly related to similarities in their structural configuration. Most of what is known regarding the mechanism of action of these compounds is based on structure-receptor binding relationships, structure-induction relationships, and structure-toxicity relationships (Goldstein and Safe 1989; Safe 1990). Most of the studies providing this information used parenteral routes of exposure and/or *in vitro* test systems, as explained below. It is beyond the scope of this profile to discuss these studies in detail.

A limited number of studies have shown that some PBB congeners bind to a cellular receptor (Ah [aryl hydrocarbon] receptor), which regulates the synthesis of a variety of proteins. This receptor was identified in the cytosol of mouse liver cells (Poland et al. 1976) and, subsequently, in extrahepatic tissues of laboratory animals, mammalian cell cultures, and human organs and cell cultures (Goldstein and Safe 1989). The structure-binding relationships for the coplanar 3,3',4,4',5-pentabromobiphenyl, the monoortho substituted congener 2,3,3',4,4',5-hexabromobiphenyl, and the diortho substituted analog 2,2,'5,5'-tetrabromobiphenyl were examined in rat liver cytosol (Safe et al. 1985). At PBB concentrations 1,000-fold (10 μM) greater than tetrachlorordibenzo-*p*-dioxin (TCDD) concentrations (10 nM), the coplanar congener completely displaced radiolabeled 2,3,7,8-TCDD from the cytosolic Ah receptor protein, the monoortho analog partially displaced the radiolabel, and 2,2,'5,5'-tetrabromobiphenyl was the least active competitor. The latter congener is relatively nontoxic and does not induce AHH. The Ah-binding characteristics of 3,3',4,4'-tetrabromobiphenyl and 3,3'4,4'5,5'-hexabromobiphenyl, both coplanar, were also examined in rat and mice liver cytosol (Millis et al. 1985). The results showed than the tetrabromobiphenyl was 10 times more effective than the hexabromobiphenyl in displacing radiolabeled 2,3,7,8-TCDD from the receptor. The stereospecific nature of the binding (high affinity seen with congeners substituted in both *para* and two or more *meta* positions) strongly suggests that a biological receptor mediates the responses caused by some PBBs.

The ability of PBBs to induce hepatic Phase I xenobiotic metabolizing enzymes (cytochrome P-450-dependent monooxygenases) is well documented (Dannan et al. 1978b, 1982a, 1982b, 1983; Ecobichon et al. 1979; Moore et al. 1978, 1979; Parkinson et al. 1983; Robertson et al. 1982; Schramm et al. 1985). PBB mixtures were classified as "mixed-type" inducers of hepatic microsomal monooxygenases and resembled a mixture of phenobarbital (PB)-like plus 3-methylcholanthrene (MC) as inducers of P-450

isozymes from CYP1A and CYP2B families. The CYP1A1 and CYP1A2 genes are induced by Ah receptor agonists, such as 2,3,7,8-TCDD and MC, and the structure-induction relationships for PBBs as inducers of these P-450 isozymes and their related activities have also been determined (Dannan et al. 1983; Parkinson et al. 1983; Robertson et al. 1982). For example, when injected intraperitoneally to immature male Wistar rats, the coplanar derivatives, 3,4,4'-tri-, 3,4,4',5-tetra-, 3,3',4,4'-tetra-, 3,3',4,4'5-penta-, and 3,3',4,4',5,5'-hexabromobiphenyl had a pattern of induction resembling that of MC (Robertson et al. 1982). Similar type experiments have shown that monoortho-bromo-substituted analogs of the coplanar PBBs, such as 2,3',4,4'-tetra-, 2,3',4,4',5-penta-, and 2,3',4,4',5,5'-hexabromobiphenyl, exhibit a mixed-type induction activity and resemble FireMaster BP-6 in their mode of induction (Dannan et al. 1978b; Parkinson et al. 1983). Yet a third group of PBB congeners, the diortho-bromo analogs of the coplanar PBBs, resemble PB in their mode of induction (PB induces the CYP2B1 and CYP2B2 genes). Among the diortho-bromo-substituted PBBs studied are 2,2,'5,5'-tetra-, 2,2'4,5,5'-penta-, 2,2',4,4',5,5'-hexa-, and 2,2',3,4,4',5,5'-heptabromobiphenyl (Moore et al. 1979; Parkinson et al. 1983). Results from studies with some dibromobiphenyls revealed that 4,4'-dibromobiphenyl resembled PB in its mode of induction (Robertson et al. 1982), whereas 2,2'-dibromobiphenyl had no significant effect on hepatic microsomal drug-metabolizing enzymes (Moore et al. 1979). The results of these experiments indicated that coplanar PBB congeners substituted in both *para* and one or more *meta* positions are MC-type inducers, diortho substituted congeners are PB-type inducers, and monoortho analogs of the coplanar PBBs are mixed-type inducers. These results were qualitatively similar to those obtained with PCBs and support the idea of a common receptor-mediated mechanism of action for PBBs. PBBs are also efficacious inducers of hepatic phase II metabolizing enzymes such as glutathione transferases, UDP glucuronyl transferases, and epoxide hydrolase (Parkinson et al. 1983; Schramm et al. 1985). For example, when intraperitoneally injected in rats, FireMaster BP-6 efficaciously induced hepatic glutathione transferases while concomitantly depressing selenium-dependent glutathione perioxidase activity, an important antioxidant enzyme in the liver (Schramm et al. 1985).

Many studies that examined structure-induction relationships for several PBB congeners also studied structure-toxicity relationships. Thymus and spleen weight were significantly reduced in rats by a series of MC-type inducers (Robertson et al. 1982). Further experiments in rats revealed that of a series of PBB congeners, only MC-type inducers significantly decreased thymus weight and body weight; PB-type, mixed-type, and MC-type inducers increased relative liver weight (Parkinson et al. 1983). Results from feeding studies in rats indicate that 3,3',4,4',5,5'-hexabromobiphenyl (MC-type) and 2,2',4,4',5,5'-hexa-bromobiphenyl (PB-type) increased liver weight; however, only the MC-type inducer decreased body weight and thymic and splenic weight, and caused lymphocytic depletion in the thymus (Render et al.

1982). Similar results were obtained when the toxicities of 3,3',4,4'-tetrabromobiphenyl (MC-type) and 2,2'5,5'-tetrabromobiphenyl (weak PB-type) were compared in rats (Robertson et al. 1983a). Only 3,3',4,4'-tetrabromobiphenyl caused significant reductions in growth rate and thymus size and marked depletion of lymphocytes from the thymic cortex. Results from studies with FireMaster BP-6 revealed that the pattern of toxic responses and the magnitude of the responses attributed to this mixture are consistent with it being composed of both MC-type and PB-type congeners; the most toxic responses being attributed to the MC-type congeners (Akoso et al. 1982a, 1982b; Dannan et al. 1982a, 1982b; Ecobichon et al. 1979; Parkinson et al. 1983; Render et al. 1982). These results suggest a correlation between immunological and hepatic effects and the ability to induce AHH activity and that the most toxic congeners are those that resemble the structural configuration of 2,3,7,8-TCDD. This relationship further supports the idea of a common receptor-mediated mechanism of action. Other PBB congeners (*ortho*-substituted) induce other types of effects, such as neurotoxicity, by yet unknown but Ah receptor independent mechanisms.

Some information on structure-promotion relationships for PBBs is available from studies that used two-stage liver and skin carcinogenesis models. In the liver promotion studies, development of enzyme-altered hepatic foci (putative preneoplastic lesions) was assessed in rats that were partially hepatectomized, initiated with diethylnitrosamine and promoted with PBBs (Buchmann et al. 1991; Dixon et al. 1988; Evans and Sleight 1989; Jensen and Sleight 1986; Jensen et al. 1982, 1983; Sleight 1985). Both MC-type (3,3',4,4',5,5'-hexabromobiphenyl and 3,3',4,4'-tetrabromobiphenyl) and PB-type (2,2',4,4',5,5'-hexabromobiphenyl) congeners showed hepatic promoting activity with varying potencies, indicating that this response is partially Ah-receptor independent. FireMaster BP-6 was a more effective promoter than its major constituent congener 2,2',4,4',5,5'-hexabromobiphenyl (Jensen et al. 1982), which also indicates that other congeners are very effective as promoters, or possibly that the combination of congeners with mixed- or PB-type activity have a synergistic or additive effect. Although both MC- and PB-type congeners promote two-stage hepatic tumor activity, it appears that the MC-type congeners may exert their effects indirectly by causing hepatotoxic (cytotoxic effects and necrosis), whereas the PB-type congeners may act as mitogens (stimulate cellular growth and division). In a skin tumor assay, HRS/J hairless mice were initiated with MNNG and promoted with PBBs (Poland et al. 1982). FireMaster FF-1 and 3,3',4,4',5,5'-hexabromobiphenyl were effective skin tumor promoters, but 2,2',4,4',5,5'-hexabromo-biphenyl showed no activity, suggesting that, unlike rat liver tumor promotion, promoter activity in the mouse skin tumor model is Ah receptor-dependent. Another indication that promotion of tumors by PBBs is not solely an Ah-receptor mediated process is provided by the results of an *in vitro* gap junctional intercellular intercommunication assay (Kang et al. 1996). Gap junctional intercellular

intercommunication in normal human breast epithelial cells was inhibited by 2,2',4,4',5,5'-hexaCB in a dose-dependent manner, but not by the coplanar congener 3,3',4,4',5,5'-hexaCB. Inhibition of gap junctional intercellular communication is generally regarded as a mechanistic marker for tumor promotion (as well as several other toxicological end points).

Expression of the toxic response, which is species and strain dependent, is initiated by the binding of individual congeners with the Ah receptor. The responsiveness of a particular organ or cell depends on the affinity of the receptor for the ligand molecule (Goldstein and Safe 1989). For example, certain inbred strains of mice, typified by C57BL/6J, have a cytosolic Ah receptor protein with a relatively high binding affinity for inducers of benzo[a]pyrene hydroxylase such as 3-MC, ß-naphthoflavone, 2,3,7,8-TCDD, and other isostereomers of 2,3,7,8-TCDD. In contrast, other inbred mouse strains, such as DBA/2J, have reduced levels of the Ah receptor. Responsiveness to aromatic hydrocarbons is inherited in a simple autosomal dominant mode. Nonresponsiveness has been attributed to a mutation resulting in a receptor with a diminished affinity (Okey et al. 1989). This defective receptor is almost completely unresponsive to weak inducers such as 3-MC and has reduced sensitivity to more potent inducers such as 2,3,7,8-TCDD. Studies with PBBs have shown that treatment of C57BL/6J and DBA/2J with FireMaster BP-6 resulted in the induction of hepatic microsomal benzo[a]pyrene hydroxylase only in the C57BL/6J strain and aminopyrine N-demethylase (PB inducible) in both strains of mice (Robertson et al. 1984a). However, 3,3',4,4'-tetrabromobiphenyl, a more potent MC-type inducer than the BP-mixture, induced benzo[a]pyrene hydroxylase in both strains of mice but did not induce aminopyrine N-demethylase in either strain of mice. Also, after treatment with the dioxin-like congener 3,3',4,4'-tetrabromobiphenyl, thymic atrophy was only observed in the responsive strain (Robertson et al. 1984a). In general, studies summarized in Section 3.2 in which more than one strain was tested (mice or other species) do not address the possible strain-dependency of the toxic responses observed. It must be mentioned, however, that differences in the response between tissues, strains, or species, do not exclusively indicate differences in receptor affinities, but most likely reflect the fact that the battery of enzyme activities (see below) controlled by the Ah locus varies within the tissue, strain, and animal species.

Initial binding of a PBB congener to the Ah receptor is followed by an activation or transcription step and subsequent accumulation of occupied nuclear receptor complexes. These complexes interact with a specific DNA sequence in the CYP1A1 gene (which regulates the expression of cytochrome P-450IA1 isozymes), changing its secondary or supersecondary structure (Elferinck and Whitlock 1990), which leads to enhancement of the CYP1A1 gene expression. A specific nucleotide sequence present in multiple copies to which the nuclear complex binds has been identified (Denison et al. 1989). Ultimately,

newly synthesized enzymes and macromolecules resulting from the pleiotropic response to the PBB-receptor complex are believed to be responsible for many of the effects caused by PBBs and other halogenated aromatic hydrocarbons (see Chapter 2).

No studies were located regarding the mechanism of endocrine effects (thyroid toxicity, estrogenicity) of PBBs.

Polybrominated Diphenyl Ethers. Some PBDEs have been shown to bind to the Ah receptor in a limited number of studies. For example, Meerts et al. (1998) indirectly examined the Ah receptor-mediated properties of 17 PBDE congeners in a recombinant H4II rat hepatoma cell line showing Ah receptor mediated expression of a luciferase reporter gene. The tested congeners varied from dibromo-substituted to heptabromo-substituted, and with the exception of 4,4'-diBDE and 3,3',4,4'-tetraBDE, all had at least one *ortho* substitution. Seven of the congeners showed luciferase expression, indicating their ability to activate the Ah receptor. The only discernable pattern of receptor activation that appeared to emerge from these results was that greater receptor activation was obtained with the penta- and hexaBDEs than with tri- and tetraBDEs. More recently, Chen et al. (2001) studied the affinities of a series of 18 PBDE congeners and 3 commercial PBDE mixtures for rat hepatic Ah receptor through competitive binding assays. The analysis showed that both the congeners and mixtures had binding affinities 10^{-2}–10^{-5} times that of 2,3,7,8-TCDD. The congener with the highest affinity among the tested congeners was 2,2',3,4,4'-pentaBDE, although its relative binding affinity was only 2% that of 2,3,7,8-TCDD. No binding activity could be determined for a decaBDE mixture. In contrast with PCBs, the binding affinities did not appear to relate to the planarity of the molecule, which according to Chen et al. (2001), was possibly due to the fact that the large size of bromine atoms expands the Ah's receptor binding site.

The enzyme induction properties of PBDEs have been less studied than for other structurally similar chemicals, but the existing information suggests that they can be classified as mixed-type inducers of hepatic microsomal monooxygenases (Darnerud et al. 2001; de Wit 2002; Hardy 2002b). Few studies have examined the structure-induction relationships for PBDEs. Chen et al. (2001) examined the ability of 12 PBDE congeners and 3 commercial mixtures to induce EROD activity in chick and rat hepatocytes, in liver cell lines from rainbow trout, rat, and human, and in a human intestinal cell line. The number of bromine substitutions in the congeners tested ranged from 3 to 7. In all cell types, 3,3',4,4'-tetraBDE, 2,2',4,4',6-pentaBDE, 2,3',4,4'-tetraBDE, and 3,3',4,4',5-pentaBDE were the strongest inducers. Congeners 2,2',4,4',5,5'-hexaBDE and 2,2',3,4,4',5',6-heptaBDE were weak inducers in all cell types, whereas 2,3',4,4'-tetraBDE and 2,2', 3,4,4'-pentaBDE were very weak inducers in rat hepatocytes and

inactive in the other cells. Congeners 2,2',4,4'-tetraBDE and 2,2'4,4',5-pentaBDE, which are prominent in the environment, were not inducers in any cell line, and neither were 2,4,4'-triBDE, 2,2',4,4',5,6'-hexa-BDE, or the penta-, octa-, or decaBDE mixtures. For those congeners that had measurable EROD induction activity, their relative potencies were 10^{-3}–10^{-6} that of 2,3,7,8-TCDD. In general, the EROD induction activity paralleled the strength of the Ah receptor binding with the notable exception of 2,2',3,4,4'-pentaBDE, which despite its relatively strong Ah receptor binding affinity (see above), showed no evidence of activating the Ah receptor to its dioxin-response element (DRE) binding form and was only a weak EROD inducer.

Studies on structure-toxicity relationships have not been conducted, but relevant information is available for PCDEs. Howie et al. (1990) examined the immunotoxic potencies of various PCDE congeners on the inhibition of the splenic PFC response to SRBC antigen and found the following potency order: 2,3,3',4,4',5-hexaCDE > 3,3',4,4',5-pentaCDE > 2, 3',4,4',5-pentaCDE > 3,3',4,4'-tetraCDE > 2,2',4,4',5,5'-hexaCDE > 2,2',4,5,5'-pentaCDE > 2,2',4,4',5,6'-hexaCDE. In general, this potency order paralleled their potencies as inducers of hepatic microsomal AHH and EROD. Worth noticing is the fact that the resulting ranking order of potency did not follow the order that would have been expected for a response known to be Ah receptor-mediated, such as the inhibition of the PFC response to challenge with SRBC antigen. For example, the coplanars 3,3',4,4'-tetraCDE and 3,3',4,4',5-pentaCDE were less immunotoxic than their respective monoortho-substituted analogs; this was true also for their enzyme induction potencies. These findings showed that increasing *ortho*-substitution is less effective in reducing the "dioxin-like" activity of these compounds. Howie et al. (1990) suggested that the ether bridge in the polyCDE molecules increases the bond length between the two phenyl rings, thus diminishing the effects of *ortho* substituents on the biochemical and toxic potencies of these compounds.

Evidence for thyroid hormone involvement in PBDE toxicity includes observations in rats and mice that were orally exposed to commercial mixtures of deca-, octa-, or pentaBDE (see Section 3.2.2.2, Endocrine Effects). The main findings include (1) histological changes in the thyroid indicative of glandular stimulation (e.g., follicular cell hyperplasia similar to that induced by a hypothyroid state) (IRDC 1976; Norris et al. 1973, 1975b; NTP 1986; WIL Research Laboratories 1984), and (2) decreased serum thyroxine (T_4) levels with no changes in serum TSH (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998;WIL Research Laboratories 1984; Zhou et al. 2001, 2002). Considering these data, the structural resemblance of PBDEs to T_4, and information from studies of individual congeners as summarized below, it appears that, depending on dose, duration, and mixture/congener, PBDEs can disrupt the production, transport, and disposition of thyroid hormones.

The mechanism(s) by which PBDEs decrease serum levels of T_4 is not completely characterized, but appears to involve induction of hepatic microsomal enzymes, which could lead to increased metabolic clearance of thyroid hormones and increased binding affinity to thyroid hormone receptors and transport proteins. The apparent lack of effect of PBDEs on TSH levels suggests that direct effects on the thyroid leading to inhibition of T_4 synthesis are unlikely. The induction of hepatic UDPGT by PBDEs has been demonstrated in several studies (Fowles et al. 1994; Hallgren et al. 2001; Zhou et al. 2001, 2002) and this could increase the UDPGT-catalyzed deactivation and excretion of T_4 (i.e., the conjugation of T_4 with glucuronic acid). An indication that increased UDPGT activity may not be the main mechanism for the reduced T_4 levels is provided by Hallgren et al. (2001), who found that exposure to $18 mg/kg/day pentaBDE for 14 days caused serum T_4 reductions in both mice and rats with no effect on UDPGT activity in the mice and increased UDPGT in the rats only at higher dose levels. In contrast, the decreases in serum T_4 correlated with the induction of microsomal phase I enzymes (EROD and MROD). As discussed below, increased microsomal enzyme activity could increase the formation of hydroxylated PBDE metabolites that can bind to T_4 plasma transport proteins. This would serve to increase the number of occupied sites on T_4-binding proteins and subsequently result in decreased serum levels of T_4.

The possible interaction of PBDEs with T_4 binding to human transthyretin (TTR) was investigated in an *in vitro* competitive binding assay (Meerts et al. 1998, 2000). Testing of 17 congeners, ranging from di- to heptaBDEs, showed that none of the parent compounds competed with T_4 for binding to human TTR. Incubation of the congeners with rat liver microsomes induced by PB (CYP2B enriched), β-naptho-flavone (CYPIA enriched), or clofibrate (CYP4A3 enriched) indicated that metabolism is necessary to compete with T_4-TTR binding and that potency is likely to be both congener and metabolic enzyme-specific. The CYP2B-enriched liver microsomes were the most potent, causing 9 of the 17 congeners to generate metabolites (not identified) that were effective in displacing T_4 from TTR (60% inhibition): 4,4'-diBDE, 2,4,4'-triBDE, 2,4,6-triBDE, 2,2',4,4-tetraBDE, 2,2',4,6'-tetraBDE, 2,4,4',6-tetraBDE, 3,3,4,4'-tetraBDE, 2,2',4,4',6-pentaBDE, and 2,3',4,4',6-pentaBDE. No T_4-TTR inhibition occurred with the higher brominated diphenyl ethers (i.e., 2,2',3,4,4',5'-hexaBDE, 2,2',4,4',5,5'-hexaBDE, 2,3,4,4',5,6-hexaBDE, and 2,3,3',4,4',5,6-heptaBDE), although it was not verified that these PBDEs were metabolized during the *in vitro* microsomal incubations. Three pure hydroxylated PBDEs, synthesized for their structural resemblance with the thyroid hormones 3,5-diiodothyronine (3,5-T_2), 3,3',5-triiodo-thyronine (T_3), and 3,3',5,5'-tetraiodothyronine (T_4), were also tested in the T_4-TTR competition binding assay. The relative potencies showed that the T_4-like (2,6-dibromo-4-[2,4,6-tribromophenoxy]phenol) and T_3-like (2-bromo-4-[2,4,6-tribromophenoxy]phenol) hydroxylated PBDEs were 1.42- and 1.22-fold more potent, respectively, than T_4, and the percentage competition at 500 nM exceeded that of the natural

ligand; the T_2-like hydroxylated PBDE (4-[2,4,6-tribromophenoxy]phenol) showed low affinity for TTR (0.41-fold less potent than T_4). Because the PBDEs were able to compete with T_4-TTR binding only after metabolic conversion by induced rat liver microsomes, and considering that thyroid hormones are also hydroxy-halogenated diphenyl ethers, the results of this study suggest an important role for hydroxylation in the mechanism of thyroid toxicity.

4'-Hydroxyl derivatives of 1,3,5-triBDE, 1,3,3',5'-tetraBDE, and 1,3,3',5,5'-pentaBDE were tested for affinity to the human thyroid hormone receptor proteins THR-α and THR-β *in vitro* (Marsh et al. 1998). These congeners were tested because they theoretically show the highest structural similarity to T_4 and T_3. None of the hydroxylated derivatives effectively competed with the thyroid hormones for binding to either receptor (affinities were 4–>1,000 times less than for T_4 and T_3). Because the tested congeners were the most likely to have affinity for the thyroid hormone receptor, it is likely that other hydroxylated PBDE congeners will have even lower potential for receptor binding.

2,2',4,4'-TetraBDE did not competitively inhibit binding of T_4 to sites in rat choroid plexus homogenates following *in vitro* or *in vivo* exposure (Sinjari et al. 1998). In the *in vivo* study, choroid plexus homogenate from rats that were orally treated with 6 or 18 mg/kg/day for 14 days showed T_4 binding that was 80 and 63%, respectively, of that in controls. TTR is the only T_4-binding protein synthesized by the choroid plexus and is the main protein involved in T_4 transport from blood to brain in both rats and humans (Sinjari et al. 1998).

The estrogenic and antiestrogenic activities of several PBDE congeners and three hydroxylated PBDEs were tested *in vitro* using human breast cell line assays based on estrogen receptor (ER)-dependent luciferase reporter gene expression (Meerts et al. 2001). The hydroxylated PBDEs, tribromophenoxy)phenol, 2-bromo-4-(2,4,6-tribromophenoxy)phenol, and 2,6-dibromo-4-(2,4,6-tri-bromophenoxy)phenol, have bromine substitution patterns similar to those of the thyroid hormones T_2, T_3, and T_4, respectively. Eleven of 17 PBDE congeners showed estrogenic activity (dose-dependent luciferase induction) in the ER-CALUX assay with T47D.Luc cells, although the most potent PBDE congeners (2,2',4,4',6-pentaBDE > 2,4,4',6-tetraBDE > 2,2',4,6'-tetraBDE > 2,4,6-triBDE > 2,3',4,4',6-pentaBDE) had EC_{50} values that were 250,000–390,000 times less potent than 17β-estradiol (E_2). In contrast, the T_3- and T_2-like hydroxylated PBDEs showed estrogenic potencies exceeding that of E_2 (no estrogenic activity was induced by the T_4-like hydroxylated PBDE). Antiestrogenic potencies were determined in the ER-CALUX assay by treating T47D.Luc cells with the PBDEs and hydroxylated PBDEs in the presence of E_2. Only 2,2',4,4',5,5'-hexaBDE, 2,3,4,4',5,6-hexaBDE, and

2,3,3',4,4',5,6-heptaBDE, which did not induce luciferase activity alone, caused reductions in E_2-induced luciferase activity. Three of the compounds with potent estrogenic activity in the ER-CALUX assay, 2,4,6-triBDE, 2,2',4,4',6-pentaBDE, and 4-(2,4,6-tribromophenoxy)phenol, were also tested for estrogenicity in ERα-specific and ERβ-specific human embryonic kidney cell lines (293-ERα-Luc and ERβs-Luc cells, respectively). The hydroxylated PBDE was potent in the ERα-specific cells (maximum luciferase induction similar to E_2) and also showed activity in the ERβ-specific cells (maximum 50% induction compared to E_2), whereas the ERα- and ERβ-specific cell lines were less responsive to 2,4,6-triBDE (34.2 and 7.8% induction compared to E_2) and 2,2',4,4',6-pentaBDE (. 20 and < 2% relative induction). These results indicate that pure and hydroxylated congeners of PBDEs can be agonists of both ERα and ERβ receptors and that metabolism of PBDEs may produce more potent pseudoestrogens. The common structural features among the estrogenic PBDEs in this study are two *ortho* (2,6)-bromine atoms on one phenyl ring, at least one *para*-bromine atom (preferably on the same phenyl ring as the *ortho* bromines), and nonbrominated *ortho*-*meta* or *meta* carbons on the other phenyl ring (Meerts et al. 2001).

3.5.3 Animal-to-Human Extrapolations

Residue levels of PBBs and PBDEs in humans reflect multiple exposure pathways and congener-specific elimination and thus, in general, represent steady state body burdens that do not match the congener profiles in the original exposure sources. For example, profiles of PBB and PBDE congeners in human milk do not resemble the pattern of any of the commercial mixtures, as illustrated by the finding that the major PBDE congener in milk from Swedish mothers was 2,2',4,4'-tetraBDE (BDE-47), which comprised approximately 55% of the total PBDEs (Darnerud et al. 1998). As discussed in Chapter 6, residue analyses indicate that tetra- to hexa-congeners predominate in humans, aquatic mammals, birds, fish, and other biota, indicating that the biological fate of PBB and PBDE congeners is qualitatively similar in various animal species. Interspecies differences in the quantitative disposition of PBBs and PBDEs may exist. For example, the metabolism and urinary excretion of a single oral dose of 2,2',4,4'-tetraBDE was significantly slower in rats than in mice (Orn and Klasson-Wehler 1998).

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view 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 chemicals are derived from plants and are similar in structure and action to endogenous

estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral functions. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Concern has been raised that many industrial chemicals, including PBBs and PDBEs, are endocrine-active compounds capable of having widespread effects on humans and wildlife (Colborn et al. 1993; Crisp et al. 1998; Daston et al. 1997; Safe and Zacharewski 1997). 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 a very important system for normal structural and functional development of sexual organs and the brain.

Polybrominated Biphenyls. PBBs have the potential to interact with the endocrine system based on effects that mainly include changes in levels of thyroid and female reproductive hormones. No studies were located that investigated the estrogenic and antiestrogenic activity of PBBs *in vitro* or *in vivo* at the level of the estrogen receptor.

The thyroid gland is an unequivocal target of PBBs in animals, and evidence in humans is suggestive of a similar relationship. A spectrum of effects has been observed in rats exposed for acute and intermediate durations, ranging from decreases in serum levels of T_4 and T_3 to histological and ultrastructural changes in the follicles (Akoso et al. 1982b; Allen-Rowlands et al. 1981; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978a; Norris et al. 1975a, 1975b; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978). The preponderance of these studies tested FireMaster FF-1 or FireMaster BP-6 in rats, although chronic exposure to FireMaster FF-1 induced thyroid follicular hyperplasia in mice (NTP 1992). Thyroid effects also occurred in offspring of treated rats and pigs (Meserve et al. 1992; Werner and Sleight 1981). Effects in workers exposed to unspecified PBBs and/or decabromobiphenyl included increased serum

FSH, low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers (Bahn et al. 1980).

Serum levels of the adrenal hormones corticosterone B, dehydroepiandrosterone, and dehydro-epiandrosterone sulfate were decreased in rats fed $0.25 mg/kg/day FireMaster BP-6 for 5–7 months (Byrne et al. 1988). Serum corticosterone levels and adrenal weight did not change in rats exposed to #6 mg/kg/day of an unspecified PBB mixture for a shorter duration of 20 days (Castracane et al. 1982).

Increased menstrual cycle duration and prolonged implantation bleeding were observed in female monkeys fed FireMaster FF-1 in approximate daily dose levels of 0.012 mg/kg for 7 months before breeding and during pregnancy (Allen et al. 1979; Lambrecht et al. 1978). A corresponding decrease in serum levels of progesterone suggests that the reproductive effects in the monkeys are related to PBB-induced endocrine imbalance. Implantation was completely blocked in 40–67% of female rats treated with FireMaster BP-6 by gavage in dose levels $28.6 mg/kg on alternate days between gestation days 0 and 14 (Beaudoin 1979).

Delayed vaginal opening, an effect suggesting retarded sexual maturation, was observed in F_1 generation rats whose only PBB exposure was from the mothers fed a diet providing 5 mg/kg/day FireMaster FF-1 from day 8 of pregnancy until weaning at 28 days postpartum (McCormack et al. 1981).

Two studies of women exposed during the Michigan contamination episode found no associations between serum levels of PBBs and breast feeding (Michels Blanck et al. 2000b; Thomas et al. 2001). Determinants of PBB serum decay were investigated in women who had a mean initial PBB level of 20.9 ppb, a mean time between the first and last measurement of 4.2 years, and at least two measurements taken when they were not pregnant (Michels Blanck et al. 2000b). The median PBB half-life was estimated to be 13.5 years. Subject-specific decay rates were regressed on various predictor variables. Results included the finding that breast feeding, as either a continuous variable or as categorized by duration (<3, 3–9, or >9 months), was not associated with serum PBB decay, although increasing number of pregnancies was weakly associated with a slower rate of serum PBB decay (the effect had borderline statistical significance). Additional information on the design and results of this study is provided in Section 3.8.1. Thomas et al. (2001) found no relationship between serum levels of PBBs and the frequency and duration of lactation in Michigan women. Characteristics of the study cohort included a mean initial serum PBB level of 17.5 ppb, an estimated mean serum PBB level at delivery of 9.4 ppb, mean duration of breast-feeding as main source of nutrition of 2.6 months, and mean total duration of

breast feeding of 4.1 months. Exposure was treated as a categorical variable by dividing the women into groups of low (reference) exposure (#1 ppb), moderate exposure (>1–#7 ppb), and high exposure (>7 ppb), and three outcomes of interest were analyzed: (1) the decision to breast feed (yes/no), (2) the duration (months) of breast-feeding as the main source of nutrition, and (3) the total duration (months) of breast-feeding. None of the three outcomes was significantly associated with serum PBB levels. Additional information on the design and results of this study is provided in Section 3.2.2.5.

The issue of breast cancer has received attention following reports of high levels of organochlorine compounds in breast cancer patients. A relationship between increasing serum levels of PBBs and increasing risk of breast cancer was indicated in case-control studies of women exposed during the Michigan contamination episode (Henderson et al. 1995; Hoque et al. 1998), but the results are only suggestive due to factors such as small number of cases, insufficient information on known breast cancer risk factors, and confounding exposures to other organochlorine chemicals. The evidence for an association between breast cancer and PCBs is also not conclusive (Agency for Toxic Substances and Disease Registry 2000), and the hypothesis that environmental exposure to PCBs can cause breast cancer in humans is controversial (Safe and Zacharewski 1997; Wolff and Toniolo 1995). Overall, the evidence for an association between breast cancer and PBBs is inconclusive and needs further study.

Polybrominated Diphenyl Ethers. Results of *in vitro* estrogen receptor and thyroid hormone transport protein binding assays and *in vivo* studies of thyroid hormone homeostasis indicate that PBDEs have the potential to disrupt normal endocrine function.

The estrogenic and antiestrogenic activities of 17 PBDE congeners and 3 hydroxylated PBDEs were tested *in vitro* using human breast cell line assays based on ER-dependent luciferase reporter gene expression (Meerts et al. 2001). Eleven of 17 PBDE congeners showed estrogenic activity (dose-dependent luciferase induction) in the ER-CALUX assay with T47D.Luc cells, although the most potent PBDE congeners (2,2',4,4',6-pentaBDE > 2,4,4',6-tetraBDE > 2,2',4,6'-tetraBDE > 2,4,6-triBDE > 2,3',4,4',6-pentaBDE) had EC_{50} values that were 250,000–390,000 times less potent than that of the natural ligand, 17β-estradiol (E_2). In contrast, two of the hydroxylated PBDEs, 4-(2,4,6-tribromophenoxy)phenol, 2-bromo-4-(2,4,6-tribromophenoxy)phenol (which have bromine substitution patterns similar to the thyroid hormones T_2 and T_3, respectively) had estrogenic potencies exceeding that of E_2. Three of the compounds with potent estrogenic activity in the ER-CALUX assay, 2,4,6-triBDE, 2,2',4,4',6-pentaBDE, and 4-(2,4,6-tribromophenoxy)phenol, were also tested for estrogenicity in ERα-specific and ERβ-specific human embryonic kidney cell lines (293-ERα-Luc and

ERβs-Luc cells, respectively). The hydroxylated PBDE was potent in the ERα-specific cells (maximum luciferase induction similar to E_2) and also showed activity in the ERβ-specific cells (maximum 50% induction compared to E_2), whereas the ERα- and ERβ-specific cell lines were less responsive to 2,4,6-triBDE and 2,2',4,4',6-pentaBDE. These results indicate that pure congeners of PBDEs can be agonists of both ERα and ERβ receptors and that metabolism to hydroxylated PBDEs may increase estrogenic potency.

The same 17 PBDE congeners and three hydroxylated PBDEs were also tested for possible interaction with T_4 binding to human TTR, a plasma transport protein of thyroid hormones, in an *in vitro* competitive binding assay (Meerts et al. 1998, 2000). None of the pure congeners competed with T_4 for binding to human TTR. Incubation of the congeners with rat liver microsomes induced by PB (CYP2B enriched), β-napthoflavone (CYPIA enriched), or clofibrate (CYP4A3 enriched) indicated that 9 of the 17 pure congeners generated metabolites (not identified) that were able to displace T_4 from TTR: 4,4'-diBDE, 2,4,4'-triBDE, 2,4,6-triBDE, 2,2',4,4-tetraBDE, 2,2',4,6'-tetraBDE, 2,4,4',6-tetraBDE, 3,3,4,4'-tetraBDE, 2,2',4,4',6-pentaBDE, and 2,3',4,4',6-pentaBDE. Testing of the three known hydroxylated PBDEs, used for their structural resemblance with the thyroid hormones 3,5-diiodothyronine (3,5-T_2), 3,3',5-triiodothyronine (T_3), and 3,3',5,5'-tetraiodothyronine (T_4) showed that the T_4-like (2,6-dibromo-4-[2,4,6-tribromophenoxy]phenol) and T_3-like (2-bromo-4-[2,4,6-tribromophenoxy]phenol) hydroxylated PBDEs were 1.42- and 1.22-fold more potent, respectively, than T4; the T_2-like hydroxylated PBDE (4-[2,4,6-tribromophenoxy]phenol) showed low affinity for TTR (0.41-fold less potent than T_4). Because the PBDEs were able to compete with T_4-TTR binding only after metabolic conversion by induced rat liver microsomes, and considering that thyroid hormones are also hydroxy-halogenated diphenyl ethers, the results of this study suggest an important role for hydroxylation in the mechanism of thyroid toxicity.

2,2',4,4'-TetraBDE did not competitively inhibit binding of T_4 to sites in rat choroid plexus homogenates following *in vitro* or *in vivo* exposure (Sinjari et al. 1998). TTR is the only T_4-binding protein synthesized by the choroid plexus and is the main protein involved in T_4 transport from blood to brain in both rats and humans (Sinjari et al. 1998).

4'-Hydroxyl derivatives of 1,3,5-triBDE, 1,3,3',5'-tetraBDE, and 1,3,3',5,5'-pentaBDE were tested for affinity to the human thyroid hormone receptor proteins, THR-α and THR-β, *in vitro* (Marsh et al. 1998). These congeners theoretically show the highest structural similarity to T_4 and T_3. None of the hydroxylated derivatives effectively competed with the thyroid hormones for binding to either receptor (affinities were 41–>1,000 times less than for T_4 and T_3). Because the tested congeners were the most

likely to have affinity for the thyroid hormone receptor, it is likely that other hydroxylated PBDE congeners will have even lower potential for receptor binding.

Studies of serum hormone levels and organ histology indicates that the thyroid is a particularly sensitive target of PBDEs. Reduced serum T_4 levels and follicular cell hyperplasia have been consistently observed in rats and mice orally exposed to PBDEs. Acute-duration studies showed decreases in serum T_4 in rats exposed to $10 mg/kg/day octaBDE or $30 mg/kg/day pentaBDE for 4 days and in rats and mice exposed to $18 mg/kg/day pentaBDE for 14 days (Darnerud and Sinjari 1996; Hallgren et al. 2001; Zhou et al. 2001). Effects observed in intermediate-duration studies include thyroid hyperplasia in rats exposed to $8 mg/kg/day octaBDE for 30 days (Norris et al. 1973, 1975a, 1975b) and reduced serum T_4 in rats exposed to $10 mg/kg/day pentaBDE for 90 days (WIL Research Laboratories 1984). Exposure to pentaBDE on gestation day 6 through postnatal day 21 caused serum T_4 reductions at 30 mg/kg/day in maternal rats and at $10 mg/kg/day in their offspring (Zhou et al. 2002). Intermediate-duration exposure to a 77% decaBDE/22% nonaBDE commercial mixture caused thyroid hyperplasia in rats at doses of $80 mg/kg/day for 30 days (Norris et al. 1973, 1975a, 1975b). Chronic (103-week) exposure to high-purity decaBDE ($97%) did not induce thyroid histopathological changes in rats at #2,550 mg/kg/day, although follicular cell hyperplasia developed in mice exposed to 2,240 mg/kg/day (NTP 1986).

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. In general, methodology has not yet been developed for assessing health risks of chemicals in children.

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 PBBs and PBDEs in the same manner as the general population, primarily via consumption of contaminated foods. Exposure also may occur by transfer of PBBs and PBDEs that have accumulated in women's bodies to the fetus across the placenta. Because PBBs and PBDEs are lipophilic substances, they can additionally accumulate in breast milk and be transferred to nursing infants.

Placental transfer, although it may be limited in absolute amounts, is a concern because of possible effects of PBBs and PBDEs on sensitive immature tissues, organs, and systems, with potentially serious long-lasting consequences. Transfer of PBBs and PBDEs via breast milk could be relatively 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 PBBs and PBDEs during sensitive periods of development, it is not known if the susceptibility of children to the health effects of these chemicals differs from that of adults. Younger children may be particularly vulnerable to PBBs and PBDEs because, compared to adults, they are growing more rapidly and are generally expected to have lower and distinct profiles of biotransformation enzymes, as well as much smaller fat depots for sequestering these lipophilic chemicals. No specific information was located regarding the pharmacokinetics of PBBs in children or nutritional factors that may influence the absorption of PBBs.

No biomarkers of exposure or effect for PBBs or PBDEs have been validated in children or in adults exposed as children. There also are no biomarkers in adults that identify previous childhood exposure. No studies were located regarding interactions of PBBs or PBDEs with other chemicals in children or adults. No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to PBBs or PBDEs, 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.

Polybrominated Biphenyls. Information on health effects of PBBs in children is available from several studies of the Michigan contamination episode. A 1976 medical history questionnaire study of 342 Michigan children likely to have been exposed to PBBs found that the number of subjectively reported symptoms of ill health, including several symptoms of neurological effects, did not increase with increasing serum PBB levels (assayed in 1976), but rather decreased; general neurological examinations did not reveal a pattern of abnormality among the Michigan children (Barr 1980). Studies of fetal mortality rates in Michigan (Humble and Speizer 1984) and of physical and neuropsychological development in Michigan children exposed during the contamination episode (Schwartz and Rae 1983; Seagull 1983; Weil et al. 1981) did not conclusively correlate the ingestion of PBBs with effects, as summarized below.

Examination of approximately 100 children presumably exposed *in utero* or in early infancy during the peak of the Michigan contamination episode and whose families lived on farms known to be contaminated with PBBs has not revealed any consistent or marked abnormalities. No significant abnormalities were found by physical and neuropsychological examination of 33 of these exposed children when they had a mean age of 37.2 months, compared with a group of 20 age-matched, non-exposed control children (Weil et al. 1981). However, subjective interviews with parents suggested that more exposed children than control children had frequent upper respiratory illnesses such as colds, runny noses, and sore throats (Weil et al. 1981). Administration of 5 of 18 possible neuropsychological development tests from the McCarthy Scales of Children's Abilities to 19 of these exposed children at .2.5–4 years of age showed a statistically significant negative correlation between PBB levels in fat tissue and developmental abilities in four of the five tests (Seagull 1983). Subsequent administration of the full battery of 18 neuropsychological tests, as well as I.Q. tests, to the same group of children when .4–6 years old, found that the exposed children's performances were within the normal range in all areas assessed (Schwartz and Rae 1983). Due mainly to the small data set and the inconsistency of the results, the available data do not conclusively establish or eliminate the possibility that *in utero* and early infancy exposure to PBBs might adversely affect the development of human children.

Neurobehavioral alterations have been observed in animals following gestational and lactational exposure to PBBs. Performance deficits in tests of operant behavior were seen in 6-month-old offspring of rats that were exposed to $0.2 mg/kg/day of FireMaster BP-6 by gavage from day 6 of gestation until weaning (Henck and Rech 1986), but not in 75-day-old offspring of rats exposed to $0.5 mg/kg/day for 4 weeks prior to mating (Geller et al. 1985). Effects on acquisition of forward locomotion, cliff avoidance, cage emergence, and open-field activity were found in offspring of rats exposed to $0.2 mg/kg/day of FireMaster BP-6 in the diet from day 6 of gestation through Pnd 24 and tested through Pnd 60 (Henck et al. 1994). Testing of mouse offspring at 30–120 days of age following maternal exposure to FireMaster FF-1 by gavage on every other day during gestation and through weaning showed altered negative geotaxis and avoidance response latencies at $3 mg/kg/day and reduced acoustic startle responsiveness and motor activity at 10 mg/kg/day (Tilson 1992).

Animal studies of FireMaster FF-1 and FireMaster BP-6 have also shown that hexabromobiphenyl PBB mixtures can induce non-neurological developmental toxicity. Embryolethal effects or increased mortality among nursing young were observed in rats (Beaudoin 1977, 1979; Groce and Kimbrough 1984) and mice (Luster et al. 1980) after oral exposure during gestation and in monkeys after exposure before conception and during pregnancy (Allen et al. 1979; Lambrecht et al. 1978). Structural

malformations in fetuses, including cleft palate, were also observed in rats (Beaudoin 1977) and mice (Corbett et al. 1975) after exposure to these PBBs during gestation. Increased incidences of fetuses with extra ribs were found in a study of rats orally exposed to a commercial octabromobiphenyl mixture during gestation (Waritz et al. 1977), although decabromobiphenyl was not embryotoxic, fetotoxic, or teratogenic in rats (Millischer et al. 1980). Other studies with FireMaster FF-1 and FireMaster BP-6 found that body weight gain was reduced in the offspring of rats and mice after exposure during gestation and/or lactation (Corbett et al. 1975; Groce and Kimbrough 1984; McCormack et al. 1981, 1982c; Meserve et al. 1992). Liver effects, including increased liver weight and hepatic cytochrome P-450 enzymic activity, hepatocyte enlargement, vacuolization, and/or other degenerative changes, occurred in the offspring of rats, mice, and swine fed FireMaster FF-1 or FireMaster BP-6 during gestation and/or lactation (Chhabra et al. 1993; Moore et al. 1978; NTP 1992; Werner and Sleight 1981).

Other effects in offspring of animals exposed to PBBs during gestation and lactation include altered thyroid hormone levels. Serum T_4 levels were reduced in 15-day-old offspring of rats that were exposed to 2.5 mg/kg/day FireMaster BP-6 in the diet from Gd 0 through Pnd 15 (Meserve et al. 1992). The pups had received pituitary stimulation by an injection of corticotropin-releasing factor or adrenal stimulation by an injection of adrenocorticotropic hormone. Serum concentrations of T_3 and T_4 were significantly reduced in 4-week-old nursing offspring of swine that were fed $1.25 mg/kg/day dietary doses of FireMaster BP-6 during the second half of gestation and throughout lactation (Werner and Sleight 1981). These effects in offspring are consistent with evidence that the thyroid gland is an unequivocal target of PBBs in adult animals. A spectrum of thyroid effects, ranging from decreases in serum T_4 and T_3 levels to histological and ultrastructural changes in the follicles, has been documented in adult rats orally exposed to PBBs (mainly FireMaster BP-6 and FF-1) for acute and intermediate durations (Akoso et al. 1982b; Allen-Rowlands et al. 1981; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978a; Norris et al. 1975a, 1975b; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978). Additionally, there is suggestive limited evidence of thyroid effects in adult humans; effects in workers exposed to unspecified PBBs and/or decaBDE included increased serum FSH, low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers (Bahn et al. 1980).

No information was located on possible immunological effects of PBBs in children, and data in adult humans are limited and largely inconclusive. Altered lymphocyte transformation responses among populations exposed to PBBs during the Michigan contamination episode have been reported in some studies (Bekesi et al. 1978; Roboz et al. 1985), but other investigations were not able to confirm these findings (Landrigan et al. 1979; Silva et al. 1979; Stross et al. 1981). No correlation can be established

between altered immune parameters and serum PBB levels based on the available data. Exposure to PBBs caused altered immune responses in a variety of animal species, which suggests that humans may also be affected. Studies in animals, mostly intermediate-duration studies in rodents, showed that a variety of immunological parameters such as spleen and thymus weights (Gupta and Moore 1979; Gupta et al. 1981; NTP 1983), antibody production (Loose et al. 1981), and lymphoproliferative responses (Howard et al. 1980; Luster et al. 1978, 1980) can be affected by treatment with commercial PBB mixtures, although some of these effects were only seen at PBB levels that cause overt toxicity (Luster et al. 1978, 1980).

Levels of PBBs in breast milk have been measured in women exposed as a result of the Michigan contamination episode. The milk concentrations of PBBs in women from the lower peninsula of Michigan (exposed area) were generally higher than in breast milk of females from the upper peninsula (farthest from the sources) (Brilliant et al. 1978). PBB levels in breast milk of five women from exposed farms ranged from 0.21–92.7 ppm (Cordle et al. 1978; Humphrey and Hayner 1976). On a lipid basis, the ratio of PBBs in breast milk to maternal serum was 107–122 to 1 and in adipose tissue to breast milk was 1.1–1.5 to 1 in a cohort of Michigan residents (Eyster et al. 1983; Landrigan et al. 1979). No monitoring information was located on PBBs in breast milk for U.S. populations outside of Michigan.

Determinants of PBB serum decay were investigated in Michigan women who had a mean initial PBB level of 20.9 ppb, a mean time between the first and last measurement of 4.2 years, and at least two measurements taken when they were not pregnant (Michels Blanck et al. 2000b). Assuming that PBBs reached equilibrium in the body before substantial amounts were eliminated and before the first serum measurements were taken, the authors estimated the median PBB half-life to be 13.5 years. Subject-specific decay rates were regressed on various predictor variables. Results of the analysis included the finding that an increasing number of pregnancies between the first and last measurement was associated with a slower rate of serum PBB decay (the effect had borderline statistical significance). Breast feeding as either a continuous variable or as categorized by duration (<3, 3–9, or >9 months) was not associated with serum PBB decay. Additional information on the design and results of this study is provided in Section 3.8.1. Another study of women exposed to PBBs during the Michigan contamination episode similarly found no relationship between serum levels of PBBs and the frequency and duration of lactation (Thomas et al. 2001). Characteristics of the study cohort included a mean initial serum PBB level of 17.5 ppb, an estimated mean serum PBB level at delivery of 9.4 ppb, a mean duration of breast-feeding as the main source of nutrition for 2.6 months, and a mean total duration of breast-feeding of 4.1 months. Exposure was treated as a categorical variable by dividing the women into groups of low (reference)

exposure (#1 ppb), moderate exposure (>1–#7 ppb), and high exposure (>7 ppb). Three outcomes of interest were analyzed: (1) the decision to breast feed (yes/no), (2) the duration (months) of breast-feeding as the main source of nutrition, and (3) the total duration (months) of breast-feeding. None of the three outcomes was significantly associated with serum PBB levels, even after controlling for various confounding determinants, including histories of previous breast-feeding and thyroid disorders. Additional information on the design and results of this study is provided in Section 3.2.2.5.

Polybrominated Diphenyl Ethers. No information was located on health effects of PBDEs in newborn or older children. Thyroid and neurobehavioral alterations have been observed in animals following pre- and/or postnatal exposure to commercial PBDE mixtures and single PBDE congeners, indicating that these are effects of concern in exposed children.

Serum levels of thyroid hormones were reduced in offspring of rats exposed to PBDEs during gestation and lactation and in rats exposed as weanlings. Exposure to pentaBDE from Gd 6 through the end of lactation caused serum T_4 decreases in maternal rats (on Gd 20 and Pnd 22) at 30 mg/kg/day and in their offspring (on Pnds 4 and 14) at $10 mg/kg/day (Zhou et al. 2002). Assessment of weanling (28-day-old) rats that were orally exposed to PBDEs for 4 days and evaluated for thyroid hormone changes on the day after the last exposure showed that octaBDE caused significantly reduced serum T_4 and T_3 levels at $10 and $60 mg/kg/day, respectively (Zhou et al. 2001). Similar exposure to pentaBDE caused serum T_4 and T_3 decreases at higher dose levels of $30 and $100 mg/kg/day, respectively, whereas decaBDE had no effect on levels of any thyroid hormones (T_4, T_3, or FSH). The results of these studies are consistent with findings of reduced serum T_4 hormone levels and follicular cell hyperplasia in adult rats and mice confirming that the thyroid is a sensitive target of PBDE toxicity, especially octaBDE and pentaBDE at doses as low as 8–10 mg/kg/day (Darnerud and Sinjari 1996; Hallgren et al. 2001; Norris et al. 1973, 1975a, 1975b; WIL Research Laboratories 1984). Also, *in vitro* evidence shows that PBDEs can effectively compete with T_4 for binding to the human transport protein transthyretin (Meerts et al. 1998, 2000).

Altered thyroid hormone homeostasis can potentially cause neurodevelopmental effects because development of the central nervous system is dependent on thyroid hormones, but very little information is currently available on potential neurotoxic effects of PBDEs. Data are essentially limited to the results of three behavioral tests in animals showing some alterations in spontaneous locomotion behavior and learning and memory ability in mice that were tested at 2 months of age and as adults (4 months) following neonatal exposure (Pnds 3, 10, or 19) to single low oral doses of the congeners 2,2',4,4'-tetra-

BDE and 2,2',4,4',5-pentaBDE (Eriksson et al. 1998, 1999, 2001). One of the studies found effects in mice treated at either 3 or 10 days of age, but not at 19 days of age, suggesting that there is a critical window for the induction of behavioral disturbances (Eriksson et al. 1999). No studies were located that evaluated neurological effects of PBDEs in animals exposed as adults.

No information is available regarding the immunosuppressive potential of PBDEs in young animals, and data in adult animals are essentially limited to findings in acute-duration oral studies of relatively high doses of pentaBDE. The plaque-forming splenic cell antibody response to injected sheep red blood cells was significantly reduced in mice exposed to 72 mg/kg/day pentaBDE for 14 days (Fowles et al. 1994), and *in vitro* production of IgG immunoglobulin from mitogen-stimulated splenocytes was reduced in mice exposed to 36 mg/kg/day pentaBDE for 14 days (Darnerud and Thuvander 1998). Other 14-day studies in mice found no changes in natural killer cell activity at dosages #72 mg/kg/day (Fowles et al. 1994) or numbers of splenic and thymic lymphocyte subsets at dosages #36 mg/kg/day (Darnerud and Thuvander 1998), although 18 mg/kg/day of the single congener 2,2',4,4'-tetraBDE caused significantly reduced numbers of total lymphocytes and CD4+, CD8+, and CD45R+ subtypes in spleen (Darnerud and Thuvander 1998).

Information on the reproductive toxicity of PBDEs is limited to a one-generation study of decaBDE in rats that found no exposure-related functional effects (Dow Chemical Co. 1975; Norris et al. 1975a, 1975b). Developmental toxicity studies have shown no evidence of teratogenicity of deca-, octa-, and pentaBDE in rats and rabbits, although fetotoxic effects, including skeletal ossification variations at maternally toxic doses have been observed (Argus Research Laboratories 1985b; Breslin et al. 1989; Dow Chemical Co. 1975, 1985; Life Science Research Israel Ltd. 1987; Norris et al. 1975a, 1975b; WIL Research Laboratories 1986).

Some PBDE congeners have estrogenic activity *in vitro* (Meerts et al. 2001). Although 11 of 17 PBDE congeners were active (ER-dependent luciferase induction) in the ER-CALUX assay using a human breast cell line, the most potent PBDE congeners (2,2',4,4',6-pentaBDE > 2,4,4',6-tetraBDE > 2,2',4,6'-tetraBDE > 2,4,6-triBDE > 2,3',4,4',6-pentaBDE) had EC_{50} values that were much less potent (250,000–390,000 times) than that of the natural ligand, 17β-estradiol (E_2). In contrast, two hydroxylated PBDEs, 4-(2,4,6-tribromophenoxy)phenol, and 2-bromo-4-(2,4,6-tribromophenoxy)phenol (which have bromine substitution patterns similar to the thyroid hormones T_2 and T_3, respectively) had estrogenic potencies exceeding that of E_2. Three of the congeners with potent estrogenic activity in the ER-CALUX assay, 2,4,6-triBDE, 2,2',4,4',6-pentaBDE, and 4-(2,4,6-tribromophenoxy)phenol, were also tested for

estrogenic activity in ERα-specific and ERβ-specific human embryonic kidney cell lines. The hydroxylated PBDE was potent in the ERα-specific cells (maximum luciferase induction similar to E_2) and showed some activity in the ERβ-specific cells (maximum 50% induction compared to E_2), whereas the ERα- and ERβ-specific cell lines were less responsive to 2,4,6-triBDE and 2,2',4,4',6-pentaBDE. These *in vitro* findings suggest that pure congeners are weak ER agonists compared to E_2 and that hydroxylated metabolites are more likely to be responsible for physiological responses to PBDEs as indicated by the ER-dependent luciferase induction assay.

PBDEs are pervasive environmental contaminants that bioaccumulate in the mother's body and can be transferred to infants through the placenta and breast milk. Considering the continued widespread production and use of PBDEs, particularly commercial pentaBDE mixtures whose constituent tetra- to hexaBDE congeners are highly bioaccumulative, as well as the time lag from current-year usage to exposure via the food chain, it is probable that tissue concentrations among the general population will continue to rise. The increasing temporal trend for PBDEs in human tissues is illustrated by findings of an exponential increase of PBDEs in Swedish human breast milk from 1972 to 1997 with a doubling rate of 5 years (Norén and Meironyté (1998, 2000). The milk concentrations of PBDEs (sum of eight congeners) on a lipid basis were 0.07 ppb in 1972 and 4 ppb in 1997 (Meironyté et al. 1999). Analysis of samples from 11 Finnish women showed that PBDE concentrations (sum of four congeners, lipid basis) were similar in breast milk and placenta, with ranges of 0.99–5.89 and 1.00–4.40 ppb, respectively (Strandman et al. 2000). The four highest sum concentrations were from women following their first childbirth. No PBPK models have been developed for PBDEs that could be used to quantitatively predict transfer of PBDEs via breast milk or across the placenta.

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 PBBs and PBDEs 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 PBBs and PBDEs 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 PBBs and PBDEs

Polybrominated Biphenyls. PBBs are environmental contaminants found mainly, but not exclusively, in body tissues and fluids of populations with known exposure to PBBs. Because they are lipophilic and have long half-lives, certain PBB congeners preferentially accumulate in lipid-rich tissues, especially adipose, and are present in serum and human milk. Both serum and adipose PBB levels are indicators of exposure, but monitoring PBBs simultaneously in samples of both types is more reliable than in serum only. The serum/adipose partition ratios for groups of pregnant and nonpregnant Michigan women and chemical workers ranged between 1:140 and 1:260; the value for Michigan male farmers was 1:325–329 (Eyster et al. 1983). These values agree with those reported by other investigators for similar populations (Landrigan et al. 1979; Wolff et al. 1982). The importance of a dual determination of PBBs in serum and adipose can be illustrated with the following example. In a Michigan cohort, 70% of 839 subjects were identified as having had exposure by their serum PBB levels. When adipose tissue results were added, an additional 24% indicated exposure (Wolff et al. 1982). The partition ratio of . 1:300 made the adipose limit of detection a more sensitive indicator of exposure, even though the limit of detection in adipose was one order of magnitude higher than in serum. Partition ratios below those reported from groups expected to be in equilibrium may indicate current or recent exposure (Anderson 1985).

Using an animal physiological compartment model scaled to humans by adjusting tissue volume, blood flow, and clearance and rate constant parameters, it was predicted that human intake of 9.8 g of 2,2',4,4',5,5'-hexabromobiphenyl from milk consumption over a 230-day period would result in peak tissue concentrations of 720 and 2.1 ppm in adipose and blood, respectively, at 8 months, and 443 and 1.3 ppm, respectively (Tuey and Matthews 1980). The elimination rate after 5 years would be 1.63 mg/day, the body burden would be 5.2 g, and the half-life would be 6.5 years. When a dose of 0.1 mg/day for 10 months was simulated, the excretion rate in a lean individual was estimated at 10.2 μg/day; overweight individuals had an excretion rate of 4.1 μg/day. PBB in adipose tissue from the lean and overweight subjects were predicted to be 2,769 and 1,103 ppb, respectively. PBB in serum would be 8.1 ppb in lean subjects and 3.2 ppb in overweight subjects. These predictions point to the importance of the percentage of body fat in the equilibrium dynamics of PBBs and indicate that because lean individuals have a smaller fat compartment, all of their body tissues will have higher concentrations of PBB than those in fatter individuals of the same exposure (Tuey and Matthews 1980). The assumptions on which the predictions are based do not reflect possible differences in fat and lean subjects

due to the way that PBBs are compartmentalized and/or excreted as a percent of the total body burden, or in decay rates due to differential partitioning.

As indicated above, PBBs are persistent chemicals due to their lipophilicity. Some studies have reported practically no change in serum PBB levels over a 12–18-month period (Wolff et al. 1979b) or over a 3-year period (Landrigan et al. 1979). The half-life of 6.5 years predicted by Tuey and Matthews (1980) is shorter than half-life values determined using sera data from the Michigan PBB cohort (Lambert et al. 1990; Michels Blanck et al. 2000b; Rosen et al. 1995). A median half-life of 12.0 years (95% CI 4–97 years) was estimated based on two serum measurements from 15 women ($20 years of age) with an initial serum PBB level of $5 ppb (Lambert et al. 1990). An analysis of 51 women ($18.8 years of age) and 112 men ($18.1 years of age) with at least two measurements 1 year apart and an initial PBB level of $20 ppb found a median half-life of 13.0 years (95% CI 6.3–infinite years) and 10.0 years (95% CI 6.7–20.0 years), respectively (Rosen et al. 1995). Based on a median half-life of 10.8 years (95% CI 9.2–14.7 years) for the entire group (163 persons, median PBB level 45.5 ppb), it was estimated that it will take more than 60 years for their PBB levels to fall below a detection limit of 1 ppb.

Determinants of PBB serum decay were investigated in a group of 380 Michigan women ($16 years of age) who had an initial PBB level of at least 2 ppb and at least two measurements taken when they were not pregnant (Michels Blanck et al. 2000b). The mean initial PBB level was 20.9 ppb (standard deviation 78.7), and the mean time between the first and last measurement was 4.2 years (range 16.0–75.2 years). A total of 109 women (29%) did not have a reduction in serum PBB over time. Assuming that PBBs reached equilibrium in the body before substantial amounts were eliminated and before the first serum measurements were taken, the entire body was modeled as a single compartment for PBBs with exponential decay. The median PBB half-life in the entire group was 13.5 years (95% CI 10.5–23.2 years). Subject-specific decay rate estimates were regressed on predictor variables including initial age, body mass index (BMI), smoking history, breast-feeding duration, and parity. The serum PBB decay rate was slower, resulting in a longer half-life, with higher initial PBB levels; women with initial PBB levels of <10 and >10 ppb had median half-lives of 12.9 and 28.7 years, respectively. The PBB decay rate was also slower (p=0.03) in women with an initial BMI above the median (BMI$23). Increasing number of pregnancies between the first and last measurement was also associated with slower decay, but the effect was of borderline statistical significance (p=0.06). Breast feeding as either a continuous variable or as categorized by tertiles of duration (<3, 3–9, or >9 months), age, and smoking were not associated with serum PBB decay.

The average concentration of PBBs (on an adipose basis and as hexabromobiphenyl) in pooled extracts of several hundred individual tissue samples collected in a statistically valid manner from all nine regions of the continental United States was 1–2 ppb (Lewis and Sovocool 1982). Chemical workers involved in the PBB manufacturing process had a median adipose PBB concentration of 6,000 ppb (range 400–350,500 ppb); Michigan male farmers and chemical workers not involved in the PBB manufacturing process had a median of 1,050 ppb (range 70,000–350,000 ppb) (Eyster et al. 1983).

A potential biomarker of exposure to PBBs is related to their effect on the thyroid gland. As discussed in Sections 3.2.2.2, Endocrine Effects, the thyroid gland is an unequivocal target of PBBs in animals, and evidence in humans is suggestive of a similar relationship. Effects in workers exposed to unspecified PBBs and/or decabromobiphenyl included increased serum thyrotropin, low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers (Bahn et al. 1980). A spectrum of thyroid effects has been observed in exposed rats, ranging from decreases in serum levels of serum T_4 and T_3 to histological and ultrastructural changes (Akoso et al. 1982b; Allen-Rowlands et al. 1981; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978a; Meserve et al. 1992; Norris et al. 1975a, 1975b; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978; Werner and Sleight 1981). Additional studies could better characterize thyroid effects of PBBs in humans and develop specific correlations between levels and duration of exposure and alterations in serum T_4 and T_3 levels. These potential biomarkers are not specific to PBBs because PBDEs and other antithyroid agents can have similar effects.

Polybrominated Diphenyl Ethers. PBDEs are also persistent environmental contaminants that accumulate in adipose tissue, serum, and breast milk serum of the general population due to their lipophilic characteristics. PBDEs in breast milk are useful markers of maternal body burdens as well as lactational and *in utero* exposures. The predominant congeners identified in milk and other human tissues are 2,2',4,4'-tetraBDE (BDE-47), 2,2'4,4',5-pentaBDE (BDE-99), and 2,2'4,4',5,5'-hexaBDE (BDE-153) (all *ortho-para* substituted congeners). Considering the continued widespread production and use of PBDEs, particularly commercial pentaBDE mixtures whose tetra- to hexaBDE congeners are highly bioaccumulative, as well as the time lag from current-year usage to exposure via the food chain, it is highly likely that tissue concentrations among the general population will continue to rise. The increasing temporal trend for PBDEs in human tissues is suggested by findings of an exponential increase of PBDEs in Swedish human breast milk from 1972 to 1997 with a doubling rate of 5 years (Norén and Meironyté (1998, 2000). In the 1997 sample, the concentration of PBDE (sum of eight congeners) was 4 ppb on a lipid basis, whereas the 1972 sample contained 0.07 ppb (Meironyté et al. 1999). PBDEs have been detected in human placenta at concentrations similar to those in breast milk from the same women;

concentrations (sum of four congeners, lipid basis) ranged from 0.99 to 5.89 ppb in milk and from 1.00 to 4.40 ppb in placenta (Strandman et al. 2000).

Estimates of PBDE serum concentrations among electronics-dismantling workers before and after exposure-free vacation (median duration 28 days, range 21–35 days) indicate that the higher brominated congeners have shorter half-lives than lower brominated congeners (Sjödin et al. 1999b). The median percentage decrease in serum concentrations, based on 5–11 measurements per congener, were 14 (range 3.5–39), 14 (2.1–38), 14 (6.7–42), 30 (7.9–52), and 66 (47–100) for 2,2',4,4'-tetraBDE (BDE-47), 2,2',4,4',5,5'-hexaBDE (BDE-153), 2,2',4,4',5,6'-hexaBDE (BDE-154), 2,2',3,4,4',5',6-heptaBDE (BDE-183), and 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE-209), respectively. Although actual half-lives were not calculated, the data suggest that the half-lives of the lower brominated congeners were <1 year.

Congener patterns in humans may provide information on the nature or pathway of PBDE exposures (Hooper and McDonald 2000). Low tetra:deca congener ratios are suggestive of direct, recent, or occupational exposures to the parent PBDE mixture, whereas higher ratios may indicate an environmental pathway where exposures result from PBDEs that have leached from the parent mixtures and have been degraded in the environment.

A potential biomarker of exposure to PBDEs relates to their effect on the thyroid gland. As discussed in Sections 3.2.2.2, Endocrine Effects, thyroid changes in rats and mice include reduced serum thyroxine (T_4) levels with no changes in serum TSH (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998;WIL Research Laboratories 1984; Zhou et al. 2001, 2002). Additional studies are needed to characterize thyroid effects of PBDEs in humans and develop specific correlations between levels and duration of exposure and alterations in serum levels of T_4. This potential biomarker is not specific to PBDEs because PBBs and other antithyroid agents can have similar effects.

3.8.2 Biomarkers Used to Characterize Effects Caused by PBBs and PBDEs

Polybrominated Biphenyls. A recent study has used caffeine as a potential tool to characterize exposure and/or effect of PBBs (Lambert et al. 1990). In this test, caffeine is used as a metabolic probe of cytochrome P-450 isozymes activity from the CYP1A family, which in animals is significantly induced by PBBs (Safe 1984). The caffeine breath test (CBT) is primarily useful for detecting induction of CYP1A2 activity in human liver, and for that reason, it also has been used as a marker for exposure to PCBs, CDDs, and CDFs (Lambert et al. 1992). A volunteer population of 50 Michigan subjects with previously high serum PBB levels and 50 with undetectable or low serum levels was compared to a control population not exposed to PBBs (Lambert et al. 1992). Two tests were conducted, the CYP1A2-dependent caffeine 3-N-demethylase activity was monitored by the CBT, and 7-N-demethylase activity was monitored by the caffeine urinary metabolite ratio (CMR). PBB-exposed subjects had higher CBT values ($p<0.02$) than urban nonsmokers, but the values were comparable to those of urban smokers. The correlation between serum PBB levels and the CBT value was poor ($r^2=0.2$). The CMR value in PBB-exposed subjects was also higher than that of urban nonsmokers ($p<0.05$); there was no correlation between serum PBB levels and CMR values. Generally, smokers have higher CBT values than nonsmokers due to the presence of polycyclic aromatic hydrocarbons (PAH) in tobacco smoke, which induce CYP1A (Kotake et al. 1982).

The thyroid gland is a sensitive target of PBBs. As discussed in Section 3.2.2.2, Endocrine Effects, effects in exposed workers included increased serum thyrotropin, low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers (Bahn et al. 1980). Thyroid effects in PBB-treated rats included reduced serum levels of serum T_4 and T_3 (Akoso et al. 1982b; Allen-Rowlands et al. 1981; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978a; Meserve et al. 1992; Norris et al. 1975a, 1975b; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978; Werner and Sleight 1981). Therefore, serum levels of T_4 and/or other thyroid hormones are potential biomarkers of effect for PBBs. Although information is needed on the specific amount of change in these biomarkers associated with a demonstrably adverse effect, changes in these parameters might indicate potential impairment of health.

Many reports have been published regarding possible associations between PBB exposure and adverse health effects in populations from the state of Michigan. An early study compared the health status of people on quarantined farms with people in nonquarantined farms in the same area (Humphrey and Hayner 1975). The results showed no pattern of differences between the groups. Moreover, no abnormalities of heart, liver, spleen, or nervous system that could be related to PBB exposure were found

in physical examinations. A follow-up study examined the prevalence of selected symptoms in groups of varying potential exposure 4 years after exposure (Landrigan et al. 1979). In general, symptoms were more prevalent in two self-selected groups and were least prevalent in the group composed of chemical workers. No positive associations were found between serum PBB concentrations and symptom frequencies; yet a third group of studies reported an increased incidence of symptoms in Michigan farmers relative to a group of control Wisconsin farmers (Anderson et al. 1978a, 1978b, 1978c, 1979). As observed in other epidemiology studies, self-selected groups, which had lower PBB concentrations in serum, reported a high incidence of symptoms, compared to randomly selected groups. No specific biomarker of effect could be identified in the Michigan contamination episode. Furthermore, the prevalence of the reported symptoms had no consistent relationship to the extent or types of exposure, and most objective clinical measurements have failed to show a significant relationship to PBB exposure (Fries 1985a). Additional information regarding biomarkers for effects can be found in OTA (1990) and CDC/ATSDR (1990). For a more detailed discussion of the health effects caused by PBBs see Section 3.2.

Polybrominated Diphenyl Ethers. The thyroid is a critical target for PBDEs in animals and, based on these data (see Section 3.2.2.2 Endocrine Effects), serum T_4 level is a potential biomarker of effect in humans. Although this biomarker is not specific to PBDEs because other antithyroid agents can have similar effects, changes in T_4 can be considered to indicate potential impairment of health.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Polybrominated Biphenyls. PBBs are potent inducers of liver and kidney P-450 enzymes (MFO) (Haake et al. 1985; Halvorson et al. 1985; Shepherd et al. 1984), and as such, they could potentially enhance or decrease the toxicity of any substance that is metabolized by the P-450 system. PBBs are thought to potentiate the hepatotoxicity and nephrotoxicity of halogenated hydrocarbons and other substances by inducing P-450s that biotransform them to more toxic metabolites (Ahmadizadeh et al. 1984; Kluwe and Hook 1978; Kluwe et al. 1978, 1979, 1982; Kuo and Hook 1982; Roes et al. 1977). In these studies, rats and/or mice were given diets containing FireMaster BP-6 that provided doses of 0.13–13 mg/kg/day for periods of 10–28 days prior to intraperitoneal challenge with the halogenated hydrocarbons. Nephrotoxicity was assessed by measuring kidney weights and the levels of blood urea nitrogen, and by the accumulation of *p*-aminohippurate and/or tetraethylammonium (TEA) in renal cortical slices. Hepatotoxicity was assessed by relative liver weights and by levels of SGPT and/or SGOT. In most cases, exposure to PBBs alone did not affect the parameters of nephrotoxicity in animals. However,

exposure to PBBs alone usually caused increased relative liver weights and elevated levels of SGOT and SGPT. Pre-exposure to PBBs increased the hepatotoxicity and nephrotoxicity of chloroform (Ahmadizadeh et al. 1984; Kluwe and Hook 1978; Kluwe et al. 1978) and carbon tetrachloride (Kluwe et al. 1979, 1982) and the nephrotoxicity of trichloroethene and 1,1,2-trichloroethane (Kluwe et al. 1978, 1979). PBB pretreatment in dietary studies also potentiated the nephrotoxicity of the antibiotic, cephaloridine, in rats (Kuo and Hook 1982).

Pretreatment with PBBs also potentiated the lethality of chloroform, carbon tetrachloride, and 1,1,2-trichloroethane by decreasing the LD_{50} values (Kluwe et al. 1978, 1979) and the lethality of bromobenzene by decreasing the time to death (Roes et al. 1977) in mice after challenge with the halogenated hydrocarbon. In contrast, pretreatment of mice with PBBs in dietary studies increased the LD_{50} value of 1,2-dibromo-3-chloropropane (DBCP) but had no effect on the LD_{50} value of 1,2-dibromoethane (EDB) (Kluwe et al. 1981). Also, PBBs were found to reverse the depletion of nonprotein sulfhydryls (e.g., glutathione) caused by DBCP and EDB in the livers and kidneys of mice, suggesting that PBB exposure protected the mice from the lethality of DBCP by making glutathione more available for conjugation with the toxic metabolites.

No potentiation of toxicity was found when rats were co-exposed to diets containing PBB and mirex, photomirex, or kepone, compared with toxicity elicited by each of these substances alone (Chu et al. 1980).

Polybrominated Diphenyl Ethers. No specific information was located regarding interactions between PBDEs and other chemicals. PBDEs are inducers of hepatic microsomal enzymes (Carlson 1980a, 1980b; Fowles et al. 1994; Hallgren et al. 2001; Zhou et al. 2001, 2002) and therefore could potentially enhance or decrease the toxicity of any substance that is metabolized by the P-450 system.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to PBBs and PBDEs than will most persons exposed to the same level of PBBs and PBDEs 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 PBBs and PBDEs, or compromised function of organs affected by PBBs and PBDEs. Populations who are at greater risk due to their

unusually high exposure to PBBs and PBDEs are discussed in Section 6.7, Populations With Potentially High Exposures.

Limited information was located on populations that may be unusually susceptible to PBBs and PBDEs. As indicated in Section 3.4.4.2, breast milk constitutes the most important route of excretion of PBBs in lactating females, and this is likely to be the case for PBDEs as well. Therefore, women with high body burdens of PBBs and/or PBDEs who breast-feed may be placing their infants at a higher risk of potential health effects. Experiments in animals and model simulations in humans have shown that reduction in body fat markedly decreases the elimination half-life of PBBs (Domino et al. 1982; Tuey and Matthews 1980). For example, when a dose of 0.1 mg/day for 10 months was simulated in humans, the excretion rate in a lean individual was estimated at 10.2 μg/day; overweight individuals had an excretion rate of 4.1 μg/day. The cumulative excretion was 51% of the dose in lean subjects compared to 20.7% in overweight subjects. These data indicate that overweight individuals may be at higher risk because they store PBBs for a longer time than lean subjects. On the other hand, because lean individuals have a smaller fat compartment, their body tissues will contain higher concentrations of PBB than those in subjects with more fat who received the same exposure (Tuey and Matthews 1980); thus, leaner individuals may be more vulnerable to short-term effects than fatter individuals. Because of this phenomenon, a sudden reduction in body fat, such as that which could occur during dieting, may cause a redistribution of PBBs to potential target organs, which would also increase the potential for adverse health effects to such individuals.

Pregnant women and developing infants and fetuses should be viewed as sensitive populations for exposure to PBBs, PBDEs, and other thyroid hormone disrupting chemicals (Glinoer 1990; McDonald 2002; Morreale de Escobar et al. 2002). The condition of pregnancy normally puts a significant strain on the maternal thyroid system, which can be exacerbated by iodine deficiency; according to data from 1988 to 1994, iodine deficiency is prevalent in approximately 12% of the general population and 15% of women of child-bearing age in the United States (Hollowell et al. 1998). Thyroid hormones are essential for normal development of the nervous system, lung, skeletal muscle, and possibly other organ systems, and the fetus is dependent on maternal thyroid hormones at least until the fetal thyroid begins to produce T_4 and T_3, which occurs in humans at approximately 16–20 weeks of gestation (Zoeller and Crofton 2000). The potential of PBDEs to disrupt maternal, fetal, and newborn thyroid hormone levels is demonstrated by the Zhou et al. (2001, 2002) studies of pentaBDE (technical mixture) in rats as discussed in Section 3.2.2.2 (Endocrine Effects subsection).

People with exposure to anti-thyroid drugs (e.g., lithium), thyroid disease, or otherwise compromised thyroid function might have a more pronounced response to PBBs and PBDEs because of their underlying limitations in thyroid hormone production. Similarly, people with compromised function of other organs, such as those with liver or kidney diseases (e.g., liver cirrhosis or hepatitis B), could be considered more susceptible to health effects of PBBs and PBDEs.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to PBBs and PBDEs. 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 PBBs and PBDEs. 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 PBBs and PBDEs.

3.11.1 Reducing Peak Absorption Following Exposure

Ingested PBBs and PBDEs are absorbed by the gastrointestinal tract of humans and animals (see Section 3.4). Although specific recommendations for clinical treatment of acute intoxication from ingested PBBs and PBDEs were not located, recommendations based on experiences with PCBs are relevant. Treatments for acute poisonings from PCBs and related substances include the induction of emesis or gastric lavage and stomach pumping to decrease gastrointestinal absorption of the chemicals (Lemesh 1992). These procedures would not be beneficial if performed too long after exposure occurred. Administration of activated charcoal as a slurry, either aqueous or mixed with a saline cathartic or sorbitol, is frequently recommended to decrease the gastrointestinal absorption of PCBs, but the value of this treatment for reducing absorption of PCBs, PBBs, and PBDEs is unknown (HSDB 1992). Repetitive administration of activated charcoal might be useful in preventing reabsorption of metabolites. Rice bran fiber decreased absorption of PCBs in the gastrointestinal tract and had a stimulatory effect on fecal excretion of PCBs in rats (Takenaka et al. 1991), but it is unclear if rice bran would be of benefit in poisoned humans.

The detection of PBBs and PBDEs in the serum and fat of people who were occupationally exposed to these chemicals indicates that PBBs and PBDEs can also be absorbed by the lungs and skin in humans. Although no specific methods to reduce absorption of dermally applied or inhaled PBBs or PBDEs were

located, multiple washings of contaminated skin with soap and water immediately following exposure have been suggested to reduce the dermal absorption of PCBs (HSDB 1992). Studies with monkeys showed that soap and water was as effective as or better than such solvents as ethanol, mineral oil, or trichlorobenzene in removing PCBs from skin (Wester et al. 1990).

3.11.2 Reducing Body Burden

PBBs and PBDEs tend to accumulate in lipid-rich tissues and are slowly metabolized and eliminated from the body (see Section 3.4). Several methods to enhance the elimination of PBBs from the body have been examined in animals and are also relevant to PBDEs, including the restriction of caloric intake (to reduce total body fat), and the administration of various agents that interact with bile acids including activated charcoal, mineral oil and bile-binding resins such as cholestyramine (Kimbrough et al. 1980; McConnell et al. 1980; Polin and Leavitt 1984; Polin et al. 1985, 1991; Rozman et al. 1982). It should be mentioned, however, that based on the pharmacokinetic considerations discussed in Section 3.8.1, a rapid breakdown of fat, as might occur in dieting, might lead to a transient increase in PBB and PBDE levels in serum and other body tissues, possibly posing a significant re-exposure problem. Although some of the studies observed no enhanced elimination (Kimbrough et al. 1980; McConnell et al. 1980), others identified treatments that were effective in enhancing the biliary and intestinal elimination of PBB residues (Polin et al. 1991; Rozman et al. 1982). Polin et al. (1991) found that dietary intervention to reduce PBBs was dose dependent; treatment with 10% mineral oil and a 45% reduction in food intake resulted in a 69 and 23% reduction in body burden in rats fed PBBs at dietary concentrations of 0.1 and 100 ppm, respectively (Polin et al. 1991). A combination of mineral oil, colestipol, and dietary restriction was successful in reducing the PBB body burdens in chickens (Polin and Leavitt 1984; Polin et al. 1985), while each treatment alone had no effect in reducing PBB body burden. A 3-week treatment regimen that included dietary supplements of polyunsaturated oil, vitamins, and minerals, and heat stress has been applied in a pilot study to seven human subjects that were known to have been exposed to PBBs; following treatment, statistically significant reductions were measured in PBB concentrations in fat (Schnare et al. 1984). Although the lack of a separate control group complicates interpretation of the results of this study (each subject served as his/her own control), this treatment was developed for the purpose of reducing body burdens of fat-soluble psychoactive drugs (Schnare et al. 1984). A liquid diet was used for 16 individuals who developed symptoms following exposure to PCBs and polychlorinated dibenzofurans (Imamura and Tung 1984). Symptoms were reduced several months after the fasting period. This study is limited in that a control group was not used, and body burdens were not measured. Mobilization of PBBs or PBDEs from adipose tissue is not recommended in individuals with hepatic or renal disease (Lemesh 1992).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are no known methods for interfering with the mechanism of action of PBBs or PBDEs. Although the mechanism of action of PBBs and PBDEs is not completely understood, experimental evidence accumulated in recent years indicates that some PBB and PBDE congeners exert toxic actions by a process involving several steps (Safe 1984). This process begins with the binding of particular congeners to the Ah receptor and leads ultimately to enhancement of the CYP1A1 gene expression (see Section 3.5). It appears, therefore, that interfering with the initial step, binding to the receptor, or with any of the subsequent steps, would possibly prevent the expression of the toxic effects. It must be mentioned that several compounds have been identified that partially antagonize one or more Ah receptor-mediated responses (Bannister et al. 1989); their use, however, has been limited to experimental studies in animals. These compounds were successful antagonists when given before or at the same time as an Ah receptor activator (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) (Bannister et al. 1989). Therefore, the potential for interfering with the mechanism of PBB/PBDE effects after exposure has occurred is largely untested.

PBBs and PBDEs may also cause toxicity by other mechanisms of action. For example, some PBB congeners can be metabolized to reactive arene oxides (Kohli and Safe 1976; Kohli et al. 1978) that may alkylate critical cellular macromolecules and result in injury. PBDEs may disrupt thyroid hormones by induction of hepatic microsomal UDPGT, which increases the rate of T_4 conjugation and excretion, or by mimicking T_4 or T_3; PBDEs and their hydroxy metabolites are structurally similar to these thyroid hormones which are also hydroxy-halogenated diphenyl ethers (see Section 3.5.2). Clinical interventions designed to interfere with this mechanism or the metabolism of PBBs have yet to be developed.

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 PBBs and PBDEs 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 PBBs and PBDEs.

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 PBBs and PBDEs

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PBBs and PBDEs are summarized in Figures 3-4 and 3-5, respectively. The purpose of this figure is to illustrate the existing information concerning the health effects of PBBs and PBDEs. 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* (Agency for Toxic Substances and Disease Registry 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.

As indicated in Figure 3-4, information is available regarding systemic, immunological, neurological, developmental, reproductive, and carcinogenic effects of PBBs in humans. The information on effects in humans is derived from the Michigan contamination episode that involved chronic-duration oral exposure to contaminated food and from occupational exposure data in which it was assumed that exposure was predominantly through skin contact, although inhalation exposure cannot be ruled out.

Figure 3-4. Existing Information on Health Effects of PBBs

	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

Figure 3-5. Existing Information on Health Effects of PBDEs

	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

Information on health effects in animals is extensive and available for all effect categories, but is nearly completely limited to oral exposure studies, which appears to reflect experimental practicality and concern for what is thought to be the most prevalent and likely route of environmental exposure.

A limited amount of information is available on the systemic and carcinogenic effects of PBDEs in humans (Figure 3-5). Information on health effects of PBDEs in animals is available for all effect categories but, like PBBs, is mainly limited to oral exposure studies. In general, the health effects of PBDEs are less adequately studied than for PBBs (and PCBs).

3.12.2 Identification of Data Needs

Acute-Duration Exposure.

Polybrominated Biphenyls. The hepatotoxicity of PBBs in rats and mice is reasonably well characterized for acute-duration oral exposure (Bernert et al. 1983; Corbett et al. 1975; Gupta and Moore 1979; Gupta et al. 1981; Kimbrough et al. 1978b, 1980, 1981; Lee et al. 1975a, 1975b; Norris et al. 1975a; Raber and Carter 1986; Waritz et al. 1977). Effects on body weight in rats and mice and on the thyroid in rats are also well documented (Allen-Rowlands et al. 1981; Corbett et al. 1978; Fraker 1980; Gupta and Moore 1979; Kimbrough et al. 1981), and thyroid effects occurred at doses as low as those causing liver effects. Insufficient acute data exist to definitely establish if the thyroid effects are more critical than effects in the liver, but extensive data on thyroid effects from longer term studies and the functional nature of the changes suggest that this is the case and justify using a thyroid effect as the basis for an acute oral MRL. Acute oral studies in other species would clearly establish the most sensitive target and species for acute exposure. Tests with monkeys, guinea pigs, and mink would be informative because intermediate- and chronic-duration studies indicate that these species are more sensitive than the rat and that endocrinological effects are particularly sensitive end points.

Information on toxic effects of acute-duration exposure to PBBs by routes other than oral are limited to data on hepatic, renal, dermal, and ocular effects of inhalation and dermal exposure in rats or rabbits (Millischer et al. 1980; Needham et al. 1982; Norris et al. 1975a; Waritz et al. 1977), but these data may not be reliable due to study limitations and possible delayed lethality. Quantitative data for inhalation and dermal absorption of PBBs are lacking. Studies of inhalation and dermal absorption following exposure to soil containing PBBs (i.e., bioavailability studies) would be useful for assessing risk at a hazardous waste site. Further studies identifying target organs and examining the dose-response relationship

following acute inhalation and dermal exposure to PBBs would also be informative, although exposure via soil and acute toxicosis is not likely to ever be a concern.

Polybrominated Diphenyl Ethers. Acute-duration studies have documented effects of PBDEs mainly on the liver, thyroid, and body weight of orally exposed rats and mice (Argus Research Laboratories 1985a; Carlson 1980a, 1980b; Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren et al. 2001; IRCD 1974, 1975a, 1975b; Life Science Research Israel Ltd. 1987; NTP 1986; WIL Research Laboratories 1986; Zhou et al. 2001, 2002). The available data indicate that the thyroid is a particularly sensitive target of acute oral exposure and justify using thyroid effects as the basis for an acute oral MRL, but acute effects of PBDEs on the liver are not as well characterized as thyroid effects. Other studies indicate that immunosuppression and neurobehavior are important and potentially critical health end points for acute exposure to PBDEs that need to be further investigated (see discussions of data needs for Immunotoxicity and Neurotoxicity). Studies in other species would help to clearly establish the most sensitive target and species for acute exposure, as well as which animal toxicity data are the most relevant to humans and useful for assessing acute health risks.

Intermediate-Duration Exposure.

Polybrominated Biphenyls. The preponderance of toxicity data for PBBs are available from animals exposed to FireMaster FF-1 or FireMaster BP-6 in the diet or by gavage in intermediate-duration studies (Akoso et al. 1982a, 1982b; Allen et al. 1978; Allen-Rowlands et al. 1981; Aulerich and Ringer 1979; Byrne et al. 1987, 1988; Castracane et al. 1982; Darjono et al. 1983; Gupta and Moore 1979; Gupta et al. 1981; Kasza et al. 1978a, 1978b; Ku et al. 1978; Lambrecht et al. 1978; Lee et al. 1975a, 1975b; Loose et al. 1981; McCormack et al. 1978; Norris et al. 1975a; NTP 1983; Ringer et al. 1981; Sepkovic and Byrne 1984; Sleight and Sanger 1976; Sleight et al. 1978; Waritz et al. 1977; Werner and Sleight 1981). Studies have been performed with various species (rats have been tested most extensively), and there is evidence indicating that monkeys, guinea pigs, and mink may be the most sensitive. The liver, skin, stomach, and thyroid are unequivocal targets, but existing studies do not identify NOAELs for toxic effects in these organs in rats and/or more sensitive species. Hematologic changes indicative of anemia are consistently reported effects in various species, but the relative importance of these effects is not known. Evidence suggests that the LOAELs for thyroid effects in rats and hepatic effects in guinea pigs are similar (Akoso et al. 1982b; Sleight and Sanger 1976), but reproductive and developmental effects occurred in monkeys at a lower dosage. The serious nature of the developmental toxicity (fetal death) precludes derivation of an intermediate-duration oral MRL. Additional intermediate-duration dose-response studies determining

NOAELs for the most sensitive end points, as well as the most sensitive species, would be useful for possible MRL derivation. Studies addressing interspecies differences could help to better characterize the relative sensitivity of monkeys and humans, particularly the possibility that monkeys are more sensitive than humans, as indicated by the high reproductive/developmental toxicity of PPBs in this species that has not been noted in PBB-exposed workers or the Michigan cohort. These studies could also help elucidate the toxicological significance of effects in the thyroid and other endocrine organs, particularly since the reproductive effects may be related to endocrine imbalance.

Limited information is available on effects of PBBs in animals by inhalation or dermal exposure for intermediate durations (Millischer et al. 1980; Norris et al. 1975a; Waritz et al. 1977). Some inhalation data are available for octabromobiphenyl and decabromobiphenyl mixtures and some dermal data are available for octabromobiphenyl mixture, but intermediate-duration inhalation and dermal studies of FireMaster PBBs have not been performed. Studies of FireMaster FF-1 or FireMaster BP-6 would be particularly useful because these are likely to be the most toxic PBBs based on oral data and due to their higher content of potentially toxic congeners. Although the octabromobiphenyl mixture inhalation data are limited by numbers of animals, dose levels, and end points, and only one species (rat) was tested in the octabromobiphenyl mixture and decabromobiphenyl inhalation studies, it appears that these PBB mixtures are not highly toxic. Due to the inadequacies of the octabromobiphenyl mixture data and lack of any information on inhalation toxicity of the likely more potent FireMaster mixtures, there is insufficient basis for deriving an intermediate inhalation MRL. Although intermediate-duration inhalation studies of FireMaster PBBs would be particularly relevant to MRL derivation, they may not be practical due to the low volatilization potential of PBBs. The intermediate-duration dermal studies of octabromobiphenyl mixtures revealed some skin irritation in rabbits but no sensitization in guinea pigs. Additional studies could corroborate the potential for dermal irritation by PBBs and are relevant because the skin is a route of concern for exposure at or near hazardous waste sites. Intermediate-duration inhalation and dermal exposure studies of PBB-contaminated soil (e.g., bioavailability studies) that identify thresholds would be especially useful for risk assessment at a hazardous waste site.

Polybrominated Diphenyl Ethers. Available intermediate-duration oral studies in animals indicate that the liver and thyroid are the main systemic targets of repeated exposures to PBDEs as shown by effects that mainly include enlargement and histological alterations in both organs and changes in serum levels of thyroid hormones, particularly decreases in serum T_4 (Carlson 1980a; IRDC 1976, 1977; Norris et al. 1973, 1975a, 1975b; WIL Research Laboratories 1984; Zhou et al. 2001, 2002). Hepatic effects occurred at the lowest LOAEL and were used as the basis for an intermediate oral MRL, but thyroid effects

occurred at doses as nearly as low as those causing liver effects and the data are insufficient to clearly characterize liver effects as more critical than effects in the thyroid. Studies designed to identify NOAELs for deca-, octa-, and pentaBDE could provide a better basis for an intermediate duration MRL, as well as help to ascertain the most appropriate PBDE mixture on which to base a chronic MRL. Additionally, mechanistic studies indicate that PBDE-induced serum T_4 depression may be related to hepatic enzyme induction. Studies designed to better characterize the mechanism of action of PBDEs would help to better understand how the animal toxicity data can best be used to identify target end points and assess health risks in humans.

Chronic-Duration Exposure and Cancer.

Polybrominated Biphenyls. Information on chronic systemic toxicity of PBBs in animals is limited to an oral bioassay showing hepatic, gastric, hematologic, and/or thyroid effects in rats and mice (NTP 1992), and a study showing effects on skin, stomach, and body weight in two monkeys (Allen et al. 1979; Lambrecht et al. 1978). Although limited by the number of studies and species, the available chronic animal data corroborate the results of intermediate-duration studies with respect to the observed effects. Additional studies would be necessary to determine the most sensitive animal target organ and species for chronic exposure and to provide a basis for an MRL, as serious hepatic changes as well as weight loss, decreased survival, and developmental effects occurred at the lowest tested dosages. Because PBBs are no longer being produced, exposure is most likely to occur at a contaminated waste site. Therefore, chronic studies examining the effects of PBB-contaminated soil following oral, inhalation, and dermal exposure (i.e., bioavailability studies) would be particularly useful. Evaluations of the thyroid would be particularly informative because intermediate-duration animal studies indicate that the thyroid may be a particularly sensitive target organ.

There is sufficient evidence that commercial hexabromobiphenyl mixtures (FireMaster FF-1) are hepatocarcinogenic in rats and mice following acute, intermediate, and/or chronic exposure (Groce and Kimbrough 1984; Kimbrough et al. 1978b; NTP 1983, 1992). Additional animal studies could provide useful information on interspecies differences and carcinogenesis of other PBB mixtures.

Polybrominated Diphenyl Ethers. Information on the chronic toxicity and carcinogenicity of PBDEs is limited to two oral studies of decaBDE mixtures. In one of the studies, rats were fed a 77.4% pure decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) at doses of 0.01–1 mg/kg/day for approximately 2 years (Kociba et al. 1975; Norris et al. 1975a). Evaluations that included clinical signs,

body weight, food consumption, hematology, clinical chemistry, urine indices, and comprehensive histological examinations showed no exposure-related effects. In the other chronic study, decaBDE (94–97% pure) was fed to rats in doses of 1,120–2,550 mg/kg/day and mice in doses of 3,200–7,780 mg/kg/day for 103 weeks (NTP 1986). Histopathological changes occurred in both species that included liver effects in rats and liver and thyroid effects in mice. The highest chronic NOAELs in these studies are 1 mg/kg/day for the decaBDE/nonaBDE mixture (Kociba et al. 1975; Norris et al. 1975a) and 1,120 mg/kg/day for decaBDE (NTP 1986). Neither of these NOAELs is appropriate for estimation of a chronic oral MRL for all PBDEs because MRLs derived from these studies would be higher than the intermediate-duration oral MRL. The relative insensitivity of the chronic studies appears to be related to low potency of decaBDE compared to the pentaBDE mixture tested in the critical intermediate-duration study.

Neoplastic effects in the NTP (1986) bioassay included increased incidences of neoplastic nodules in the liver in the male and female rats and hepatocellular adenoma or carcinoma (combined) in the male mice. Slightly elevated incidences of thyroid gland follicular cell tumors were additionally observed in exposed male mice, although the increases were equivocal. No exposure-related neoplastic changes were found in the chronic study of the 77.4% decaBDE mixture (Kociba et al. 1975; Norris et al. 1975a), but the power of this study to detect carcinogenic effects is limited by the very low dose levels in comparison to those tested in the NTP bioassay.

Considering the insensitivity of the decaBDE studies for MRL derivation, as well as the lack of cancer information on the lower brominated PBB mixtures that may have higher carcinogenic potency than decaBDE, there is a need for chronic toxicity studies on pentaBDE and/or octaBDE. Evaluations that include the thyroid would be particularly informative because the acute and intermediate-duration animal studies indicate that the thyroid is a particularly sensitive target organ for PBDEs.

Genotoxicity.

Polybrominated Biphenyls. No information is available regarding potential genotoxic effects of PBBs in exposed humans. PBB mixtures or congeners were not genotoxic in any of the prokaryotic or eukaryotic animal systems tested. These include *in vitro* assays with *S. typhimurium* and *E. coli* bacteria (Haworth et al. 1983; Millischer et al. 1980; NTP 1983; Rossman et al. 1991), a host-mediated assay with *S. typhimurium* (Millischer et al. 1980), and *in vitro* assays with hamster cells (Galloway et al. 1987; Kavanagh et al. 1985; Williams et al. 1984), rat liver cells (Kavanagh et al. 1985; Williams et al. 1984),

mouse liver and lymphoma cells (Myhr and Caspary 1991; Williams et al. 1984), and human fibroblasts (Williams et al. 1984). PBBs also were inactive in *in vivo* unscheduled DNA synthesis assays with rat and mouse hepatocytes (Mirsalis et al. 1985, 1989) and in a micronucleus test with mice (Millischer et al. 1980). However, only some of these studies tested commercial PBB mixtures (Kavanagh et al. 1985; Millischer et al. 1980; Myhr and Caspary 1991; NTP 1983; Rossman et al. 1991; Williams et al. 1984). Additional studies of commercial mixtures could more fully characterize the genotoxic potential of PBBs, and provide information regarding differences in potencies of different mixtures and the sensitivities of different organisms. Cytogenic analysis of human populations exposed to PBBs in occupational settings, or exposed by consumption of food contaminated with PBBs, might make it possible to more adequately assess the genotoxic potential of these compounds in humans.

Polybrominated Diphenyl Ethers. A limited amount of information has been published on the genotoxicity of PBDEs. Cytogenetic examination of bone marrow cells showed no increase in aberrations in maternal and neonatal rats following maternal oral exposure to a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for 90 days prior to mating and during mating, gestation, and lactation (Norris et al. 1973, 1975a). *In vitro* assays found that decaBDE did not induce gene mutations in bacteria (*S. typhimurium*) or mammalian cells (mouse lymphoma L5178Y cells), and did not induce sister chromatid exchange or chromosomal aberrations in Chinese hamster ovary cells (NTP 1986). *In vitro* exposure to the single congeners 2,2',4,4'-tetraBDE, 3,4-diBDE, and 2-monoBDE caused increased recombinogenic activity in Chinese hamster SPD8 and Sp5V79 cells (Helleday et al. 1999). Although the weight of available evidence indicates that decaBDE is not genotoxic, studies using lower brominated mixtures and a wider variety of assay types would help to better characterize the genotoxic potential of PBDEs.

Reproductive Toxicity.

Polybrominated Biphenyls. A limited amount of information is available regarding reproductive effects in humans after exposure to PBBs. No evidence for PBBs-related effects on sperm counts, motility, or sperm morphology was found in a group of male Michigan workers exposed to PBBs by inhalation or dermal contact (Rosenman et al. 1979). No relationship was found between serum levels of PBBs and the frequency and duration of lactation in women exposed during the Michigan contamination episode (Thomas et al. 2001).

Although no alterations in fertility or litter size were observed in mink fed PBB-containing diets prior to breeding and during pregnancy (Aulerich and Ringer 1979; Ringer et al. 1981) or in the F_1 or F_2 generations of female F_0 rats fed PBB-containing diets during postimplantation gestation through weaning (McCormack et al. 1981), implantation was completely blocked in 40–67% of female rats exposed by gavage to PBBs between Gds 0 and 14 (Beaudoin 1979). Additionally, a lengthening of the menstrual cycle and prolonged implantation bleeding with decreased serum progesterone were observed in two of seven female monkeys fed a PBB-containing diet prior to and during pregnancy (Allen et al. 1979; Lambrecht et al. 1978). The dosage causing these reproductive effects in monkeys was the lowest tested in any intermediate-duration study of PBBs. In addition, alterations of male reproductive organs in rats (Gupta and Moore 1979) and in a monkey (Allen et al. 1978) have been observed after intermediate-duration exposure to lethal oral doses of PBBs. Histopathological alterations were not observed in male or female reproductive organs after intermediate- or chronic-duration, oral exposure of rats or mice to nonlethal doses of PBBs (NTP 1983, 1992). The animal data suggest that PBBs may cause adverse effects on reproductive organs and their function(s) and that reproductive organ functions during the early phases of pregnancy may be particularly sensitive to PBBs. Additional studies in animals exposed by oral and other routes, including multi-generation studies with pre-breeding exposure to assess effects on fertility in both males and females, might help to further identify the reproductive processes affected by PBBs and to determine the dose-response relationships. Studies elucidating the NOAEL region and relative susceptibility of sensitive species (e.g., monkeys) to reproductive and developmental effects would be particularly useful, as these data could enable derivation of an intermediate oral MRL.

Polybrominated Diphenyl Ethers. Information on the reproductive toxicity of PBDEs is limited to a single one-generation oral study of decaBDE in rats that found no exposure-related functional effects (Dow Chemical Co. 1975; Norris et al. 1975a, 1975b). Tests of octaBDE and/or pentaBDE, particularly second-generation studies designed to assess effects on fertility in both sexes, would better characterize the reproductive toxic potential of PBDEs and assure the adequacy of the intermediate oral MRL.

Developmental Toxicity.

Polybrominated Biphenyls. No studies were located regarding developmental effects in humans or animals after inhalation or dermal exposure to PBBs. Studies of fetal mortality rates in Michigan (Humble and Speizer 1984) and of physical and neuropsychological development in Michigan children exposed *in utero* or in early infancy during the peak of the 1973 contamination episode (Schwartz and Rae 1983; Seagull 1983; Weil et al. 1981) did not conclusively correlate the ingestion of PBBs with

developmental effects. Oral acute-, intermediate-, and chronic-duration studies of FireMaster FF-1 or FireMaster BP-6 in several species have reported fetotoxic and developmental effects, including embryolethality or increased mortality among nursing young (Allen et al. 1979; Beaudoin 1977, 1979; Groce and Kimbrough 1984; Lambrecht et al. 1978; Luster et al. 1980), fetal malformations (Beaudoin 1977; Corbett et al. 1975; Waritz et al. 1977), growth retardation in offspring (Allen et al. 1979; Aulerich and Ringer 1979; Corbett et al. 1975; Groce and Kimbrough 1984; Lambrecht et al. 1978; McCormack et al. 1981; Meserve et al. 1992; Ringer et al. 1981), liver effects in offspring (Moore et al. 1978; Werner and Sleight 1981), and performance deficits in tests of operant behavior in offspring (Henck and Rech 1986; Tilson 1992). A limited amount of data is available for octabromobiphenyl and decabromobiphenyl mixtures, which indicates that these PBBs are less developmentally toxic than FireMaster FF-1 or FireMaster BP-6 (Millischer et al. 1980; Waritz et al. 1977). Because FireMaster FF-1 caused developmental effects in monkeys at the lowest dosage tested in any study of PBBs, a chronic oral MRL could not be calculated; studies determining developmental NOAELs in sensitive species, therefore, would be particularly relevant. Additional studies regarding inhalation or dermal exposure to PBBs might help to determine whether or not the developmental toxicity of PBBs is route-specific. Studies on the mechanism(s) of action of PBBs in different animal species may provide a better understanding of the physiological and biochemical basis for the developmental toxicity of PBBs and a better basis for extrapolating from animal data in the evaluation of the hazard presented by PBBs to the development of human fetuses and children.

Polybrominated Diphenyl Ethers. Oral developmental toxicity studies have shown no evidence of teratogenicity of deca-, octa-, and pentaBDE in rats and rabbits, although fetotoxic effects, including skeletal ossification variations at maternally toxic doses, have occurred (Argus Research Laboratories 1985b; Breslin et al. 1989; Dow Chemical Co. 1975, 1985; Life Science Research Israel Ltd. 1987; Norris et al. 1975a, 1975b; WIL Research Laboratories 1986). Although effects of gestational exposure to PBDEs included minimally increased post-implantation loss in rats and increased skeletal variations in rabbits at octaBDE doses as low as 10 and 15 mg/kg/day (Argus Research Laboratories 1985b; Breslin et al. 1989; Life Science Research Israel Ltd. 1987), respectively, the available evidence appears to adequately show that developmental toxicity is not a critical effect of concern for PBDEs.

Immunotoxicity.

Polybrominated Biphenyls. Information regarding immunological effects of PBBs in humans is equivocal. Some groups of investigators reported altered lymphocyte transformation responses in

subjects accidentally exposed to PBBs through contaminated food (Bekesi et al. 1978, 1985; Roboz et al. 1985). Other investigators could not confirm this in the same populations (Landrigan et al. 1979; Silva et al. 1979). Carefully designed follow-up studies of these populations would provide valuable information regarding possible immunological effects of PBBs. Additional research on the binding of PBBs with different plasma fractions could be fruitful, since it appears that on a per cell basis in exposed subjects, there is . 100-fold excess of PBB in white cell fractions, compared to the erythrocyte fraction (Roboz et al. 1980, 1985). Acute oral data in rats and mice provided information regarding histopathology of the thymus, spleen, and lymph nodes (Fraker 1980; Fraker and Aust 1980; Gupta et al. 1981). Data from oral intermediate-duration studies in experimental animals suggest that the immune system may be one of the most sensitive targets for PBBs (Farber et al. 1978; Fraker 1980; Vos and van Genderen 1973, 1974). PBBs decreased the resistance of mice to infection by reducing antibody production (Loose et al. 1981), decreased the responsiveness of lymphocytes to mitogenic stimulation in rats and mice (Luster 1978, 1980) and pigs (Howard et al. 1980), altered thymus weight in rats (NTP 1983), and caused thymus atrophy in dogs (Farber et al. 1978), guinea pigs (Vos and van Genderen 1973), and cattle (Moorhead et al. 1977). No studies were located regarding the immunological effects of PBBs in animals after inhalation or dermal exposure. Due to the relatively low vapor pressure of PBBs, inhalation is not a predominant route of exposure. Additional oral studies using a battery of immunological tests would be useful to further define the immunological effects of PBBs.

Polybrominated Diphenyl Ethers. Information regarding the immunosuppressive potential of PBDE mixtures is essentially limited to evidence from acute-duration oral studies in animals exposed to relatively high doses of pentaBDE. The plaque-forming splenic cell antibody response to injected sheep red blood cells was significantly reduced in mice exposed to 72 mg/kg/day pentaBDE for 14 days (Fowles et al. 1994), and *in vitro* production of IgG immunoglobulin from pokeweed mitogen-stimulated splenocytes was reduced in mice exposed to 36 mg/kg/day pentaBDE for 14 days (Darnerud and Thuvander 1998). Other 14-day studies in mice found no changes in natural killer cell activity at #72 mg/kg/day (Fowles et al. 1994) or numbers of splenic and thymic lymphocyte subsets at #36 mg/kg/day (Darnerud and Thuvander 1998), although 18 mg/kg/day of the single congener 2,2',4,4'-tetraBDE caused significantly reduced numbers of total lymphocytes and CD4+, CD8+, and CD45R+ subtypes in the spleen (Darnerud and Thuvander 1998). Additional oral studies using a battery of immunological tests and a lower range of doses would serve to better characterize the immunotoxic potential of PBDEs.

Neurotoxicity.

Polybrominated Biphenyls. One study was located regarding neurological effects in humans after inhalation and/or dermal exposure to PBBs (Brown et al. 1981). No studies were located regarding neurological effects in animals after inhalation or dermal exposure to PBBs. Although neurological symptoms were reported with some frequency by certain residents of Michigan who were likely to have consumed PBB-contaminated food, several studies of Michigan residents (including workers in PBB manufacturing who presumably were exposed predominately by inhalation and dermal contact) found no statistically significant associations between levels of PBBs in serum or fat (from oral or dermal exposure to PBBs) and frequencies of subjectively reported neurological symptoms or performance on neuropsychological tests (Anderson et al. 1978c, 1979; Barr 1980; Brown and Nixon 1979; Brown et al. 1981; Landrigan et al. 1979; Stross et al. 1981; Valciukas et al. 1978, 1979). Studies of the neuropsychological development of children exposed *in utero* or in early infancy, likewise, were inconclusive in establishing an association with PBB exposure (Schwartz and Rae 1983; Seagull 1983; Weil et al. 1981). Subtle effects in neurobehavioral tests were found in rodents, including decreased motor activity (Geller et al. 1979; Tilson and Cabe 1979) and hind limb weakness (Cabe and Tilson 1978) after intermediate-duration, oral exposure and performance deficits in tests of learning behavior in the offspring of female mice and female rats exposed during gestation and lactation (Henck and Rech 1986; Henck et al. 1994; Tilson 1992). Histopathological alterations of brain or spinal nerve tissue revealed no abnormalities in rats or mice after intermediate- or chronic-duration oral exposure (NTP 1983, 1992). Periodic neurobehavioral testing of animals exposed to PBBs at multiple doses for chronic durations would be useful for determining if longer-term exposure leads to more severe neurological effects than those observed with intermediate-duration exposures.

Polybrominated Diphenyl Ethers. Very little information is available on the potential neurotoxic effects of PBDEs. Data are essentially limited to the results of three behavioral tests in animals showing some alterations in spontaneous locomotion behavior and learning and memory ability in mice that were tested at 2 months of age and as adults (4 months) following neonatal exposure (Pnds 3, 10, or 19) to single low oral doses of the congeners 2,2',4,4'-tetraBDE and 2,2',4,4',5-pentaBDE (Eriksson et al. 1998, 1999, 2001). Additional oral studies using a battery of neurobehavioral tests, particularly in developing animals, are needed to better characterize the potential for PBDEs to cause neurotoxic effects in humans.

Epidemiological and Human Dosimetry Studies.

Polybrominated Biphenyls. Epidemiology studies of people exposed by ingesting PBB-contaminated food as a result of the 1973 Michigan PBB contamination episode or who were exposed occupationally in the manufacture or distribution of PBBs have not provided conclusive evidence that detectable effects have occurred as a result of exposure to PBBs (Anderson et al. 1978c, 1979; Barr 1980; Henderson et al. 1995; Hoque et al. 1998; Humble and Speizer 1984; Landrigan et al. 1979; Thomas et al. 2001; Valciukas et al. 1978, 1979). Clinical examinations, including neuropsychological, liver function, and sperm count testing, of people who may have experienced the highest exposures did not conclusively identify particular effects or clinical signs associated with exposure (Brown and Nixon 1979; Brown et al. 1981; Rosenman et al. 1979; Schwartz and Rae 1983; Seagull 1983; Stross et al. 1981; Weil et al. 1981). No relationship was found between serum levels of PBBs and the frequency and duration of lactation in women exposed during the Michigan contamination episode (Thomas et al. 2001). A relationship between increasing serum levels of PBBs and increasing risk of breast cancer was indicated in case-control studies of women exposed during the Michigan episode (Henderson et al. 1995; Hoque et al. 1998), but the results are only suggestive due to factors such as small number of cases, insufficient information on known breast cancer risk factors, and confounding exposures to other organochlorine chemicals. The evidence for an association between breast cancer and PBBs is inconclusive and warrants further study. Continued monitoring of the Michigan cohort for prevalence of other types of cancer as the cohort ages are also of interest, because lifetime and short-term exposure to PBBs are known to cause cancer in animals, and the residence time of PBBs in the body is expected to be long. If human exposure to PBBs is found to be occurring at a hazardous waste site, the nearby population should be studied for both exposure and effect data.

Polybrominated Diphenyl Ethers. A limited amount of epidemiological information is available for PBDEs. Plasma levels of various organohalogen compounds, including the congener 2,2',4,4-tetraBDE, as well as serum hormone levels (free and total T_3 and T_4, TSH, free testosterone, follicle-stimulating hormone, lutenizing hormone, and prolactin), were analyzed in 110 men who consumed fatty fish from the Baltic Sea (Hagmar et al. 2001). There was a weak negative correlation between 2,2',4,4'-tetraBDE and plasma TSH after age adjustment, but 2,2',4,4'-tetraBDE could not explain more than 10% of the variance in TSH. No clear association was found between risk of non-Hodgkin's lymphoma and adipose tissue levels of 2,2'4,4'-tetraBDE in a case-control study of 77 Swedish men and women (Hardell et al. 1998; Lindstrom et al. 1998). 2,2'4,4'-TetraBDE was used as a marker for total PBDE exposure in both of these studies.

Animal data raise particular concern for effects of PBDEs on the thyroid as well as possible immunological, neurodevelopmental, and carcinogenic effects of exposure. Epidemiological investigations are needed to better characterize the potential for PBDEs to induce these and other kinds of effects. Considering the possibility that PBDEs can be transferred to the fetus across the placenta and that greater amounts might be transferred to nursing infants via breast milk, as well as evidence that perinatal exposure to PCBs and other similar chemicals may induce subtle neurological damage and immunological and thyroid effects in children, transgenerational studies would be particularly informative. Limitations that are likely to constrain the epidemiological investigations, such as unmeasured PBDE exposure concentrations and lack of controls for confounding co-exposures, should be addressed.

Biomarkers of Exposure and Effect.

Exposure.

Polybrominated Biphenyls. PBBs are stored primarily in adipose tissue and are present in serum and human milk of exposed populations. Several studies have shown that serum and adipose PBB levels are biomarkers of exposure (Brilliant et al. 1978; Humphrey and Hayner 1975; Lambert et al. 1990; Landrigan et al. 1979; Michels Blanck et al. 2000b; Rosen et al. 1995; Wolff et al. 1982). It has been proposed that measurement of PBB levels in adipose tissue may be a more reliable prediction of body burden than serum levels because of the high adipose/serum PBB partition ratio (Anderson 1985). However, once a stable correlation between adipose/serum levels has been characterized, serum levels are a better choice for surveillance and monitoring (Anderson 1985). Further studies on the predictive value of levels of PBB (particularly congeners) in serum and adipose tissue in individuals exposed to PBBs for acute, intermediate, and chronic durations would provide valuable information that could lead to early detection of PBB exposure.

A potential biomarker of exposure to PBBs is related to their effect on the thyroid gland. Effects in exposed workers included increased serum thyrotropin, low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers (Bahn et al. 1980), and effects in exposed rats included reduced levels of serum T_4 and T_3 (Akoso et al. 1982b; Allen-Rowlands et al. 1981; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978a; Meserve et al. 1992; Norris et al. 1975a, 1975b; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978; Werner and Sleight 1981). Additional studies could better characterize thyroid effects of PBBs in humans and develop specific correlations between levels and duration of exposure and alterations in serum hormone levels.

Polybrominated Diphenyl Ethers. PBDEs also accumulate in adipose tissue, serum, and breast milk of the general population due to their lipophilic characteristics. Concentrations of PBDEs in breast milk are useful, non-invasive markers of maternal body burdens and of *in utero* and lactational exposures, but body burden assessments are limited by a lack of time-trend data for PBDEs in the milk of U.S. populations (Hooper and McDonald 2000). Breast milk monitoring programs are needed to provide time-trend data and to verify findings that PBDE levels have been exponentially increasing in breast milk during the past 25 years (Norén and Meironyté 1998, 2000). Studies on the predictive value of levels of PBDEs in serum and adipose tissue could provide useful information for detection and monitoring of exposure.

A potential biomarker of exposure to PBDEs relates to their effect on the thyroid gland. Thyroid changes in rats and mice include reduced serum T_4 levels with no changes in serum TSH (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998;WIL Research Laboratories 1984; Zhou et al. 2001, 2002). Additional studies could characterize thyroid effects of PBDEs in humans and develop specific correlations between levels and duration of exposure and alterations in serum levels of T_4.

Effect.

Polybrominated Biphenyls. There are no specific biomarkers of effects for PBBs. Numerous studies have attempted to correlate serum and adipose PBB levels with an array of symptoms and health complaints in PBB exposed subjects from the state of Michigan (Anderson et al. 1978a, 1978b, 1978c, 1979; Bekesi et al. 1978; Humphrey and Hayner 1975; Landrigan et al. 1979; Stross et al. 1979). Thus far, no significant correlation has been found. Continued follow-up studies on the Michigan cohort would provide information on effects that may have a long latency, such as cancer. Elevated levels of two cytochrome P-450I-dependent enzymes were observed among PBB exposed subjects, relative to controls (Lambert et al. 1990). The thyroid is a sensitive target for PBBs and characteristic changes include reduced serum levels of T_4 and other thyroid hormones (Akoso et al. 1982b; Allen-Rowlands et al. 1981; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978a; Meserve et al. 1992; Norris et al. 1975a, 1975b; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978; Werner and Sleight 1981), indicating that they are potential biomarkers of effect. Levels of CYP enzymes and thyroid hormones, however, are not specific for PBB exposure. Further studies designed to identify specific biomarkers of effects of PBBs would facilitate medical surveillance leading to early detection of potentially adverse health effects and possible treatment. Congener-specific analysis may be useful for characterizing dioxin-like health effects.

Polybrominated Diphenyl Ethers. Biomarkers that could be used to characterize health effects caused specifically by PBDEs have not been identified. The thyroid is a critical target for PBDEs in animals, as discussed in Section 3.2.2.2, Endocrine Effects, and serum T_4 is a potential biomarker of effect for these chemicals in humans. Although this biomarker is not specific to PBDEs because other antithyroid agents can have similar effects, changes in T_4 could be considered to indicate potential impairment of health.

Absorption, Distribution, Metabolism, and Excretion.

Polybrominated Biphenyls. There are no quantitative data regarding absorption in humans via the inhalation route, but data from occupationally exposed individuals and individuals who ingested food contaminated with PBBs suggest that exposure by the oral or dermal route may lead to considerable accumulation of PBBs in tissues (Anderson et al. 1978c; Eyster et al. 1983; Landrigan et al. 1979). The animal data indicate that the main component of a commercial PBB mixture (2,2,'4,4',5,5'-hexa-bromobiphenyl) is efficiently absorbed by the oral route (Matthews et al. 1977; Tuey and Matthews 1980). Data regarding absorption after inhalation exposure was limited to a single study (Waritz et al. 1977). There are no data regarding absorption via the dermal route. No studies were located in which several doses of different PBB congeners were administered by the inhalation, oral, and dermal routes, and for various exposure periods. Such studies could provide information on the relationship between bromination patterns and absorption efficiency and rates of absorption by the different routes of exposure. In addition, studies with different PBB mixtures could help determine possible interaction effects among congeners that could affect absorption.

Distribution data are limited to qualitative information derived from cases of accidental ingestion of food contaminated with PBBs, cases of occupational exposure via dermal contact (Eyster et al. 1983; Landrigan et al. 1979) and autopsy reports (Miceli et al. 1985). These data suggest that PBBs distribute preferentially to tissues with high fat content regardless of the route of exposure. Data derived from oral administration of PBBs to animals indicate that PBBs are distributed first to liver and muscle and then to adipose tissue where they are stored (Domino et al. 1982; Lee et al. 1975; Matthews et al. 1977). Little information regarding distribution of PBBs could be drawn from the limited number of studies in animals administered PBBs by the inhalation or dermal routes. Additional well-conducted studies by these routes of exposure would provide useful information regarding possible route-dependent distribution patterns. Studies regarding distribution through the placenta after inhalation and dermal exposure were not available.

Data regarding biotransformation of PBBs in humans are limited to individuals who accidentally consumed food contaminated with PBBs or who were exposed to PBBs in the workplace (Wolff and Aubrey 1978; Wolff et al. 1979a). The use of human cell systems in culture might be considered a useful addition to whole animal studies for studying the metabolic fate of PBBs. There are studies regarding the metabolism of some PBB congeners after oral administration to rats (Sparling et al. 1980), rabbits (Kohli et al. 1978), and pigs (Kohli and Safe 1976). However, the PBBs mainly studied were monobromobiphenyls and dibromobiphenyls, which are only trace components of FireMaster mixtures. Therefore, studies on the *in vivo* metabolism of the main components of commercial PBB mixtures would provide valuable information regarding the metabolic disposition of highly brominated congeners. A limited amount of information is available on the metabolism of PBBs in farm animals (e.g., dairy cows, chickens). This is a data gap because people exposed to PBBs during the Michigan PBB contamination episode were predominately exposed by consuming products of farm animals. Although information regarding metabolism after inhalation or dermal exposure is lacking, there is no evidence to suggest that other pathways would operate after exposure by these routes.

Studies regarding urinary or fecal excretion of PBBs in humans were not located; however, elimination of PBBs through maternal milk is well documented (Brilliant et al. 1978; Eyster et al. 1983; Jacobson et al. 1984; Landrigan et al. 1979). Fecal excretion of unabsorbed PBBs appears to be the main route of elimination of highly brominated congeners after oral exposure (Matthews et al. 1977; Norris et al. 1975a; Rozman et al. 1982), whereas polar derivatives formed by lower brominated congeners appeared to be excreted mainly in the urine (Kohli and Safe 1976; Kohli et al. 1978; Sparling et al. 1980). Although data regarding excretion in animals after inhalation and dermal exposure were not located, there is no reason to believe that results from additional studies would reveal different patterns of excretion.

Polybrominated Diphenyl Ethers. A limited amount of data is available on the toxicokinetics of PBDEs. There are data gaps in a number of areas, particularly for octaBDE and pentaBDE mixtures and the tetra and hexa congeners that are most prevalent in the environment. Quantitative absorption studies could corroborate the conclusions on oral uptake in animals that are based on elimination and excretion data. Metabolism studies would help to characterize the enzymes involved as well as the transformation of some congeners to biologically active hydroxylated BDEs and the debromination of decaBDE to lower brominated BDEs.

Comparative Toxicokinetics.

Polybrominated Biphenyls. The data suggest that there are qualitative differences in the toxicokinetic disposition of PBBs among humans and among animal species (Wolff and Aubrey 1978; Wolff et al. 1979a). However, these differences appear to be highly dependent on the specific congener or mixture studied. In general, all species absorb PBBs, with varying efficiency, and accumulate PBBs in tissues rich in fat. Once absorbed, PBBs are distributed in a biphasic manner in all examined animal species (Domino et al. 1982; Ecobichon et al. 1983; Matthews et al. 1977). No studies were located that provide information regarding differences or similarities in metabolic disposition of PBBs between humans and animals. Limited data in humans indicate that fecal excretion of PBB residues occur (Eyster et al. 1983). Experimental data in animals suggest that the rate and extent of PBB elimination in the urine and feces are dependent on the degree and pattern of bromination (Kohli et al. 1978; Matthews et al. 1977; Sparling et al. 1980). 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, but the database is not complete enough for identifying a most sensitive species. Although the toxicological data in humans are limited and inconclusive, adverse immune effects observed in humans (Bekesi et al. 1978) have also been observed in rats, mice, and pigs (Howard et al. 1980; Luster et al. 1978, 1980) suggesting that any of these species may represent a suitable animal model for humans. The only reported PBPK model for PBBs describes the distribution and body burden of the major component of FireMaster mixtures, 2,2',4,4',5,5'-hexa-bromobiphenyl, in the rat (Tuey and Matthews 1980). The serum mean half-life of 6.5 years predicted using this model is shorter than half-life values of approximately 12–29 years estimated using human sera data from the Michigan PBB cohort (Lambert et al. 1990; Michels Blanck et al. 2000b; Rosen et al. 1995). This indicates a need for an improved PBPK model for extrapolating animal data to humans and/or for studies designed to produce data for improving the performance of PBPK analyses.

Polybrominated Diphenyl Ethers. Insufficient data are available to determine whether qualitative differences in the toxicokinetic disposition of PBDEs exist between humans and animals and among animal species. Differences are likely to be dependent on the specific congener or mixture studied, and pharmacokinetic modeling studies could help to determine the validity of extrapolating data. Most of the available toxicokinetic studies of PBDEs have been performed in rats, and studies in other species could help to ascertain the most relevant animal model.

Methods for Reducing Toxic Effects.

Polybrominated Biphenyls. The mechanism by which PBBs enter the blood stream in humans is not known; consequently, there are no established methods for reducing absorption. Studies in experimental animals that could identify substances that prevent or delay absorption and that do not represent a toxic risk *per se* would be valuable. There are no established methods for reducing body burden in humans, but studies in animals and model simulations in humans indicate that reducing body fat markedly increases elimination of PBBs (Domino et al. 1982; Tuey and Matthews 1980). The effect of reduction of body fat (e.g., by dieting and exercising) in PBB-exposed humans has not been fully researched.

The mechanism of toxic action of PBBs is not completely understood and no methods exist to block the toxic response due to exposure to PBBs. A more complete characterization of the cytosolic Ah receptor protein, to which some PBB congeners are thought to bind, and understanding of physiological effects of receptor blockage would be useful for the possible identification of blockers of Ah receptor-mediated toxic effects. Further studies aimed at elucidating the nonreceptor-mediated mechanism of action of some PBBs would also be valuable.

Polybrominated Diphenyl Ethers. The mechanism by which PBDEs enter the blood stream is not known, there are no established methods for reducing body burden of PBDEs, and the mechanisms of toxic action of PBDEs are incompletely understood. Types of studies that could address these data gaps and possibly provide information on reducing toxic effects of PBDEs are discussed in the preceding subsection on PBBs.

Children's Susceptibility.

Polybrominated Biphenyls. Information on health effects of PBBs in children is available from several studies of the Michigan feed contamination episode. A 1976 study of Michigan children likely to have been exposed to PBBs found that the number of subjectively reported symptoms of ill health, including several symptoms of neurological effects, did not increase with increasing serum PBB levels, but rather decreased; general neurological examinations did not reveal a pattern of abnormality among the Michigan children (Barr 1980). Studies of fetal mortality rates in Michigan (Humble and Speizer 1984) and of physical and neuropsychological development in Michigan children exposed during the contamination episode (Schwartz and Rae 1983; Seagull 1983; Weil et al. 1981) did not conclusively correlate the ingestion of PBBs with effects. Neurobehavioral alterations have been observed in rats following

gestational and lactational exposure to PBBs (Henck and Rech 1986; Henck et al. 1994; Tilson 1992). Other effects in offspring of rats exposed to PBBs during gestation and lactation include decreased serum levels of thyroid hormone levels (Meserve et al. 1992; Werner and Sleight 1981). These effects in offspring are consistent with evidence that the thyroid gland is an unequivocal target of PBBs in adult animals. No information was located on possible immunological effects of PBBs in children, and data in adult humans are limited and largely inconclusive (Bekesi et al. 1978; Landrigan et al. 1979; Roboz et al. 1985; Silva et al. 1979; Stross et al. 1981), but exposure to PBBs caused altered immune responses in a variety of animal species, which suggests that children may also be affected. Continued assessment of children exposed to PBBs during the Michigan contamination episode, with particular emphasis on evaluation of cognitive abilities, thyroid function, and immune competence, would help to better assess the susceptibility of children to PBBs.

Polybrominated Diphenyl Ethers. No information was located on health effects of PBDEs in newborn or older children. Thyroid and neurobehavioral alterations have been observed in animals following pre- and/or postnatal exposure to commercial PBDE mixtures and single PBDE congeners, indicating that these are potential effects of concern in exposed children. Serum levels of thyroid T_4 and T_3 hormones were reduced in offspring of rats that were orally exposed to pentaBDE during gestation and lactation and in rats exposed as weanlings (Zhou et al. 2002). Alterations in spontaneous locomotion behavior and learning and memory ability were observed in mice that were tested at 2 months of age and as adults (4 months) following neonatal exposure to single low oral doses of the congeners 2,2',4,4'-tetraBDE and 2,2',4,4',5-pentaBDE (Eriksson et al. 1998, 1999, 2001). One of these studies found effects in mice treated at either 3 or 10 days of age, but not at 19 days of age, suggesting that there was a critical window for the induction of behavioral disturbances (Eriksson et al. 1999). Additional studies are needed to better characterize the potential susceptibility of children to the effects of PBDEs on the thyroid and neurodevelopment, particularly considering the possibility that these effects are related to the dependence of central nervous system development on thyroid hormones. No information is available regarding the immunosuppressive potential of PBDEs in children or young animals, indicating that studies of immune competence in developing animals would also help to more fully assess children's susceptibility to PBDEs.

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

Ongoing studies that are relevant to health effects of PBBs and PBDEs, as identified in the Federal Research in Progress database (FEDRIP 2002) and the websites of various government agencies, are listed in Table 3-6.

Table 3-6. Ongoing Studies on the Health Effects of PBBs and PBDEs

Investigator	Affiliation	Research description	Sponsor
Hammock B	University of California, Davis, California	Support for testing hypotheses regarding the association of PBBs, PBDEs, and other known xenobiotic immunotoxicants and neurotoxicants with autism	NIEHS/EPA[1]
Huwe JK	Agricultural Research Service, Fargo, North Dakota	Development of effective remediation procedures for PBDEs and other persistent organic pollutants in animal tissues and their environment	USDA
Ludewig G	University of Kentucky, Lexington, Kentucky	A multispecies approach to analyze the toxic effects of PBDEs on organs and development	EPA
Palmer BD	University of Kentucky Medical Center, Lexington, Kentucky	Multidisciplinary/multispecies investigation of endpoints and mechanisms of action for PBDEs and PCDEs, including structure-activity relationships for endocrine disruption	NIEHS/EPA[1]
Robertson L	University of Kentucky Medical Center, Lexington, Kentucky	Laboratory synthesis of pure PBDE and PCDE congeners and their metabolites	NIEHS/EPA[1]
Sikka HC	State University of New York College at Buffalo, Buffalo, New York	Disposition and metabolism of PBDEs in fish	NOAA[2]
Trosko JE	Michigan State University, East Lansing, Michigan	Epigenic effects of PBBs and other environmental toxicants on cellular communication pathways	NIEHS/EPA[1]

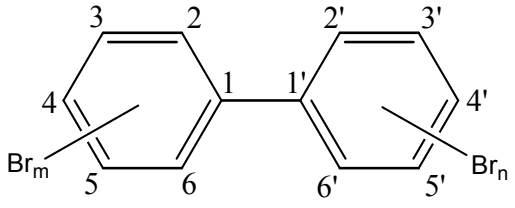
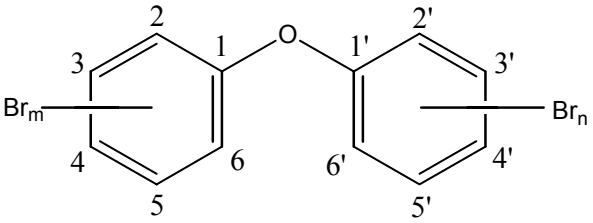
[1]NIEHS/EPA Superfund Basic Research Program
[2]National Sea Grant College Program

EPA = U.S. Environmental Protection Agency; NIEHS = National Institute of Environmental Health Sciences; NOAA = National Oceanic and Atmospheric Administration; USDA = U.S. Department of Agriculture

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs) are each classes of structurally similar brominated hydrocarbons. PBBs are a class of chemical compounds in which 2–10 bromine atoms are attached to the biphenyl molecule. PBDEs are a class of chemical compounds in which 2–10 bromine atoms are attached to the diphenyl ether molecule. Monobrominated structures (i.e., one bromine atom attached to the molecule) are often included when describing PBBs and PBDEs. The general chemical structures of PBBs and PBDEs are similar when viewed in one dimension, differing only in an ether linkage, as shown below:

 where m + n = 1 to 10	 where m + n = 1 to 10
PBBs	PBDEs

It can be seen from the structures that a large number of brominated compounds are possible. The 209 possible compounds for both PBBs and PBDEs are called “congeners”. PBBs and PBDEs can also be categorized by degree of bromination. The term “homolog” is used to refer to all PBBs and PBDEs with the same number of bromines (e.g., tribromobiphenyls and tribromodiphenyl ether). Based on the number of bromine substituents, there are 10 homologous groups of PBBs and PBDEs (monobrominated through decabrominated). Each homologous group contains one or more congeners. The mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decabromo-congeners can exist in 3, 12, 24, 42, 46, 42, 24, 12, 3, and 1 forms, respectively. Homologs with different substitution patterns are referred to as isomers. For example, the dibromobiphenyl and dibromodiphenyl ether homologs both contain 12 isomers. The numbering system for PBBs and PBDEs are 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. In a PBB molecule, the benzene rings can rotate around the bond connecting them; the two extreme configurations are planar (the two benzene rings are in the same plane; dihedral angle=0E) and nonplanar (the two benzene rings are in perpendicular planes to each other; dihedral angle=90E). 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 bromine atoms forces the benzene rings to adopt configuration with a larger dihedral angle or nonplanar configuration. The benzene rings of non-*ortho* substituted PBBs, as well as mono-*ortho* substituted PBBs, may assume a small dihedral angle (in which the dihedral angle is small, but >0E) or "near" planar configuration. These molecules 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 nonplanar congeners. In contrast, the benzene rings in a PBDE molecule do not rotate freely around the ether linkage connecting them due to a high barrier to rotation resulting from a 120E bend at the ether linkage and steric effects due to the large size of bromine atoms. As a consequence, PBDEs do not assume planar dioxin-like configurations (Hardey 2002).

Like PCBs, the 209 congeners for PBBs and PBDEs 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 numbers, also referred to as congener, IUPAC, or BZ numbers, are widely used for identifying individual congeners of PBBs and PBDEs. For example, the PBB congener, 2,2',4,4',5,5'-hexabromobiphenyl, may be referred to as BB-153 in this document. Likewise, the PBDE congener, 2,2',4,4'-tetrabromodiphenyl ether may be referred to as BDE-47 in this document. The identities of several PBB and PBDE congeners are shown in Table 4-1 (WHO 1994a, 1994b).

Polybrominated Biphenyls. Michigan Chemical Corporation, the major producer of PBBs from 1970 to 1976, marketed mixtures of PBBs under the trade name FireMaster (e.g., BP-6 and FF-1). Other producers of PBBs in the United States included White Chemical Corporation (Bayonne, New Jersey) and Hexcel Corporation (Sayreville, New Jersey), which both produced technical mixtures of octabromobiphenyl and decabromobiphenyl until 1979. The trade names of some commercial PBB mixtures formerly produced in other countries are Berk Corporation, Great Britain (e.g., BerkFlam, Flammex), Chemische Fabrik Kalk, Germany (e.g., Bromkal), and Ugine Kuhlmann (now Atofina in France) (e.g., Adine).

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners

		CAS No.[a]	
IUPAC No.[b]	Compound/ substituents	Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
	Biphenyl	92-52-4	92-52-4
	Monobromo-	26264-10-8	101-55-3
1	2	2052-07-7	
2	3	2113-57-7	
3	4	92-66-0	
	Dibromo-	27479-65-8	2050-47-7
4	2,2N	13029-09-9	
5	2,3	115245-06-2	
6	2,3N	49602-90-6	
7	2,4	53592-10-2	
8	2,4N	49602-91-7	
9	2,5	57422-77-2	
10	2,6	59080-32-9	
11	3,3N	16400-51-4	
12	3,4	60108-72-7	
13	3,4N	57186-90-0	
14	3,5	16372-96-6	
15	4,4N	92-86-4	
	Tribromobiphenyl	51202-79-0	49690-94-0
16	2,2’,3		
17	2,2’,4		
18	2,2N,5	59080-34-1	
19	2,2’,6		
20	2,3,3’		
21	2,3,4		
22	2,3,4’		
23	2,3,5		
24	2,3,6		
25	2,3’,4		
26	2,3N,5	59080-35-2	
27	2,3’,6		
28	2,4,4N	6430-90-6	
29	2,4,5	115245-07-3	
30	2,4,6	59080-33-0	

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners *(continued)*

		CAS No.[a]	
IUPAC No.[b]	Compound/ substituents	Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
31	2,4N,5	59080-36-3	
32	2,4N,6	64258-03-3	
33	2’,3,4		
34	2’,3,5		
35	3,3’,4		
36	3,3’,5		
37	3,4,4N	6683-35-8	
38	3,4,5	115245-08-4	
39	3,4N,5	72416-87-6	
	Tetrabromobiphenyl	40088-45-7	40088-47-9
40	2,2’,3,3’		
41	2,2’,3,4		
42	2,2’,3,4’		
43	2,2’,3,5		
44	2,2’,4,5’		
45	2,2’,3,6		
46	2,2’,3,6’		
47	2,2N,4,4'	66115-57-9	
48	2,2’,4,5		
49	2,2N,4,5'	60044-24-8	
50	2,2’,4,6		
51	2,2N,4,6'	97038-95-4	
52	2,2N,5,5'	59080-37-4	
53	2,2N,5,6'	60044-25-9	
54	2,2N,6,6'	97038-96-5	
55	2,3,3N,4	97038-99-8	
56	2,3,3’,4’		
57	2,3,3’,5		
58	2,3,3’,5’		
59	2,3,3’,6		
60	2,3,4,4’		
61	2,3,4,5	115245-09-5	
62	2,3,4,6	115245-10-8	
63	2,3,4’,5		
64	2,3,4’,6		
65	2,3,5,6		

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners *(continued)*

		CAS No.[a]	
IUPAC No.[b]	Compound/ substituents	Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
66	2,3N,4,4N	84303-45-7	
67	2,3',4,5		
68	2,3',4,5'		
69	2,3',4,6		
70	2,3N,4N,5	59080-38-5	
71	2,3',4',6		
72	2,3',5,5'		
73	2,3',5',6		
74	2,4,4',5		
75	2,4,4N,6	64258-02-2	
76	2',3,4,5		
77	3,3N,4,4N	77102-82-0	
78	3,3',4,5		
79	3,3N,4,5N	97038-98-7	
80	3,3N,5,5N	16400-50-3	
81	3,4,4N,5	59589-92-3	
	Pentabromobiphenyl	56307-79-0	32534-81-9
88	2,2N,3,4,6	77910-04-4	
89	2,2',3,4,6'		
90	2,2',3,4',5		
91	2,2',3,4',6		
92	2,2',3,5,5'		
93	2,2',3,5,6		
94	2,2',3,5,6'		
95	2,2N,3,5N,6	88700-05-4	
96	2,2',3,6,6'		
97	2,2',3',4,5		
98	2,2',3',4,6		
99	2,2N,4,4N,5	81397-99-1	
100	2,2N,4N,4N,6	97038-97-6	
101	2,2N,4,5,5N	67888-96-4	
102	2,2N,4,5,6N	80274-92-6	
103	2,2N,4,5N,6	59080-39-6	
104	2,2N,4,6,6N	97063-75-7	
105	2,3,3',4,4'		
106	2,3,3',4,5		
107	2,3,3',4',5		

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners *(continued)*

		CAS No.[a]	
IUPAC No.[b]	Compound/ substituents	Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
108	2,3,3’,4,5’		
109	2,3,3’,4,6		
110	2,3,3’,4’,6		
111	2,3,3’,5,5’		
112	2,3,3’,5,6		
113	2,3,3’,5’,6		
114	2,3,4,4N,5	96551-70-1	
115	2,3,4,4’,6		
116	2,3,4,5,6	38421-62-4	
117	2,3,4’,5,6		
118	2,3N,4,4N,5	6788-97-5	
119	2,3N,4,4N,6	86029-64-3	
120	2,3N,4,5,5N	80407-70-1	
121	2,3’,4,5’,6		
122	2’,3,3’,4,5		
123	2N,3,4,4N,5	74114-77-5	
124	2’,3,4,5,5’		
125	2’,3,4,5,6’		
126	3,3N,4,4N,5	84303-46-8	
127	3,3N,4,5,5N	81902-33-2	
	Hexabromobiphenyl	36355-01-8	36483-60-0
128	2,2N,3,3N,4,4N	82865-89-2	
129	2,2’3,3’,4,5		
130	2,2N,3,3N,4,5N	82865-90-5	
131	2,2’,3,3’,4,6		
132	2,2N,3,3N,4,6N	119264-50-5	
133	2,2N,3,3N,5,5N	55066-76-7	
134	2,2’,3,3’,5,6		
135	2,2N,3,3N,5,6N	119264-51-6	
136	2,2’,3,3’,6,6’		
137	2,2N,3,4,4N,5	81381-52-4	
138	2,2N,3,4,4N,5N	67888-98-6	
139	2,2’,3,4,4’,6		
140	2,2’,3,4,4’,6		
141	2,2N,3,4,5,5N	120991-47-1	
142	2,2’,3,4,5,6		
143	2,2’,3,4,5,6’		

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners *(continued)*

		CAS No.[a]	
IUPAC No.[b]	Compound/ substituents	Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
144	2,2N,3,4,5N,6	119264-52-7	
145	2,2',3,4,6,6'		
146	2,2',3,4',5,5'		
147	2,2',3,4',5,6		
148	2,2',3,4',5,6'		
149	2,2N,3,4N,5N,6	69278-59-7	
150	2,2N,3,4N,5,6N	93261-83-7	
151	2,2N,3,5,5N,6	119264-53-8	
152	2,2',3,5,6,6'		
153	2,2N,4,4N,5,5N	59080-40-9	
154	2,2N,4,4N,5,6N	36402-15-0	
155	2,2N,4,4N,6,6N	59261-08-4	
156	2,3,3N,4,4N,5	77607-09-1	
157	2,3,3N,4,4N,5N	84303-47-9	
158	2,3,3',4,4',6		
159	2,3,3N,4,5,5N	120991-48-2	
160	2,3,3',4,5,6		
161	2,3,3',4,5',6		
162	2,3,3',4',5,5'		
163	2,3,3',4',5,6		
164	2,3,3N,4N,5N,6	82865-91-5	
165	2,3,3',5,5',6		
166	2,3,4,4',5,6		
167	2,3N,4,4N,5,5N	67888-99-7	
168	2,3N,4,4N,5N,6	84303-48-0	
169	3,3N,4,4N,5,5N	60044-26-0	
	Heptabromobiphenyl	35194-78-6	68928-80-3
170	2,2N,3,3N,4,4N,5	69278-60-0	
171	2,2',3,3',4,4',6		
172	2,2N,3,3N,4,5,5N	82865-92-7	
173	2,2',3,3',4,5,6		
174	2,2N,3,3N,4,5,6N	88700-04-3	
175	2,2',3,3',4,5',6		
176	2,2',3,3',4,6,6'		
177	2,2',3,3',4,5,6'		
178	2,2N,3,3N,5,5N,6,	119264-54-9	
179	2,2',3,3',5,6,6'		

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners *(continued)*

		CAS No.[a]	
IUPAC No.[b]	Compound/ substituents	Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
180	2,2N,3,4,4N,5,5N	67733-52-2	
181	2,2',3,4,4',5,6		
182	2,2N,3,4,4N,5,6N	119264-55-0	
183	2,2',3,4,4',5',6		
184	2,2N,3,4,4N,6,6N	119264-56-1	
185	2,2',3,4,5,5',6		
186	2,2N,3,4,5,6,6N	119264-57-2	
187	2,2N,3,4N,5,5N,6	84303-49-1	
188	2,2N,3,4N,5,6,6N	119264-58-3	
189	2,3,3N,4,4N,5,5N	88700-06-5	
190	2,3,3N,4,4N,5,6	79682-25-0	
191	2,3,3',4,4',5',6		
192	2,3,3',4,5,5',6		
193	2,3,3',4',5,5',6		
	Octabromobiphenyl	27858-07-7	32536-52-0
194	2,2N,3,3N,4,4N,5,5N	67889-00-3	
195	2,2',3,3',4,4',5,6		
196	2,2',3,3',4,4',5',6		
197	2,2N,3,3N,4,4N,6,6N	119264-59-4	
198	2,2',3,3',4,5,5',6		
199	2,2',3,3',4,5,6,6'		
200	2,2N,3,3N,4,5,6,6N	119264-60-7	
201	2,2N,3,3N,4,5N,6,6N	69887-11-2	
202	2,2N,3,3N,5,5N,6,6N	59080-41-0	
203	2,2',3,4,4',5,5',6		
204	2,2N,3,4,4N,5,6,6N	119264-61-8	
205	2,3,3',4,4',5,5',6		
	Nonabromobiphenyl	27753-52-2	63936-56-1
206	2,2N,3,3N,4,4N,5,5N,6	69278-62-2	
207	2,2N,3,3N,4,4N,5,6,6N	119264-62-9	
208	2,2N,3,3N,4,5,5N,6,6N	119264-63-0	

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners *(continued)*

		CAS No.[a]	
IUPAC No.[b]	Compound/ substituents	Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
	Decabromobiphenyl	13654-09-6	1163-19-5
209	2,2N,3,3N,4,4N,5,5N,6,6N	13654-09-6	1163-19-5

[a]Not all of PBBs have been assigned CAS numbers; with the exception of BDE-209, no CAS numbers were identified for the PBDE class.
[b]Ballschmiter and Zell 1980
[c]WHO 1994b
[d]WHO 1994a

The chemical identity of hexabromobiphenyl, octabromobiphenyl, decabromobiphenyl (BB-209), and 2,2',4,4',5,5'-hexabromobiphenyl (BB-153), the most abundant congener in commercial FireMaster FF-1 and FireMaster BP-6, are listed in Table 4-2.

Polybrominated Diphenyl Ethers. In the United States, Albemarle Corporation and Great Lakes Chemical Corporation market mixtures of PBDEs under trade names (e.g., Bromkal 70-5DE, DE-71, Tardex 50, Tardex 50 L, and Saytex 115 for pentaBDE mixtures; DE-79, FR-1208, and Saytex 111 for octaBDE mixtures; and DE 83, FR-300 BA, and Saytex 102 for decaBDE mixtures). The are also several trade names used by producers from Europe and Japan for the BDE mixtures. The chemical identities of commercial mixtures of pentaBDE, octaBDE, and decaBDE are listed in Table 4-3 (WHO 1994a).

Various synonyms and abbreviations for polybrominated diphenyl ethers exist in the literature and are shown below:

polybrominated biphenyl ethers	/ polybromobiphenyl ethers	/ PBBEs
polybrominated biphenyl oxides	/ polybromobiphenyl oxides	/ PBBEs
polybrominated diphenyl ethers	/ polybromodiphenyl ethers	/ PBDEs or PBDPEs
polybrominated diphenyl oxides	/ polybromodiphenyl oxides	/ PBDOs or PBDPOs

For consistency in this document, polybrominated diphenyl ethers or PBDEs will be used to identify this class of chemicals. The PBDE homologs are abbreviated as follows in this document:

Dibromodiphenyl ether	/	DiBDE	/	diBDE
Tribromodiphenyl ether	/	TrBDE	/	triBDE
Tetrabromodiphenyl ether	/	TeBDE	/	tetraBDE
Pentabromodiphenyl ether	/	PeBDE	/	pentaBDE
Hexabromodiphenyl ether	/	HxBDE	/	hexaBDE
Heptabromodiphenyl ether	/	HpBDE	/	heptaBDE
Octabromodiphenyl ether	/	OBDE	/	octaBDE
Nonabromodiphenyl ether	/	NoBDE	/	nonaBDE
Decabromodiphenyl ether	/	DeBDE	/	decaBDE

Table 4-2. Chemical Identity of Selected PBBs[a]

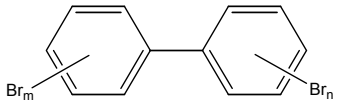
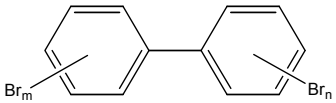
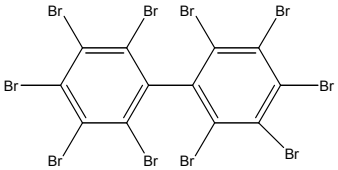
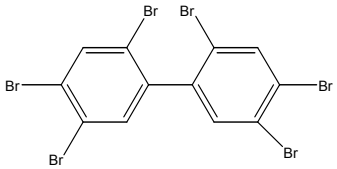
Characteristic	Hexabromobiphenyl	Octabromobiphenyl	Decabromobiphenyl	2,2',4,4'5,5'-Hexabromo-biphenyl
Synonym(s)	FireMaster BP-6[b]; FireMaster FF-1[b]	Bromkal 80[b]	Flammex B 10[b]; Adine 0102[b]; Berkflam B 10[b]	2,2',4,4'5,5'hexabromo-1,1'-biphenyl
Registered trade name(s)	FireMaster BP-6; FireMaster FF-1	Bromkal 80	Flammex B 10; Adine 0102; Berkflam B 10	None
Chemical formula	$C_{12}H_4Br_6$	$C_{12}H_2Br_8$	$C_{12}Br_{10}$	$C_{12}H_4Br_6$
Chemical structure	 m+n = 6	 m + n = 8		
Identification numbers:				
CAS registry	59536-65-1 (BP-6); 67774-32-7 (FF-1); 36355-01-8 (hexabromo mixture)	27858-07-7 (octobromo mixture) 61288-13-9 (Bromkal 80)	13654-09-6 (pure and technical)	59080-40-9
NIOSH RTECS[c]	LK 5060000 (BP-6); LK 5065000 (FF-1)	DV 570000 (octabromo mixture)	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	No data	No data	No data	No data

Table 4-2. Chemical Identity of Selected PBBs[a]

Characteristic	Hexabromobiphenyl	Octabromobiphenyl	Decabromobiphenyl	2,2',4,4'5,5'-Hexabromo-biphenyl
NCI	No data	No data	No data	No data

[a]All information obtained from IARC 1986 except where noted
[b]These are mixtures of compounds, and their compositions are given in the text.
[c]RTECS

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; RTECS = Registry of Toxic Effects of Chemical Substances

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Table 4-3. Chemical Identity of Selected Technical PBDEs

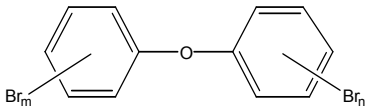
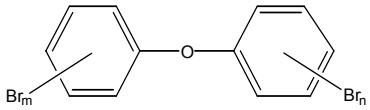
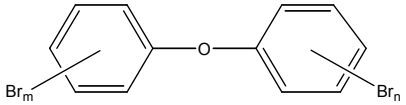
Characteristic	Pentabromodiphenyl ether	Octabromodiphenyl ether	Decabromodiphenyl ether
Synonym(s)	Pentabromodiphenyl ether; pentabromodiphenyl oxide; pentabromobiphenyl oxide; benzene, 1,1-oxybis, pentabromo derivative	Octabromodiphenyl ether; octabromodiphenyl oxide; octabromobiphenyl oxide; benzene, octabromo derivative; phenyl ether, octabromo derivative	Decabromodiphenyl ether; decabromodiphenyl oxide; decabromobiphenyl oxide; benzene, 1,1'-oxybis(2,3,5,6,-penta-bromo-) ether, bis(pentabromophenyl);
Registered trade name	DE 71; Bromkal 70-5 DE; FR 1205/1215; Bromkal 70; Bromkal G1; Pentabromprop; Tardex 50; Tardex 50 L; Saytex 115	Bromkal 7908DE; DE 79; FR 143; Tardex 80; FR 1208; Adine 404; Saytex 111	FR-300 BA; DE-83-RTM; Saytex 102; Saytex 102E; FR-1210; Adine 505; AFR 1021; Berkflam B10E; BR55N; Bromkal 81; Bromkal 82-ODE; Bromkal 83-10 DE; Caliban F/R-P 39P; Caliban F/R-P 44; Chemflam 011; DE 83; DP 10F; EB 10FP; EBR 700; Flame Cut BR 100; FR P-39; BR 100; FR 330BA; FR P-39; FRP 53; FR-PE; FR-PE(H); Planelon DB 100; Tardex 100; NC-1085; HFO-102; Hexcel PF1; Phoscon Br-250
Chemical formula	$C_{12}H_{10-y}Br_yO$ where y = 4 to 6	$C_{12}H_{10-y}Br_yO$ where y = 6 to 9	$C_{12}Br_{10}O$
Chemical structure	 m + n = 4 to 6	 m + n = 6 to 9	 m + n = 10
Identification numbers:			
CAS registry	32534-81-9	32536-52-0	1163-19-5
NIOSH RTECS	No data	No data	No data
EPA hazardous waste	No data	No data	No data

Table 4-3. Chemical Identity of Selected Technical PBDEs *(continued)*

Characteristic	Pentabromodiphenyl ether	Octabromodiphenyl ether	Decabromodiphenyl ether
OHM/TADS	No data	No data	No data
DOT/UN/IMCO shipping	No data	No data	No data
HSDB	No data	No data	No data
NCI	No data	No data	No data

Source: WHO (1994a)

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; PBB = polybrominated biphenyl; RTECS = Registry of Toxic Effects of Chemical Substances

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Polybrominated Biphenyls. Information found in the literature regarding the physical and chemical properties of hexabromobiphenyl, octabromobiphenyl, decabromobiphenyl, and 2,2',4,4',5,5'-hexabromobiphenyl is presented in Table 4-4. The data for the properties listed in Table 4-4 may not be reliable because products of questionable purity were used by earlier investigators to derive them. For example, the water solubility of hexabromobiphenyl (Neufeld et al. 1977) was reported to be the same as that of FireMaster FF-1 (Getty et al. 1977), although FireMaster FF-1 contained only 84.4% (Robertson et al. 1983b) hexabrominated biphenyls.

Of the 209 possible congeners of PBBs, only about 42 have been synthesized in pure form even on a laboratory scale (Sundstrom et al. 1976b). The PBBs produced for commercial use were mixtures of PBBs with other non-PBB impurities. The technical products were FireMaster BP-6, FireMaster FF-1, Bromkal 80, and Flammex B 10 (or Adine 0102 or Berkflam B 10) (IARC 1986). FireMaster FF-1, a white powder, was made by grinding brown flakes of FireMaster BP-6 and adding 2% calcium silicate as an anticaking agent (Fries 1985b). The exact composition of FireMaster BP-6 or FireMaster FF-1 seems to have varied between and within batches (Sundstrom et al. 1976a). Table 4-5 provides the concentrations of the PBB congeners in FireMaster FF-1 and FireMaster BP-6.

An interesting feature of commercial FireMaster FF-1 and FireMaster BP-6 is that they contain >50% of the congener 2,2',4,4',5.5',-hexabromobiphenyl (BB-153). The second most abundant congener is 2,2',3,4,4',5,5'-heptabromobiphenyl (BB-180). A detailed analysis of FireMaster BP-6 (lot 7062) was able to separate 22 congeners of PBBs that included four tri, five tetra, three penta, seven hexa, and three hepta congeners of PBBs (Robertson et al. 1983b, 1984b). The coplanar and toxic congeners 3,3',4,4'-tetra-, 3,3',4,4',5-penta-, and 3,3',4,4',5,5'-hexabrominated biphenyls were found at abundances of 0.159, 0.079, and 0.294%, respectively (Orti et al. 1983; Robertson et al. 1983b). In addition to the 22 congeners, other investigators have identified 2,2',3,3',4,4',5,6'-octa-, 2,2',3,3',4,4',5,5'-octa-, 2,2',3,3',4,4',5,5',6-nona-, and deca-bromobiphenyl in commercial PBBs (Moore et al. 1978). Other impurities detected in FireMaster FF-1 and FireMaster BP-6 were tetra-, penta-, and hexabromonaphthalene (Di Carlo et al. 1978); however, at a detection limit of 0.5 ppm, brominated dioxins and dibenzofurans were not detected in commercial FireMaster FF-1 or FireMaster BP-6 (Hass et al. 1978).

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Table 4-4. Physical and Chemical Properties of Selected PBBs[a]

Property	Hexabromobiphenyl	Octabromobiphenyl	Decabromobiphenyl	2,2',4,4',5,5'-Hexabromobiphenyl
Molecular weight	627.4	785.2	943.1	627.4
Color	White	White	White	White
Physical state	Solid	Solid	Solid	Solid
Melting point	72 EC	200–250 EC; 367–367 EC[b] (for industrial product)	380–386 EC	No data
Boiling point	No data	No data	No data	No data
Density	No data	No data	No data	No data
Odor	No data	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	11 µg/L	20–30 µg/L	Insoluble	11 µg/L[c]
Organic solvent(s)	Soluble in acetone, benzene	Soluble in methylene chloride, benzene	Moderately soluble in chlorobenzene, *o*-xylene	Acetone (6 weight percent); benzene (75 weight percent)[c]
Partition coefficients:				
Log K_{ow}	6.39[d]	5.53	8.58[e]	9.10 (estimated)[c]
Log K_{oc}	3.33–3.87[f]	No data	No data	5.088[c]
Vapor pressure	5.2×10^{-8} mmHg at 25 EC[g]	7×10^{-11} mmHg at 28 EC[h]	No data	7.6×10^{-5} mm Hg at 90 EC[c]
Henry's law constant	3.9×10^{-6} atm⋅m^3/mol[i]	No data	No data	5.7×10^{-3} atm⋅m^3/mol[c]
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data

Table 4-4. Physical and Chemical Properties of Selected PBBs[a] *(continued)*

Property	Hexabromobiphenyl	Octabromobiphenyl	Decabromobiphenyl	2,2',4,4',5,5'-Hexabromobiphenyl
Conversion factors	[j]	[j]	[j]	[j]
Explosive limits	No data	No data	No data	No data

[a]All information obtained from IARC (1978) and Norris et al. (1973) unless otherwise noted
[b]Sundstrom et al. 1976
[c]Hardy (2002)
[d]Doucette and Andren 1988
[e]The values for 2,2'4,4'6,6'- and 2,2',3,3',4,4'-hexabromobiphenyl are given as 7.20 (Chessells et al. 1992) and 8.09 (Anliker et al. 1988), respectively.
[f]Estimated from the Freundlich adsorption constants given by Jacobs et al. (1978)
[g]Jacobs et al. 1976
[h]Waritz et al. 1977
[i]Estimated from the ratio of vapor pressure and water solubility
[j]Since these compounds exist in the particle phase in the ambient atmosphere, the concentrations in air are expressed in weight per unit volume of the air.

Table 4-5. Identified PBB Congeners in FireMaster® BP-6 and FireMaster® FF-1

IUPAC No.[a]	Structure	% Composition of FireMaster BP-6	% Composition of FireMaster FF-1	References
Dibromobiphenyls				
4	2,2'-	0.020		Moore et al. 1979
Tribromobiphenyls				
18	2,2',5-	0.050		Robertson et al. 1984
26	2,3',5-	0.024		
31	2,4',5-	0.015		
37	3,4,4'-	0.021		
Tetrabromobiphenyls				
49	2,2',4,5'-	0.025		
52	2,2',5,5'-	0.052		
66	2,3',4,4'-	0.028		
70	2,3',4',5-	0.017		
77	3,3',4,4'-		<0.080	Orti et al. 1983
		0.159		Robertson et al. 1984
Pentabromobiphenyls				
95	2,2',3,5',6-	0.020		Orti et al. 1983
99	2,2',4,4',5-		<0.08	
101	2,2',4,5,5'-	2.69		Robertson et al. 1984
		4.50	3.70	Aust et al. 1981
			1.54	Orti et al. 1983
		2.60		Krüger 1988
118	2,3',4,4',5-	2.94		Robertson et al. 1984
			0.70	Robertson et al. 1984
		3.20		Krüger 1988
126	3,3',4,4',5-		<0.01	
		0.079		Robertson et al. 1984
Hexabromobiphenyls				
132	2,2'3,3',4,6'-	1		Krüger 1988
138	2,2',3,4,4',5'-	12.3		Robertson et al. 1984
		12	8.6	Aust et al. 1981
			5.23	Orti et al. 1983
		10.6		Krüger 1988
149	2,2',3,4',5',6-	2.24		Robertson et al. 1984
		1.40	1.30	Aust et al. 1981
			0.78	Orti et al. 1983

Table 4-5. Identified PBB Congeners in FireMaster® BP-6 and FireMaster® FF-1 *(continued)*

IUPAC No.[a]	Structure	% Composition of FireMaster BP-6	% Composition of FireMaster FF-1	References
153	2,2',4,4',5,5'-	53.9		Robertson et al. 1984
		47.8	47.1	Aust et al. 1981
		55.2		Orti et al. 1983
		58.5		Krüger 1988
155	2,2'4,4',6,6'-	0.5		
156	2,3,3',4,4',5-	0.980		Robertson et al. 1984
		5.0		Aust et al. 1981
		0.37		Orti et al. 1983
		1.0		Krüger 1988
157	2,3,3',4,4',5'-	0.05		Orti et al. 1983
		0.526		Robertson et al. 1984
		0.5`		Krüger 1988
167	2,3',4,4',5,5'-	5.5	3.3	Aust et al. 1981
		3.37		Orti et al. 1983
		<0.3		
		7.95		Robertson et al. 1984
		5.5		Krüger 1988
169	3,3',4,4',5,5'-	0.294		Robertson et al. 1984
Heptabromobiphenyls				
170	2,2',3,3',4,4',5-	0.256		
		1.1	1.5	Aust et al. 1981
		1.66		Orti et al. 1983
		2.4		Krüger 1988
172	2,2',3,3',4,5,5'-	<0.30		Orti et al. 1983
174	2,2',3,3',4,5,6'-	0.24		
178	2,2',3,3',5,5',6-	0.3		Krüger 1988
180	2,2',3,4,4',5,5'	6.97		Robertson et al. 1984
			24.7	Aust et al. 1981
			23.5	Orti et al. 1983
187	2,2',3,4',5,5',6-	0.392		Robertson et al. 1984
			1.0	Krüger 1988
189	2,3,3',4,4',5,5'-		0.51	Orti et al. 1983
Octabromobiphenyls				
194	2,2',3,3',4,4',5,5'-	0.9	2.4	Aust et al. 1981
			1.65	Orti et al. 1983
196	2,2',3,3',4,4',5,6'-			Moore et al. 1980
201	2,2',3,3',4,5,5',6'-			Orti et al. 1983
203	2,2',3,4,4',5,5',6-			

Source: WHO (1994b)

[a]Ballschmiter and Zell (1980)

Commercial octabromobiphenyl (Bromkal 80) contained at least four compounds. Assays of two commercial octabromobiphenyls showed the following compositions: 1.0–1.8% heptabromobiphenyl, 33.0–45.2% octabromobiphenyl, 47.4–60.0% nonabromobiphenyl, and 5.7–6.0% decabromobiphenyl (Norris et al. 1973; Waritz et al. 1977). Notably, the major component of commercial octabromobiphenyl was nonabromobiphenyl, and not octabromobiphenyl. Commercial decabromobiphenyl (Flammex B 10) contained 96.8% decabromobiphenyl, 2.9% nonabromobiphenyl, and 0.3% octabromobiphenyl (Di Carlo et al. 1978).

Pyrolysis of FireMaster BP-6 in the temperature range of 600–900 EC in the absence of oxygen produced bromobenzenes and brominated biphenyls as key products, but no brominated dioxins and dibenzofurans (Thoma and Hutzinger 1987; Thoma et al. 1987). Thermolysis of FireMaster BP-6 between 400 and 600 EC in the presence of air produced 2,3,7,8-tetrabromodibenzofuran in the percent (. 1%=10 g/kg) range (Rappe and Buser 1980). Pyrolysis of FireMaster BP-6 in an open quartz tube at 800 EC produced 0.48–1.49 g/kg 2,3,7,8-TCDD equivalent levels of polybrominated dibenzofurans (Zacharewski et al. 1988). FireMaster BP-6 hydrolyzed when refluxed with 2% potassium hydroxide in ethanol, but the possible rate of PBB hydrolysis under much milder environmental conditions remains unknown (Pomerantz et al. 1978).

Polybrominated Diphenyl Ethers. Information found in the literature regarding the physical and chemical properties of selected technical PBDE mixtures is presented in Table 4-6.

Commercially available product mixtures of PBDEs (see Table 4-3) are not pure substances, but instead are mixtures of congeners. For example, the commercial mixture pentabromodiphenyl ether denotes the main component of the mixture contains the pentabromodiphenyl ether homolog. However, the commercial pentaBDE mixture actually contains tetraBDE (24–38%), pentaBDE (50–62%) homologs with small amounts of hexaBDE (4–8%) and trace amounts of triBDE (0–1%) homologs. In this document, the commercial mixture of pentaBDE will be called “technical pentaBDE” or “technical PeBDE” to distinguish this mixture of homologs from the pentaBDE homolog which refers to polybrominated diphenyl ethers with only five bromine atoms (see Section 4.1). Commercial octabromodiphenyl ether is a mixture of hexa- hepta-, octa-, and nonabrominated diphenyl ether homologs with trace amounts of decabromodiphenyl ether (i.e., BDE-209). In this document, the commercial mixture of octaBDE will be referred to as “technical octaBDE” or “technical OBDE” to distinguish this mixture of different homologs from the octaBDE homolog which refers to

Table 4-6. Physical and Chemical Properties of Technical PBDE Mixtures

Property	Pentabromodiphenyl ether	Octabromodiphenyl ether	Decabromodiphenyl ether
Molecular weight	Mixture	Mixture	959.22[a]
Color	Clear, amber to pale yellow[a]	Off-white[a]	Off-white[a]
Physical state	Highly viscous liquid	Powder	Powder[a]
Melting point:	-7 to -3 EC (commercial)	200 EC (range, 167–257)[a]; 79–87 EC[a]; 170–220 E C[a]	290–306 EC[a]
Boiling point:	>300E C (decomposition starts above 200 EC)[a]	No data	Decomposes at >320, >400, and 425 EC[a]
Density (g/mL)	2.28 at 25 EC[a]	2.76[a]	3.0[a] 3.25[a]
Odor	No data	Faint[a]	Odorless[a]
Odor threshold:			
Water	No data	No data	Not applicable
Air	No data	No data	Not applicable
Solubility:			
Water	13.3 μg/L[b]	<1 g/L at 25 EC[a]	20–30 μg/L at 25 EC[a]
Organic solvent(s)	10 g/kg methanol; miscible in toluene[b]	acetone (20 g/L); benzene (200 g/L); methanol (2 g/L) all at 25 EC[a]	acetone (1 g/L); benzene (4.8 g/L); methanol (1 g/L); all at 25 EC[a]
Partition coefficients:			
Log K_{ow}	6.64–6.97[b]	8.35–8.90[b]	9.97[b]
Log K_{oc}	4.89-5.10[c]	5.92-6.22[c]	6.80[c]
Vapor pressure	2.2×10^{-7} - 5.5×10^{-7} mm Hg at 25 EC[b]	9.0×10^{-10}-1.7×10^{-9} mm Hg at 25 EC[b]	3.2×10^{-8} mm Hg[d]

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Table 4-6. Physical and Chemical Properties of Technical PBDE mixtures *(continued)*

Property	Pentabromodiphenyl ether	Octabromodiphenyl ether	Decabromodiphenyl ether
Henry's Law constant (atm-m^3/mole)	1.2×10^{-5} [e] 1.2×10^{-6} [c]; 3.5×10^{-6} [c]	7.5×10^{-8} [c]; 2.6×10^{-7} [c]	1.62×10^{-6} [e] 1.93×10^{-8} [b] 1.2×10^{-8} [c]; 4.4×10^{-8} [c]
Autoignition temperature	Decomposes above 200 EC[b]	No data	Not applicable[a]
Flashpoint	No data	No data	None
Flammability limits	Not applicable (flame retardant)[b]	No data	Non-flammable[a]
Conversion factors	1 ppm=23.48 mg/m^3 at 20 EC[b]	No data	No data
Explosive limits	None [d]	No data	No data

[a] WHO (1994a)
[b] EU (2001)
[c] estimated values were calculated using EPIWIN v3.10 (EPA 2001)
[d] Hardy (2002)
[e] estimate value calculated using vapor pressure and water solubility values in table.

polybrominated diphenyl ethers with only eight bromine atoms (see Section 4.1). The composition of commercial decabromodiphenyl ether is $97% of the decabromodiphenyl ether (i.e., BDE-209); the remainder is nonabromodiphenyl ether homologs and trace amounts of octabromodiphenyl ether homologs (WHO 1994a). In this document, commercial decabromodiphenyl ether will be referred to as "technical decaBDE" or "technical DeBDE" which represents 97% BDE-209 congener with 3% nona- and octaBDE homolog impurities. The compositions of commercial product mixtures of PBDEs such as technical penta-, octa-, and decaBDE are given in Table 4-7. Trace analysis of these commercial mixtures for 15-different 2,3,7,8-substituted brominate dibenzo-*p*-dioxins and dibenzofurans revealed no detectable amounts of these substances (Hardy 2002).

When pyrolysed up to 900 EC, PBDEs release polybrominated dibenzofurans (PBDFs) and polybrominated-*p*-dioxins (PBDDs) (Buser 1986; EU 2001). The amount of PCDFs and PBDDs formed depends upon the conditions of pyrolysis. For example, 2,3,7,8-tetrabromodibenzofuran in ppm concentrations can be generated during pyrolysis of decabromodiphenyl ether in the temperature range of 400–700 EC (Bieniek et al 1989). PBDFs may also be produced during the pyrolysis of polymers containing PBDEs as flame retardants (Brenner and Knies 1993; Dumler et al 1989. 1990; Lenoir et al 1994).

Table 4-7. Composition of Commercial Brominated Diphenyl Ethers

	PBDE Homologs								
Commercial Mixtures	PBDE[a]	TrBDE	TeBDE	PeBDE	HxBDE	HpBDE	OcBDE	NoBDE	DeBDE
DeBDE								0.3–3%	97–98%
OcBDE					10–12%	43–44%	31–35%	9–11%	0–1%
PeBDE		0–1%	24–38%	50–62%	4–8%				
TeBDE[b]	7.6%	No data	41–41.7%	44.4–45%	6.7%				

Source: WHO (1994a)

[a]Unknown structure
[b]No longer commercially produced

DeBDE=Decabromodiphenyl ether; HpBDE=Heptabromodiphenyl ether; HxBDE=Hexabromodiphenyl ether; NoBDE=Nonabromodiphenyl ether; OcBDE=Octabromodiphenyl ether; PBDE=Polybrominated diphenyl ether; PeBDE=Pentabromodiphenyl ether; TeBDE=Tetrabromodiphenyl ether; TrBDE=Tribromodiphenyl ether

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Polybrominated Biphenyls. The commercial production of PBBs generally involves bromination of biphenyl, a process that involves a much more specific reaction and produces a smaller number of product mixtures than chlorination (Sundstrom et al. 1976a). In one process, biphenyl is brominated with 0–20% stoichiometric excess of bromine chloride (e.g., slightly more than 10 mol of bromine chloride may be reacted with 1 mol of biphenyl to obtain decabromobiphenyl) in the presence of iron or a Friedel-Crafts catalyst (e.g., aluminum chloride). In another process, biphenyl is dissolved in ethylene bromide solvent and reacted with bromine in the presence of a catalyst (either aluminum chloride or bromide) (Neufeld et al. 1977). Research quantities of PBBs can be synthesized by the diazo coupling of brominated aniline with an excess of the corresponding bromobenzene. For example, 2,3,3',4,4',5'-hexabromobiphenyl can be synthesized by the diazo coupling of 3,4,5-tribromoaniline with 1,2,3-tribromobenzene (Kubiczak et al. 1989; Robertson et al. 1983b). Methods for laboratory scale synthesis of 42 congeners of brominated biphenyls are also available (Sundstrom et al. 1976b).

The commercial production of PBBs began in 1970. Approximately 13.3 million pounds of PBBs were produced in the United States from 1970 to 1976. Only three commercial PBB products were manufactured (i.e., hexabromobiphenyl, octabromobiphenyl, and decabromobiphenyl) and these three products were based on a limited number of congeners (Hardy 2002). Hexabromobiphenyl constituted about 11.8 million pounds (ca 88%) and octa- and decabromobiphenyl constituted . 1.5 million pounds together of this total (Neufeld et al. 1977). Over 98% of the hexabromobiphenyl was produced as FireMaster BP-6 and the residual as FireMaster FF-1 (Hesse and Powers 1978). Michigan Chemical Corporation, St. Louis, Michigan, the sole producer of hexabromobiphenyl in the United States, stopped producing this PBB in 1975. White Chemical Co., Bayonne, New Jersey, and Hexcel Corporation, Sayreville, New Jersey, manufactured octa- and decabromobiphenyl in the United States until 1979 (IARC 1986; Neufeld et al. 1977). Shortly after the 1973–1974 agriculture contamination episode in Michigan (see Section 3.2), PBB production in the United States was voluntarily discontinued (Hardy 2000); PBBs are no longer produced in the United States (SRI 2001). Re-initiation of manufacture requires approval from the EPA. Production of decaPBB in Great Britain was discontinued in 1977 and highly brominated PBBs were produced in Germany until mid-1985. Until the year 2000, the only PBB in commercial production was decabromobiphenyl, which was manufactured by one company (Atochem) in France (Hardy 2000).

Polybrominated Diphenyl Ethers. The commercial production of PBDEs generally involves bromination of diphenyl oxide to varying degrees. The degree of bromination is controlled either through stiochiometry or through control of reaction kinetics (Pettigrew 1993). Technical decabromodiphenyl ether is manufactured by bromination of diphenyl oxide in the presence of a Friedel-Crafts catalyst (e.g., aluminum bromide) and excess bromine. Technical decabromodiphenyl ether may also be produced at atmopsheric pressure by dissolving diphenyl oxide and bromine in ethylene dibromide in the presence of a Friedel-Crafts catalyst (e.g., aluminum bromide). The use of bromine in an organic solvent requires long reaction times, results in low productivity per volume, and necessitates recycling of the solvent. These limitations have led to the use of bromine as both the reactant and the solvent for this process (Dagani and Sanders 1985).

The commercial production of PBDEs began in late 1970s (WHO 1994a). In the United States, penta-, octa-, and decabromodiphenyl ethers are produced at Albemarle Corporation, Magnolia, Arkansas, and Great Lakes Chemical Corporation, El Dorado, Arkansas (SRI 2001). Technical OBDE is produced commercially in the United States as DE-79, FR-1208, and Saytex 111. Technical PeBDE is produced commercially in the United States as Bromkal 70-5DE, DE-71, Tardex 50, Tardex 50 L, and Saytex 115. Technical DeBDE (BDE-209) is produced commercially in the United States as DE-83, FR-300 BA, Saytex 102 (see Section 4.1). Six manufacturers are currently producing polybrominated diphenyl ethers in other countries: Dead Sea Bromines/Eurobrome (The Netherlands); Atofina (France); Tosoh (Japan); Matsinaga (Japan); Nippo (Japan); and Great Lakes Chemical Ltd (United Kingdom) (WHO 1994a). No current estimates of PBDE production are available (SRI 2001). In 1999, the total market demand for PBDEs in the United States was 74.9 million pounds. Technical decabromodiphenyl ether constituted about 53.6 million pounds (72%), while technical mixtures of octa- and pentabromodiphenyl ethers were 3.0 and 18.3 million pounds (4 and 24%) of this total, respectively (BSEF 2002).

Table 5-1 lists the facilities in each state that manufacture or process technical decabromodiphenyl ether (DeBDE), the intended use, and the range of maximum amounts of technical DeBDE that are stored on-site. There are 144 facilities that produce or process technical DeBDE in the United States (TRI99 2001). The data from the Toxics Release Inventory (TRI) listed in Table 5-1 should be used with caution, however, since only certain types of facilities were required to report. The TRI is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Decabromodiphenyl Ether

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	10,000	99,999	7, 8
AR	4	1,000	9,999,999	1, 4, 7, 8
CA	5	1,000	999,999	7, 8
CT	4	1,000	99,999	7, 8, 9, 14
FL	1	100,000	999,999	7
GA	4	100	99,999	7, 8
IL	2	10,000	99,999	7, 8
IN	5	0	999,999	7, 8
KS	1	100	999	11
KY	2	10,000	999,999	7
LA	1	100,000	999,999	12
MA	12	1,000	99,999	7, 8
MD	1	100,000	999,999	8
MI	6	1,000	9,999,999	1, 3, 7, 8
MN	5	1,000	99,999	6, 7, 8, 9, 12
MO	1	1,000	9,999	7
MS	1	10,000	99,999	7
NC	12	1,000	999,999	7, 8
NE	1	10,000	99,999	8
NH	1	1,000	9,999	7
NJ	3	10,000	999,999	7, 8
NY	3	10,000	99,999	6, 7, 8
OH	9	1,000	999,999	7, 8
OR	1	10,000	99,999	12
PA	8	1,000	9,999,999	7, 8
RI	3	1,000	99,999	7, 8, 10
SC	9	1,000	999,999	7, 8
TN	6	1,000	99,999	7
TX	8	100	99,999	1, 3, 7, 8, 12
VA	5	10,000	999,999	7, 8
WA	1	10,000	99,999	8
WI	2	1,000	9,999	7, 8

Source: TRI00 2002

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Imported
3. Used Processed
4. Sale Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary/Other Uses
13. Manufacture Impurity
14. Process Impurity

5.2 IMPORT/EXPORT

Polybrominated Biphenyls. PBBs are no longer being imported or exported except possibly in small quantities for laboratory uses. PBBs have not been imported from other countries into the United States, except in finished products (Neufeld et al. 1977). The two companies that manufactured octa- and decabromobiphenyl in the United States between 1976 (0.805 million pounds) and 1978 exported all of their products to Europe (Neufeld et al. 1977).

Polybrominated Diphenyl Ethers. No U.S. import or export data were located in the literature for PBDEs. In 1999, worldwide demand for technical penta-, octa-, and decabromodiphenyl ethers were 18.7 million, 8.4 million, and 121 million pounds, respectively (BSEF 2002).

5.3 USE

Polybrominated Biphenyls. PBBs are no longer used in the United States. In the past, PBBs were used as additive flame retardants used to suppress or delay combustion. Additive flame retardants are added to the polymer material, but are not chemically incorporated into the polymer matrix. Because PBBs are not chemically bound to the polymer matrix, they may migrate out of the matrix with time (WHO 1994b). PBB applications were almost exclusively limited to a particular thermoplastic (arylonitrile-butadiene-styrene, ABS) used in electronic equipment housings (Hardy 2002). Prior to termination of production, hexabromobiphenyl was used as a fire retardant mainly in thermoplastics for constructing business machine housings and in industrial (e.g., motor housing), and electrical (e.g., radio and TV parts) products. Smaller amounts were used as a fire retardant in coating and lacquers, and in polyurethane foam for auto upholstery (Neufeld et al. 1977). PBDEs and other flame retardants replaced hexabromobiphenyl after its voluntary ban in the late 1970s. Octabromobiphenyl and decabromobiphenyl were never used in the United States, probably because the hexabromobiphenyl was less expensive and equally effective as a fire retardant (Neufeld et al. 1977).

Polybrominated Diphenyl Ethers. PBDEs are used as additive flame retardants in thermoplastics. Additive flame retardants are physically combined with the polymer material being treated rather than chemically combined (as in reactive flame retardants). This means that there is a possibility that the flame retardant may diffuse out of the treated material to some extent.

PBDEs are used in different resins, polymers, and substrates at levels ranging from 5 to 30% by weight (EU 2001). Plastic materials that utilize PBDEs as flame retardants include: ABS; polyacrylonitrile

(PAN); polyamide(PA); polybutylene terephthalate (PBT); polyethylene (PE); cross-linked polyethylene (XPE); polyethylene terephthalate (PET); polypropylene (PP); polystyrene (PS); high-impact polystyrene (HIPS); polyvinyl chloride (PVC); polyurethane (PUR); and unsaturated polyester (UPE). These polymers and examples of their final products are summarized in Table 5-2 (Hardy 2002; WHO 1994a).

Currently, technical DeBDE is the most widely used PBDE flame retardant worldwide followed by technical ODBE. About 95% of technical PeBDE is used in the manufacture of flexible polyurethane (PUR) foam for furniture and upholstery. Flexible polyurethane foam is used in foam-based laminated automotive applications, for domestic furniture, and in foam-based packaging (EU 2001). Technical OBDE is mainly used in the preparation of acrylonitrile-butadiene-styrene terpolymer (ABS), which is used in the manufacture of computer and business equipment housings. Technical OBDE is also used in adhesives and coatings applications (WHO 1994a). About 40% of technical DeBDE is used in combination with antimony trioxide in high impact polystyrene applications, such as television and radio housings. Other significant uses of technical DeBDE are in textile applications, such as polyester fiber additives and coatings for automobile fabric, tarpaulins, and tents (WHO 1994a).

5.4 DISPOSAL

Polybrominated Biphenyls. PBBs are no longer commercially produced in the United States. In the past, an estimated 0.0046 pounds have been lost to sewers for every 1,000,000 pounds of PBBs produced at manufacturing sites (Neufeld et al. 1977). The Michigan Chemical Corporation discharged an estimated 0.25 pounds of PBBs/day to the Pine River as effluent (Di Carlo et al. 1978). The Michigan Chemical Corporation estimated that the solid waste generated during the manufacture of FireMaster BP-6 was .5% of the FireMaster BP-6 and FireMaster FF-1 produced (Di Carlo et al. 1978). Since Michigan Chemical Corporation produced .11.8 million pounds of Firemaster BP-6 and Firemaster FF-1 from 1970 to 1974 (Di Carlo et al. 1978), solid wastes containing a total of .590,000 pounds of PBBs would have been sent to disposal. About one-half of this waste was deposited in the Gratiot County landfill in St. Louis, Michigan (Di Carlo et al. 1978), and the rest was possibly landfilled at other locations. Contaminated animal carcasses, poultry and eggs, animal feed, butter, cheese, and other milk products following the Michigan agriculture contamination episode were disposed of in a sanitary landfill in Cadillac, Michigan (Dunckel 1975).

Table 5-2. Uses of Penta-, Octa-, and Decabromodiphenyl Ethers Commercial Mixtures in Resins, Polymers, and Substrates

Resin/polymer/ substrate	Example of final product	Pentabromo-diphenyl ether	Octabromo-diphenyl ether	Decabromo-diphenyl ether
ABS	Molded parts (e.g., TV sets/business machines. computer housings, household appliances [hairdryer, curler], automotive parts, electronics, telecommunications)		●	
Epoxy-resins	Circuit boards, protective coatings (e.g., computer, ship interiors, electronic parts)			●
Phenolic resins	Printed circuits boards (e.g., paper laminates/glass prepregs for circuit boards)	●		●
PAN	Panels, electrical components (e.g., lighting panels for elevators and rooms, housing of electrical appliances)			●
PA	Electrical connectors, automotive interior parts (e.g., computers, connectors, housing in electricl industry, board, electrical connectors, automotive industry, transportation)		●	●
PBT	Electrical connectors and components (e.g., switches fuse, switch box, computer housing, switchboard electrical connectors, stereos, business machines, military electronics)		●	●
PE/XPE	Cross-linked wire and cable, foam tubing, weather protection, and moisture barriers (e.g., power cable, building conduit, portable apparatus building control, instrument, shipboard, automotive, marine appliances, insulation of heating tubes)			●
PET	Electrical components (e.g., boxes, relays, coils, bobbins)			●

Table 5-2. Uses of Penta-, Octa-, and Decabromodiphenyl Ethers Commercial Mixtures in Resins, Polymers, and Substrates *(continued)*

Resin/polymer/ substrate	Example of final product	Pentabromo-diphenyl ether	Octabromo-diphenyl ether	Decabromo-diphenyl ether
PVC	Cable sheets (e.g., wire and cables, floor mats, industrial sheets)	●		●
PUR	Cushioning materials, packaging, padding (e.g., furniture, sound insulation panels, wood imitations, transportation)	●		
UPE	Circuits boards, coatings (e.g., electrical equipment, coatings, military and marine applications, construction panels)	●		●
Rubber	Transportation (e.g., conveyor belts, foamed pipes for insulation)	●		●
Paints/lacquers	Coatings (e.g., marine and industry lacquers for protection of containers)	●		●
Textiles	Coatings (e.g., back coatings, impregnation, carpets, automotive seating, furniture in homes and office buildings, aircraft, subways, tents, trains, and military safety clothing)	●		●

Source: WHO (1994a)

ABS = Acrylonitrile Butadiene Styrene; PA = Polyamide; PAN = Polyacrylonitrile; PBT = Polybbutylene Terephthalate; PE = Polyethylene; PET = Polyethylene Terephthalate; PP = Polypropylene; PUR = Polyurethane; PVC = Polyvinyl chloride; UPE = Unsaturated polyester; XPE = Cross-linked polyethylene;

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Approximately 11.8 million pounds of hexabromobiphenyl were used in commercial and consumer products in the United States, most in the production of plastic products with an estimated use life of 5–10 years (Neufeld et al. 1977). Since the cessation of production, all of these products, such as TV cabinet and business machine housings, must have been disposed of by land filling or incineration (Neufeld et al. 1977). The formation of polybrominated dioxins (PBDDs) and polybrominated dibenzofurans (PBDFs) during the incineration of plastics containing PBBs remains a distinct possibility (Luijk and Govers 1992; O'Keefe 1978).

Polybrominated Diphenyl Ethers. PBDEs are used as flame retardants in a wide range of products (see Section 5.3). Waste from these products may be either incinerated as municipal waste, deposited in landfills, discharged to municipal sewage treatment plants, or emitted to the atmosphere. (Darnerud et al. 2001). The disposal of plastic consumables containing PBDEs (e.g., computers) to landfills is likely to increase in the United States due to their limited useful lifespan. No study on leaching of PBDEs from landfills is available. However, PBDE-containing products are widespread and leaching may be an important long-term pathway of contamination. PBDEs are discharged in to the environment through sewage, as indicated by analysis of sewage sludge from various countries. Tetra- and pentaBDE were detected in sewage sludge from publically owned treatment works (POTWs) in the United States (La Guardia et al. 2000). The composition in the biosolids closely resembled the DE-71 commercial formulation.

Although specific data are missing, incineration is thought to be an important route of release of PBDEs into the environment. Formation of PBDFs and/or PBDDs as a result of landfill fires is also a possibility, though no data are available on the scale of this source. The results of pyrolysis experiments showed that PBDEs can form PBDFs and PBDDs (in much smaller quantities) under a wide range of heating conditions. If chlorine is present, mixed halogenated furans/dioxins can be formed (Oberg et al. 1987; Zier et al. 1991). Unless sufficiently high temperatures and long residence times are maintained, PBDFs/PBDDs can be generated during the incineration of products containing PBDEs. When heavy metals are present, the concentration of PBDDs and PBDFs are higher than when no metals are present. However, modern, properly operated municipal waste incineration should not emit significant quantities of PBDFs/PBDDs, regardless of the composition of municipal waste (WHO 1994a).

Solid wastes from the commercial production of technical OBDE, such as filter cakes, are disposed of in hazardous waste landfills (EPA 1994). These wastes may contain toluene from the production process.

No study on leaching of PBDEs from landfills is available, but PBDE-containing products are widespread, and leaching may be an important long-term pathway of contamination. PBDEs are discharged in to the environment through sewage, as indicated by analysis of sewage sludge from various countries. Volatilization of PBDEs into the surrounding air from electrical components and other products during their lifetime can also be significant (Darnerud et al. 2001).

No other information was located on the past or present volumes of PBDEs disposed of by each disposal method.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

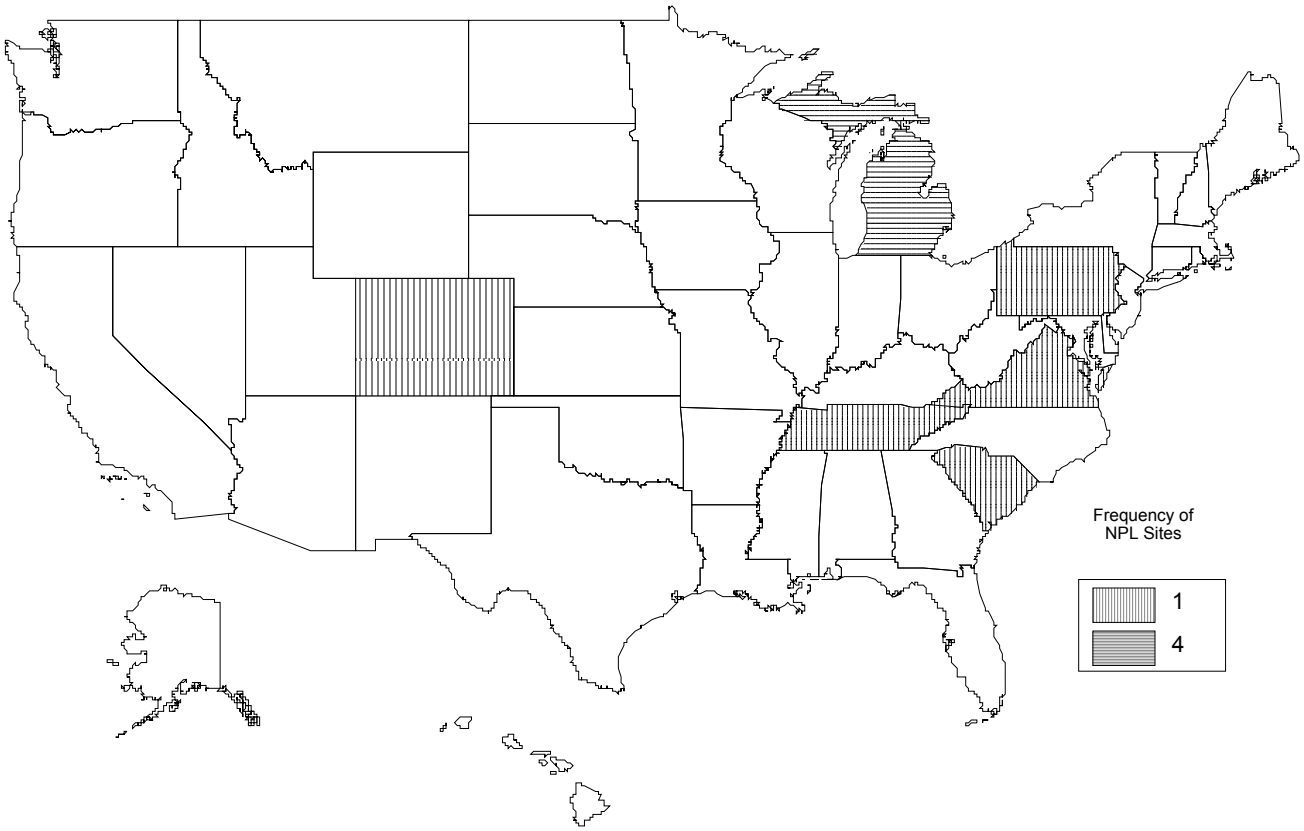
Polybrominated Biphenyls. PBBs have been identified in at least 9 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2002). However, the number of sites evaluated for PBBs is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, all are located within the United States.

The production of PBBs in the United States ceased in 1979 (IARC 1986). In the past, PBBs were released to the environment during the manufacture of these compounds and disposal of commercial and consumer products containing these compounds (Hesse and Powers 1978; Neufeld et al. 1977). One of the significant sources of environmental contamination occurred as a result of the accidental mixup of FireMaster BP-6 with cattle food in a number of farms in the lower peninsula in Michigan (see Section 3.2 for additional details concerning this incident). By June 1975, 412 farms had been quarantined. Disposal of contaminated feed, animal carcasses (poultry, dairy cattle, swine), and animal products (dairy, meat, eggs) contributed to environmental contamination (Dunckel 1975; Kay 1977). No information was located on the current levels of contamination at these locations.

PBBs can exist in 209 different congeners, but only about 42 have been synthesized (Sundstrom et al. 1976b). Environmental contamination of PBBs is likely to have occurred mainly from the two commercial products, FireMaster BP-6 and FireMaster FF-1. The principal component in both of these commercial products was 2,2',4,4',5,5'-hexabromobiphenyl or BB-153 (Robertson et al. 1983b).

PBBs are strongly adsorbed to soil and sediment (Filonow et al. 1976; Hesse and Powers 1978) and usually persist in the environment (Jacobs et al. 1978). Adsorption of PBBs generally increases as bromination and organic carbon content in soil and sediment increase (Filonow et al. 1976; Griffin and Chou 1981a, 1981b). As a result, the leaching of commercial mixtures of PBBs from soil is slow. Leaching studies with four Michigan soils, mixed with 100 mg/kg 2,2',4,4',5,5'-hexabromobiphenyl, showed that <0.6% of the compound leached through soils, with leachate quantities equivalent to 20 times the average annual rainfall in Michigan (Filonow et al. 1976). The PBBs in commercial mixtures resist both chemical and biological degradation (Jacobs et al. 1978; Kawasaki 1980; Shelton

Figure 6-1. Frequency of NPL Sites with PBB Contamination



Derived from HazDat 2002

and Tiedje 1981), although biotic debromination to lower brominated products may occur in anaerobic zones of contaminated sediment and soil (Morris et al. 1992).

PBBs with six or fewer bromine substitutions bioconcentrate in aquatic organisms such as fish, but the octabromo- and decabromobiphenyls do not bioconcentrate significantly in fish (Gobas et al. 1989; Norris et al. 1973; Opperhuizen et al. 1985; Veith et al. 1979; Zitko 1979; Zitko and Hutzinger 1976). Orchard grass, alfalfa, corn, and carrot tops grown in soil contaminated with PBBs showed no uptake of PBBs, and only minor uptake occurred in carrot roots (Jacobs et al. 1976, 1978). Although PBBs were detected in fish-eating birds and predatory animals that had consumed PBB-contaminated food (Heinz et al. 1983, 1985), the biomagnification potential of PBBs in predators resulting from such consumption remains unknown.

PBBs were detected in air, water, sediment, and soil in the vicinity of the manufacturing plants and in groundwater from a landfill site (DeCarlo 1979; Hesse and Powers 1978; Shah 1978). PBBs were also detected in soil near the contaminated farms in lower Michigan (Fries and Jacobs 1980). The distribution of PBBs was limited to the environment in the vicinity of production sites and the contaminated farm sites. Recent studies have identified PBBs in marine mammals from costal seas and the Atlantic ocean (de Boer et al 1998). Data regarding the current levels of PBBs in ambient air, drinking water, or food were not located.

No estimate on PBB intake by the general population from air, water, and food was located in the literature. However, current intake of PBBs for the general population is expected to be zero or very small. However, populations near the contaminated farms in lower Michigan may still have low exposures from air, water, and food. The level of PBBs in human tissue and body fluids in the exposed population of Michigan has been extensively studied (Brilliant et al. 1978; Cordle et al. 1978; Eyster et al. 1983; Humphrey and Hayner 1975; Lambert et al. 1990; Landrigan et al. 1979; Wolff et al. 1979a, 1982). The finding that PBBs are stored in fatty tissues of the human body and are very slowly excreted (Eyster et al. 1983) indicates a slow decline in the body burden for exposed individuals.

Polybrominated Biphenyl Ethers. The widespread use of PBDEs over the past 30 years has resulted in their ubiquitous presence in the environment. PBDEs are released into the environment from their manufacture and use as additive flame retardants in thermoplastics in a wide range of products (WHO 1994a). PBDEs containing waste may be either incinerated as municipal waste, deposited in landfills, discharged to municipal sewage treatment plants, or emitted to the atmosphere (Darnerud et al. 2001). In

the future, the disposal of plastic consumables containing PBDEs is likely to increase in the United States (NSC 1999).

PBDEs are strongly adsorbed to soil and sediment and persist in the environment. Adsorption of PBDEs generally increases as bromination and organic carbon content in soil and sediment increase. As a result, PDBEs have little or no mobility in soil and are not expected to leach. Lower BDE homologs, which exist partially in the vapor phase, have the potential for long-range transport in the atmosphere. Biodegradation will not be significant for PBDEs, but these compounds may be degraded by direct photolysis (WHO 1994a).

Monitoring studies indicate PBDEs are transported globally. Atmospheric, water, and biota levels of PBDEs tend to be dominated by lower brominated congeners (e.g., BDE-47). Biota data indicate that PBDE concentrations increase with lower brominated congeners being preferentially bioconcentrated. PBDE concentrations increase with respect to trophic level; thus, organisms that reside higher on the food chain tend to have higher concentrations of PBDE. Body burden data indicate low-level exposures to PBDEs for the general population. Humans are primarily exposed to PBDEs by inhalation of ambient or contaminated air and ingestion of contaminated food. Occupational exposure to PBDEs occurs primarily by inhalation of air containing PBDEs (WHO 1994a).

PBDEs have not been identified in any of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2002). However, the number of sites evaluated for PBDEs is not known.

6.2 RELEASES TO THE ENVIRONMENT

Polybrominated Biphenyls. The production of PBBs in the United States ceased in 1979 (IARC 1986). In the past, PBBs were released to the environment during the manufacture of these compounds and disposal of commercial and consumer products containing these compounds (Hesse and Powers 1978; Neufeld et al. 1977). One of the significant sources of environmental contamination occurred as a result of the accidental mixup of FireMaster BP-6 with cattle food in a number of farms in the lower peninsula in Michigan (see Section 3.2 for additional details concerning this incident). By June 1975, 412 farms had been quarantined. Disposal of contaminated feed, animal carcasses (poultry, cattle, swine), and animal products (meat, milk, eggs) contributed to environmental contamination (Dunckel 1975; Kay 1977).

Polybrominated Diphenyl Ethers. The widespread use of PBDEs over the past 30 years has resulted in their ubiquitous presence in the environment. The commercial production of PBDEs began in late 1970s (WHO 1994a). In 1999, the total market demand for PBDEs in the United States was 74.9 million pounds. Technical decabromodiphenyl ether constituted about 53.6 million pounds (72%), while technical mixtures of octa- and pentabromodiphenyl ethers were 3.0 and 18.3 million pounds (4 and 24%) of this total, respectively (BSEF 2002). PBDEs may be released into the environment from their manufacture and use in a wide range of consumer products (WHO 1994a). PBDEs are used as additive flame retardants in thermoplastics. Additive flame retardants are physically, rather than chemically, combined with polymers. Thus, there is a possibility that PBDEs may diffuse out of the treated materials to some extent (EU 2001). In addition to other uses, PBDE treated materials are used in foam for furniture and upholstery, computer and business equipment, adhesives and coatings (WHO 1994a). The widespread use of PBDEs over the past 30 years has resulted in their rapid increase in concentrations and ubiquitous presence in the environment. Waste from these products may be either incinerated as municipal waste, deposited in landfills, discharged to municipal sewage treatment plants, or emitted to the atmosphere (Darnerud et al. 2001). The disposal of plastic consumables containing PBDEs to landfills is likely to increase in the United States.

Releases of decabromobiphenyl ethers (DeBDEs) are required to be reported under the Superfund Amendments and Reauthorization Act (SARA) Section 313; consequently, data are available for this compound in the Toxic Release Inventory (TRI) (EPA 1995c). According to the TRI, a total of 865,109 pounds (392,407 kg) of DeBDE was released to the environment in 1999. In addition, an estimated 915,419 pounds (415,227 kg) were transferred off-site, including to publicly-owned treatment works (POTW) (TRI99 2002). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

Polybrominated Biphenyls. In the past, PBBs were released into the air during the manufacture of these compounds in three areas: through the vents of the hydrogen bromide recovery system, from the centrifugation area for recovering PBBs from slurries produced by bromination, and from the drying, pulverizing, and bagging area of the finished product (Di Carlo et al. 1978). An estimated 0.07 pounds/million pounds of the PBBs produced were lost from the hydrogen bromide recovery vent (Di Carlo et al. 1978). No data are available for the air pollution factor (amount released/million pounds produced) at the centrifugation site. The concentrations of FireMaster BP-6 in the Michigan Chemical

Corporation bagging area were 0.016–0.032 mg/L of air during the bagging operation and 0.003 mg/L of air after the completion of bagging (Di Carlo et al. 1978). In 1977, the maximum air losses of PBBs at production sites were estimated to total 1,125 pounds of PBBs for every 1 million pounds of PBBs produced (Di Carlo et al. 1978).

Another process that could release lower levels of brominated biphenyls in the air is the incineration of PBBs. Pyrolysis of hexabromobiphenyl in the absence and presence of air has produced small amounts of lower brominated biphenyls (Thoma and Hutzinger 1987). No data are available on the importance of this source for the release of PBBs in the air during the incineration of PBBs. However, since the vast majority of products containing PBBs are expected to be out of circulation after more than 25 years since the voluntary ban, incineration will not be a significant source of PBBs to air.

PBBs have been identified in 1 air sample, collected from 1,613 NPL hazardous waste sites, where they were detected in some environmental media (HazDat 2002).

Polybrominated Diphenyl Ethers. PBDEs may be released to the atmosphere during their manufacture. The estimated release of 116,239 pounds (52,725 kg) of DeBDE to the atmosphere from 55 manufacturing, processing, and waste disposal facilities in 1999 accounted for about 13.4% of the estimated total environmental releases (TRI99 2002). These releases are summarized in Table 6-1. The data from the TRI listed in Table 6-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995c). This is not a comprehensive list. In 1979, DeBDE was found in the atmosphere as particulate matter in the vicinity of plants manufacturing brominated flame retardants (Zweidinger et al. 1979); the concentration of DeBDE ranged from not detected to 72 ng/m^3. Watanabe et al. (1995) measured DeBDE in atomospheric dust from Osaka, Japan. In the regions surrounding metal recycling plants in Taiwan and Japan, a variety of tri-, tetra-, and hexaBDEs were measured in air (Watanabe et al. 1992). The concentrations in Taiwan and Japan were 23–53 and 7.1–21 pg/m^3, respectively.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Decabromodiphenyl Ether[a]

		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	10	5	No data	No data	15	No data	15
AR	4	86,610	0	0	366,543	453,153	71,301	524,454
CA	5	291	2	No data	No data	293	136,499	136,792
CT	4	1,027	No data	No data	No data	1,027	19,406	20,433
FL	1	No data	No data	No data	No data	No data	15,954	15,954
GA	4	755	0	No data	No data	755	8,515	9,270
IL	2	267	No data	No data	No data	267	9,146	9,413
IN	5	10	0	No data	No data	10	19,381	19,391
KS	1	293	No data	No data	No data	293	No data	293
KY	2	973	No data	No data	No data	973	11,560	12,533
LA	1	0	No data	No data	390,000	390,000	No data	390,000
MA	12	366	14	No data	0	380	67,745	68,125
MD	1	No data	No data	No data	No data	No data	No data	0
MI	6	2,652	0	No data	2,700	5,352	39,811	45,163
MN	5	0	No data	No data	0	0	13,665	13,665
MO	1	255	No data	No data	750	1,005	750	1,755
MS	1	121	No data	No data	No data	121	2,207	2,328
NC	12	3,647	6,272	No data	90,246	100,165	93,146	193,311
NE	1	No data	No data	No data	No data	No data	No data	0
NH	1	4	5	No data	No data	9	498	507
NJ	3	78	No data	No data	No data	78	96,868	96,946
NY	3	No data	5	No data	1,100	1,105	23,193	24,298
OH	9	389	0	No data	1,054	1,443	126,444	127,887
OR	1	0	No data	No data	10,837	10,837	No data	10,837

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Decabromodiphenyl Ether[a] (*continued*)

		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
PA	8	2,330	68	No data	No data	2,398	157,284	159,682
RI	3	265	No data	No data	No data	265	18,337	18,602
SC	9	0	2,615	No data	250	2,865	19,780	22,645
TN	6	2,755	15	No data	22,581	25,351	20,411	45,762
TX	8	2,850	5	0	2,185	5,040	5,959	10,999
VA	5	270	No data	No data	No data	270	19,142	19,412
WA	1	0	No data	No data	No data	0	No data	0
WI	2	1	No data	No data	No data	1	9,688	9,689
Total	128	106,219	9,006	0	888,246	1,003,471	1,006,690	2,010,161

Source: TRI00 2002

[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 (POTW).

Migration of PBDEs from consumer products may be a significant diffuse source of PBDEs to the atmosphere. Although no studies were found that determined the migration rate of PBDEs from polymers into the air, estimates have been calculated. Estimated migration rates for deca-, octa- and pentaBDE technical mixtures are 0.038, 0.054, and 0.39% per year, respectively (Danish EPA 1999).

PBDEs were not identified in air samples collected from 1,613 NPL hazardous waste sites (HazDat 2002).

6.2.2 Water

Polybrominated Biphenyls. In the past, PBBs were released to water during the manufacturing process. An estimated 0.0046 pounds were lost to sewers for every 1,000,000 pounds of PBBs produced at manufacturing sites (Neufeld et al. 1977). To manufacture PBBs, water was added to the reaction mixture when the desired extent of bromination was achieved. Ultimately, this water was discharged as effluent into surface water. Samples of effluents from the Michigan Chemical Corporation contained PBB concentrations #503 ppm (Di Carlo et al. 1978). Runoff water from the manufacturing plants containing PBBs also contaminated surface water (Di Carlo et al. 1978). Landfill sites used to dispose of wastes from PBB production can also be a source of PBBs in water. Concentrations of PBBs in groundwater from one such landfill in St. Louis, Michigan, were low, but those in water from a drainage ditch and catch basin were much higher (Di Carlo et al. 1978).

PBBs have been identified in 4 and 10 surface water and groundwater samples, respectively, collected from 1,613 NPL hazardous waste sites (HazDat 2002).

Polybrominated Diphenyl Ethers. PBDEs may be released to surface waters during their manufacture. The estimated release of 2,701 pounds (1,225 kg) of DeBDE to water from 11 domestic manufacturing and processing facilities in 1999 accounted for about 0.312% of the estimated total environmental releases (TRI99 2002). An additional 915,419 pounds (415,227 kg) were transferred off-site, including to POTWs (TRI99 2002). These releases are summarized in Table 6-1. The data from the TRI listed in Table 6-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995c). This is not a comprehensive list.

Industrial and urban effluents are significant sources of PBDEs to surface waters and sediments. In 1995, sediment samples were collected up- and downstream near an area where the Swedish plastics industry uses brominated flame retardants (Sellström and Jansson 1995; Sellström et al. 1998). Samples were

analyzed for TeBDEs (50 ng/g dry weight) and PeBDEs (sum of three congeners, 2,300 ng/g dry weight). These PBDEs were found in higher concentrations downstream of the plant than upstream, which indicates that the plastics industry was the most likely source of these compounds. Surficial sediment samples were collected at eight locations along River Viskan near several textile manufacturing facilities that used various brominated flame retardants in the production of textiles. The concentrations of BDE-47, -99, -100, and -209 in sediments increased as samples were collected further downstream and as more industries were passed (Sellström et al. 1998). The lowest levels of PBDEs were found upstream of the textile industries. The combined concentration of BDE-47, -99, and -100 ranged from not detected to 120 ng/g (dry weight); the concentration of BDE-209 ranged from not detected to 16,000 ng/g (dry weight). Allchin et al. (1999) surveyed the concentrations of PBDEs in sediments from several rivers and estuaries in Great Britain. Sediments were collected upstream and downstream of suspected sources of PeBDE and OBDE, including a manufacturer, several industries, landfills, and a reference site. The highest concentrations of BDE-47, BDE-99, PeBDE (as BDE-71), and OBDE (as BDE-79) were in sediments near or downstream from a manufacturing site at Newton Aycliffe on River Skerne. The highest concentrations of DeBDE (as BDE-83) were found downstream of a sewage treatment plant on River Calder. High concentrations were also detected on River Skerne downstream of a manufacturing site. BDE-99 concentrations were identical or slightly higher than BDE-47 in most sediments (Allchin et al. 1999). The sum of five PBDE congeners (BDE-47, -99, -100, -153, and -209) ranged from 0.07 to 10.6 ng/g dry weight in freshwater sediments from Denmark (Christensen and Platz 2001). The highest concentrations were found in sediment close to populated areas.

PBDEs were not identified in water samples collected from 1,613 NPL hazardous waste sites (HazDat 2002).

6.2.3 Soil

Polybrominated Biphenyls. The important former sources of PBBs in soil are manufacturing operations, disposal of PBB-containing finished products, and agricultural operations contaminated in the original episode in 1973–1974. The concentrations of PBBs in soils from bagging and loading areas of the Michigan Chemical Corporation were 3,500 and 2,500 mg/kg, respectively (Di Carlo et al. 1978). Similarly, soil from sites adjacent to the Hexcel Corp and the White Chemical Company, the manufacturers of octabromo- and decabromobiphenyl, contained decabromobiphenyl and other lower brominated biphenyls down to hexabromobiphenyl (Di Carlo et al. 1978). The disposal into landfills of solid wastes generated during the production of PBBs was another important source of PBBs in soil

(Neufeld et al. 1977). Photodecomposition of FireMaster BP-6 in soil could also be a source of lower brominated biphenyls (Ruzo and Zabik 1975; Trotter 1977) in soil.

Approximately 11.8 million pounds of hexabromobiphenyl were used in commercial and consumer products in the United States, mostly in the production of plastic products. Since the cessation of production of hexabromobiphenyl, all of these products, such as TV cabinet and business machine housings, with a usable life of 5–10 years must have been disposed of by landfilling or incineration (Neufeld et al. 1977). Disposal of these plastic materials in waste disposal sites is an important source of PBBs in soil. The migration of plastic-incorporated PBBs to soil would be very low since PBBs would be tightly bound into the plastic (Neufeld et al. 1977).

The indirect source of PBBs in soil was the contaminated farms in Michigan. Approximately 650 pounds (290 kg) of PBBs were mixed in cattle feeds that were delivered to Michigan farms during 1973–1974 (Fries 1985b). About 50% of this amount was excreted in the feces of the exposed animals and remained on the farms in places of fecal deposition and manure disposal (Fries 1985b). Soil in fields that received contaminated manure contained as high as 300 μg/kg PBBs, whereas soil in resurfaced cattle exercise lots contained as high as 1,000–2,000 μg/kg of PBBs (Fries 1985b).

PBBs have been identified in 12 soil and 5 sediment samples collected from 1,613 NPL hazardous waste sites (HazDat 2002).

Polybrominated Diphenyl Ethers. PBDEs are released to land during their manufacture and disposal. In 1999, 746,169 pounds (338,456 kg) of DeBDE were released to land from 10 domestic manufacturing, processing, and waste disposal facilities reporting releases of the compound to the environment (TRI99 2002). No releases (0 pounds) of DeBDE occurred via underground injection (TRI99 2002). Releases to the environment from facilities that produce, process, or use DeBDE are summarized in Table 6-1. The data from the TRI should be used with caution since only certain types of facilities are required to report (EPA 1995c). This is not a comprehensive list. Solid waste from commercial production of OBDE is typically disposed in landfills (EPA 1994).

PBDEs are release to land as municipal wastes with the disposal of consumer products containing PBDEs. The disposal of consumer products containing PBDEs is likely to increase worldwide due to rapid obsolescence of plastic products. For example, between 1997 and 2004, the number of obsolete computers containing flame retardants is projected to be 315 million (NSC 1999). Based on a monitor weight of 30 pounds, an estimated 350 million pounds of brominated flame retardants will be released to

landfills (NSC 1999). Although PBDEs will only be a fraction of this total, the amount of PBDEs released to the environment by disposal will still be significant.

Although no information was located, PBDEs may be released to farm land with their disposal as biosolids (i.e., sewage sludge). PBDEs were detected in biosolids from four different regions of the United States (Pardini et al. 2001). The total concentrations of PeBDE in biosolids ranged from 1,100 to 2,290 µg/kg dry weight; the levels of PeBDE were high and consistent, regardless of the region of origin. The concentration of DeBDE (BDE-209) varied widely among biosolids from different regions; the concentration of BDE-209 ranged from 84.8 to 4,890 µg/kg dry weight in the biosolid samples. Sewage sludge samples from 13 waste water treatment plants in Germany were sampled (Hagenmaier et al. 1992). The mean concentration of tri- to heptaBDEs was 8.37 ng/g with tri-, tetra-, penta-, hexa-, and heptaBDE at concentrations of 0.65, 3.06, 3.02, 0.49, and 0.22 ng/g, respectively. Levels of penta- and hexaBDEs were highest in these samples.

PBDEs were not identified in soil and sediment samples collected from 1,613 NPL hazardous waste sites (HazDat 2002).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Polybrominated Biphenyls. PBBs existed predominantly in the particulate phase in the atmosphere. Particulate phase PBBs are removed from the atmosphere by wet and dry deposition and should not travel long distances in the environment. In water, PBBs are expected to absorb strongly to suspended solids and sediment, and may bioconcentrate in aquatic organisms. The volatilization of PBBs from water to air is not expected to be important due to attenuation by adsorption in the water column. In soil, PBBs are adsorbed strongly and will be immobile. Volatilization of PBBs from soil to air is not important due to the low volatility of PBBs and strong adsorption of PBBs to soil.

Organic compounds with vapor pressures $>10^{-4}$ mmHg should exist almost entirely in the vapor phase in the atmosphere, while organic compounds with vapor pressures $<10^{-8}$ mmHg should exist almost entirely in the particulate phase (Eisenreich et al. 1981). The estimated vapor pressure of FireMaster BP-6 is 5.2×10^{-8} mmHg at 25 EC (Jacobs et al. 1976). The vapor pressure of octabromobiphenyl is 7.0×10^{-11} mmHg at 28 EC (Waritz et al. 1977). Although no data are available, the vapor pressures of

decabromobiphenyl at ambient temperatures should be lower than octabromobiphenyl. Therefore, the PBBs produced in the 1970s should have existed predominantly in the particulate phase in the atmosphere. Since the particulate phase PBBs would precipitate out by dry deposition and wet deposition due to washout (Atlas and Giam 1987), PBBs would not be expected to transport long distances in the atmosphere.

There are limited data regarding the transport and partitioning of PBBs in water. Based on an estimated Henry's law constant of 3.9×10^{-6} atm-m^3/mol (where Henry's law constant = vapor pressure/water solubility) and an estimation method (Thomas 1990), the estimated volatilization half-life of hexabromobiphenyl is 23 days. Therefore, the transport of PBBs from water to the atmosphere by volatilization is not expected to be important. This is consistent with a fish bioconcentration study where losses of octabromobiphenyl and decabromobiphenyl from water to air were insignificant (Norris et al. 1973). Soil mobility studies have shown that PBBs are strongly adsorbed by soil materials (Filonow et al. 1976; Griffin and Chou 1981a, 1981b). Therefore, transport of water-bound PBBs to particulate matter and sediment in water due to adsorption is a major transport process for PBBs in water. The detection of at least a 1,000-fold higher concentration of PBBs in Pine River sediment (where effluent from Michigan Chemical Corporation was discharged) compared with the level of PBBs in the river water confirms the importance of this transport process (Hesse and Powers 1978).

PBBs may also be transported from water to aquatic organisms where bioconcentration may take place. Data on the bioconcentration of PBBs in fish, which were generated in different laboratories, show wide variation. The experimentally determined bioconcentration factor ([BCF] = concentration in fish over concentration in water) for hexabromobiphenyl (mixtures of unspecified congeners) in the whole body of fathead minnows (*Pimephales promelas*) was 18,100 in a 32-day exposure (Veith et al. 1979). In fillet of fathead minnow, the estimated BCF was >10,000 (Hesse and Powers 1978). The lipid weight-based BCF values of 4,4'-dibromobiphenyl, 2,4,6-tribromobiphenyl, 2,2',5,5'-tetrabromobiphenyl, and 2,2',4,4',6,6'-hexabromobiphenyl in guppies (*Poecilia reticulata*) were 269,153; 114,815; 1,445,440; and 707,946, respectively (Gobas et al. 1989). It is worth noting that the BCF values decrease, rather than increase, as the degree of bromine substitution increases. A similar trend in BCF values for various PBBs was also observed in juvenile Atlantic salmon (*Salmo salar*). For example, the determined whole body BCF values for 2,6-dibromobiphenyl, 2,4-dibromobiphenyl, 3,4-dibromobiphenyl, 2,5,4'-tribromobiphenyl, 2,2',4,5'-tetrabromobiphenyl, 2,3',4',5-tetrabromobiphenyl, hexabromobiphenyl (unspecified congener), and octabromobiphenyl were 1,267; 1,343; 63; 425; 314; 111; 2–48; and 0.02, respectively (Zitko 1979; Zitko and Hutzinger 1976). The determined BCF values for 2,2',3',3',4,4'-hexabromobiphenyl and decabromobiphenyl in whole body guppies (*P. reticulata*) were 10 and 0, respectively

(Opperhuizen et al. 1985). The BCF value for octabromobiphenyl in filleted rainbow trout (*Salmo gairdneri*) was 0 (Norris et al. 1973). The lack of accumulation for the higher brominated compounds is most likely because they have very limited water solubility and are therefore not available to penetrate membranes (Zitko 1979).

PBBs are adsorbed strongly to soil, and the adsorption increases with an increase in the organic carbon content of soil (Filonow et al. 1976; Griffin and Chou 1981a, 1981b). Neither clay content nor pH of soil correlated with adsorption of hexabromobiphenyl to soil (Filonow et al. 1976). PBBs present in soil-water solution will partition to the soil by adsorption. The presence of certain specific dissolved organic carbon in natural water (e.g., leachate from a landfill) may decrease the adsorption of PBBs in sediments (Simmons and Kotz 1982). Because of the strong adsorption, PBBs will have low mobility in soil, and the leaching of PBBs from soil to groundwater will generally be insignificant (Filonow et al. 1976; Griffin and Chou 1981a, 1981b). However, the mobility of PBBs may greatly increase if methanol or other organic solvents (capable of solubilizing PBBs) are present at significant concentrations in soil (Griffin and Chou 1981b). The phenomena is commonly called "co-solvency." The transport of PBBs from soil to the atmosphere by volatilization is not important due to the low volatility of PBBs (Jacobs et al. 1976). The transport of PBBs from soil to surface water or another land area via eroded soil contained in runoff water is possible (Jacobs et al. 1976). Orchard grass and carrot tops grown in soil contaminated with PBBs showed no uptake, and carrot roots showed only minor uptake of PBBs (Jacobs et al. 1976, 1978). Therefore, the transport of PBBs from soil to plants via translocation is insignificant.

Polybrominated Diphenyl Ethers. In air, highly brominated PBDEs, which have low vapor pressures and exist in the particulate phase, will be removed from the atmosphere by wet and dry deposition. These PBDEs do not travel long distances in the environment. Lower BDE homologs, which exist partially in the vapor phase, have the potential for long-range transport in the atmosphere. In water, PBDEs are expected to adsorb strongly to suspended solids and sediment, and bioconcentrate in aquatic organisms. The volatilization of PBDEs from water to air is not expected to be important due to attenuation by adsorption in the water column. In soil, PBDEs are adsorbed strongly and will be immobile. They are not likely to leach into groundwater. Volatilization of PBDEs from soil to air is not important due to the low volatility of PBDEs and strong adsorption of PBDEs to soil.

PBDEs with vapor pressures between 10^{-4} and 10^{-8} mm Hg (di- to hexaBDE) should exist in both the vapor and particulate phase in the atmosphere, while PBDEs with vapor pressures $<10^{-8}$ mmHg (hexaBDE to DeBDE) should exist almost entirely in the particulate phase in the atmosphere (Bidleman 1988; Eisenreich et al. 1981). PBDEs have low vapor pressures, with vapor pressure tending to decrease

with increasing bromination. Watanabe and Tatsukawa (1990) determined the vapor pressures for a range of brominated PBDEs as follows (mm Hg at 25 EC): di- ($9.8x10^{-5}$–$1.4x10^{-4}$); tri- ($1.2x10^{-5}$–$2.0x10^{-5}$); tetra- ($1.8x10^{-6}$–$2.5x10^{-6}$); penta- ($2.2x10^{-7}$–$5.5x10^{-7}$); hexa- ($3.2x10^{-8}$–$7.1x10^{-8}$); and octa- ($9.0x10^{-10}$–$1.7x10^{-9}$). Vapor pressures have also been determined for commercial BDE mixtures, such as PeBDE ($2.2x10^{-7}$–$5.5x10^{-7}$ mm Hg) and DeBDE ($3.2x10^{-8}$ mm Hg at 25 EC) (EU 2001; NRC 2000). Since particulate phase PBDEs will precipitate out by wet and dry deposition, these PBDEs would not be expected to transport long distances in the atmosphere (Atlas and Giam 1987). Thus, highly brominated PBDEs (e.g., octa- through decaBDEs), which have low vapor pressures and exist solely in the particulate phase, will not be transported long distances. Although no information was located in the literature, moderately brominated PBDEs (e.g., PeBDEs and hexaBDEs) may have the potential to be transported short distances and might be found close to PBDE point sources. Lower BDE homologs (e.g., TeBDE), which exist partially in the vapor phase, have the potential for long-range transport in the atmosphere (Dodder et al. 2000a). For example, BDE-47, BDE-99, and BDE-153 were detected in air samples from urban, rural, and remote areas of the Great Lakes in the United States (Dodder et al. 2000a).

Concentrations of PBDEs in water are expected to be low due to the low water solubility of PBDEs. For example, the solubilities of the commercial mixtures of PeBDE and DeBDE are 13.3 and 20–30 µg/L, respectively (EU 2001; WHO 1994a). As consequence of their low water solubility, monitoring studies have not detected PBDEs in environmental waters (see Section 6.4.2).

PBDEs adsorb strongly onto suspended solids and sediments in the water column. Volatilization of PBDEs from water surfaces will be attenuated by adsorption, and thus is not an important fate process. Sediment-water partition coefficients (K_p) have been measured for several components of commercial PeBDEs (Watanabe 1988). K_p values for tetra-, penta-, and hexaBDEs are 28,293; 49,167; and 62,727 L/kg, respectively, which suggest strong partitioning to sediment. High $logK_{ow}$ values have been measured for PBDEs as follows (Watanabe and Tatsukawa 1990): di- (5.03); tri- (5.47–5.58); tetra- (5.87–6.16); penta- (6.46–6.97); hexa- (6.86–7.92); octa- (8.35–8.90); and deca- (9.97). Using these log K_{ow} values, log organic carbon-water partition coefficients (K_{oc}) were estimated for PBDEs: di- (4.11); tri- (4.35–4.41); tetra- (4.57–4.73); penta- (4.89–5.17); hexa- (5.11–5.69); octa- (5.92–6.22); and deca- (6.80) (Lyman et al. 1990).

PBDEs are transported from water to aquatic organisms, which results in bioconcentration in aquatic organisms. No data on the bioconcentration of PBDEs in fish were located. However, due to abundance of monitoring data illustrating the accumulation of PBDEs in fish (see Section 6.4.4), bioconcentration of PBDEs is expected to occur. In a laboratory study of Baltic blue mussels, BCFs (from water absorption)

were found to be 1,300,000 for BDE-47, 1,400,000 for BDE-99, and 1,300,000 for BDE-153 (Gustafsson et al. 1999). At several sites along the coast and in the Schelde estuary (the Netherlands), BCFs for blue mussels were determined (Booij et al. 2000). The maximum BCFs were log BCF of 9 for BDE-99 and BDE-100, and approximate log BCFs of 7.4 for BDE-28, 8.4 for BDE-47, and 8.2 for BDE-153.

Bioaccumulation of PBDEs in the aquatic food web is inversely related to the degree of bromination (Burreau et al. 2000b; Jansson et al. 1993). Thus, higher brominated congeners are rarely detected in biota. This is a result of their low solubility and high log K_{ow} values (Hardy 2000). In contrast, tetra- to hexaBDE homologs are most frequently detected in biota (Burreau et al. 1997), which would be expected due to their greater water solubility and relatively high K_{ow} values.

Concentrations of PBDEs in biota are related to the trophic level of the species. For example, Haglund et al. (1997) examined the concentrations of PBDEs in herring, salmon muscle, and gray and ringed seals collected along the Swedish coast of the Baltic sea between 1981–1988. PBDE concentrations were found to increase with trophic level.

PBDEs will be strongly adsorbed to soils based on log K_{ow} values ranging from 5.03 to 9.97 (Watanabe and Tatsukawa 1990). Thus, PBDEs present in soil pore water will bind to soil organic matter. Because PBDEs adsorb strongly to soil, they will have very low mobility (Swann et al. 1983), and leaching of PBDEs from soil to groundwater will be insignificant. Like PBBs, the presence of dissolved organic carbon in natural water (e.g., leachate from a landfill) may increase the mobility of PBDEs. The transport of PBDEs from soil to surface water via eroded soil contained in runoff water is also possible. Volatilization of PBDEs from moist soil surfaces will be attenuated by adsorption, and is not expected to be an important fate process. Volatilization of PBDEs from dry soil will not be important due to the low volatility of PBDEs (see Table 4-6).

6.3.2 Transformation and Degradation

Photolysis appears to be the dominant transformation process for PBBs and PBDEs. However, the importance of photochemical transformation reactions in the environment cannot be determined due to lack of information. Based on a very limited number of studies, biodegradation does not appear to be significant for either PBBs or PBDEs.

6.3.2.1 Air

Polybrominated Biphenyls. In air, the two processes that may result in significant degradation or transformation of PBBs are photooxidation by hydroxyl radicals and direct photolysis. The estimated half-life of pentachlorobiphenyl in air due to reaction with hydroxyl radicals is 41.6–83.2 days (Atkinson 1987a). Based on a structure-activity relationship for the estimation of half-lives for the gas-phase reactions of hydroxyl radicals with organic compounds (Atkinson 1987b), the estimated half-lives of hexabromobiphenyl and decabromobiphenyl due to reaction with OH radicals are 182 and 2,448 days, respectively. These half-lives are consistent with the half-life of pentachlorobiphenyl due to reaction with OH radicals. However, the half-lives of brominated biphenyls expected to be present in the particulate phase in the air may be even longer than the estimated half-lives due to gas phase reaction. Therefore, the transformation of the hexa- and other higher brominated PBBs in the atmosphere due to reaction with OH radicals may not be important.

Hexa- and other higher brominated biphenyls are expected to be present in the particle-adsorbed state in the atmosphere. These PBBs photolyze in solution and in soil (Hill et al. 1982; Ruzo and Zabik 1975; Trotter 1977). Since PBBs present in surface soil are known to photolyze, particle-sorbed PBBs present in the atmosphere may also undergo photolysis. The importance of the photochemical reaction under sunlight illumination conditions for the degradation/transformation of PBBs in air cannot be evaluated due the lack of information.

Polybrominated Diphenyl Ethers. In air, PBDEs may undergo indirect photolysis with hydroxyl radicals or direct photolysis with sunlight. Vapor-phase PBDEs may be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. The half-lives for this reaction in air are estimated to be 29, 140, and 476 days, respectively, for penta-, octa-, and decaBDE homologs, calculated using a structure estimation method (Meylan and Howard 1993). This estimation is calculated using an atmospheric concentration of $5x10^5$ hydroxyl radicals per cm^3 and is based on a 24-hour day of sunlight. The half-lives of PBDEs that are expected to be present in the particulate phase in the air will be longer than the estimated half-lives calculated for the gas-phase reaction. Thus, for the higher brominated PBDEs (e.g., octa- and decaBDEs), indirect photolysis with hydroxyl radicals may not be important.

In water, PBDEs are known to undergo direct photolysis (Norris et al. 1973, 1975a; Watanabe and Tatsukawa 1987). Likewise, PBDEs present in the atmosphere may also undergo photolysis. However, the importance of photolysis of PBDEs in air cannot be evaluated due the lack of information.

6.3.2.2 Water

Polybrominated Biphenyls. The photolytic degradation of PBBs in solution has been the subject of several studies. Available data in the literature indicate that brominated biphenyls photodegrade by reduction in solvents capable of proton transfer with the formation of lower brominated biphenyls. For example, the irradiation of FireMaster BP-6 and 2,2', 4,4',5,5'-hexabromobiphenyl in methanol at wavelengths >286 nm produced mainly penta- and tetrabromobiphenyl (Ruzo and Zabik 1975). FireMaster BP-6 photolyzed 7 times faster than its chlorinated counterpart, 2,2',4,4',5,5'-hexachloro-biphenyl (Ruzo and Zabik 1975). Although an earlier study tentatively identified dimethoxy tetrabromobiphenyl as a photolysis product of FireMaster BP-6 (Ruzo and Zabik 1975), later work did not detect this compound (Ruzo et al. 1976). Earlier studies indicated that the debromination usually occurs with the stepwise preferential loss of bromine from the *ortho* and *para* positions of the biphenyl ring (i.e., 2, 2', 6, and 6' positions) (De Kok et al. 1977; Ruzo and Zabik 1975; Ruzo et al. 1976; Trotter 1977). Thus, the photolysis of 2,2',4,4',5,5'-hexachlorobiphenyl, the major component of FireMaster BP-6, would be expected to produce 2,3',4,4',5-pentabromobiphenyl and subsequently 3,3',4,4'-tetrabromobiphenyl. More recent work indicates that although photolysis mainly produces debromination products, unlike in the case of an individual PBB congener, reductive debromination of *ortho* substituents is not the predominant photolytic degradation pathway for FireMaster BP-6 (Robertson et al. 1983b).

The study of photolysis of PBBs in the aqueous phase is more relevant to natural environmental situations than photolysis in proton-donating organic solvents. It was suggested that the photolysis of PBBs in aqueous solution would proceed by oxidative process of photohydroxylation, leading to the formation of phenolic compounds (Norris et al. 1973). However, photolysis of 2,4-dibromo- and 2,3',4',5-tetrabromobiphenyl in acetonitrile-water solution showed that debromination was the major reaction (Ruzo et al. 1976). No evidence of the formation of hydroxylated species (phenolic products) was found (Ruzo et al. 1976).

Several investigators assessed the biodegradation potential of PBBs under aerobic conditions, with activated sludge or pure cultures of microorganisms as microbial inoculum, and concluded that although the lower substituted biphenyls might biodegrade in aerobic water and sediment (Kong and Sayler 1983; Sugiura 1992; Yagi and Sudo 1980), the higher substituted biphenyls are resistant to aerobic biodegradation (Kawasaki 1980; Sasaki 1978; Shelton and Tiedje 1981). This is consistent with biodegradation studies in soil (see Section 6.3.2.3). It has been proposed that complete mineralization of

4-bromobiphenyl to carbon dioxide occurs via a 4-bromobenzoate intermediate by mixed bacterial cultures obtained from PBB-contaminated river sediment (Kong and Sayler 1983). However, complete mineralization was not observed for 2- and 3-bromobenzoate (Kong and Sayler 1984).

Although higher brominated biphenyls do not biodegrade in water or sediment under aerobic conditions, it has been shown that anaerobic microorganisms obtained from populated river sediments can biodegrade higher substituted PBBs, including FireMaster mixtures (Morris et al. 1992). The biodegradation involved debromination at the *meta* and *para* positions, and no *ortho* bromine removal was observed (Morris et al. 1992). However, the possibility of *ortho* bromine removal from higher brominated biphenyls under certain inoculation conditions (e.g., microorganisms from polluted river sediment repeatedly transferred on a pyruvate medium amended with Aroclor 1242) has been suggested (Morris et al. 1992).

Polybrominated Diphenyl Ethers. PBDEs may undergo debromination by direct photolysis. For example, studies indicate that DeBDE is debrominated by UV light and sunlight to lower brominated PBDEs (to triBDE with UV light and to tetraBDE with sunlight) (Norris et al. 1973, 1975a; Watanabe and Tatsukawa 1987). However, it is not known whether direct photolysis of DeBDE happens in the environment. More recent laboratory studies of the photolytic breakdown of DeBDE in toluene have shown that it is successively debrominated by UV light to lower brominated PBDEs (down to TeBDE) and that photolysis occurs very rapidly (Sellström et al. 1998). The photolysis half-life in toluene was <15 minutes. In water alone (i.e., without organic solvent), photodegradation of PBDEs does not result in the formation of lower brominated PBDEs or polybrominated dibenzofurans (PBDFs) (Norris et al. 1973). Photohydroxylation of DeBDE is expected in water, resulting in the formation of hydroxylated products, which are degraded rapidly due to increased UV absorption (WHO 1994a). No information was available on direct photolysis of other PBDEs. By comparison with DeBDE, it is likely that other PBDEs will photodegrade. However, it is not possible to predict the likely extent or rate.

No information was located in the literature about the biodegradation of PBDEs in natural waters. For PeBDE, no degradation (as CO_2 evolution) was seen after 29 days in an OECD 301B ready biodegradation test (EU 2001). The substance tested was a composite sample from two producers with the following composition: 33.7% TeBDE; 54.6% PeBDE; and 11.7% HexaBDE. The test was extended to 93 days to allow sufficient opportunity for adaption to occur. At the end of 93 days, 2.4% of the theoretical amount of CO_2 had been evolved. Thus, PeBDE is not readily biodegradable. In a laboratory study, Schmidt et al. (1993) found that 4,4'-dibromodiphenyl ether was not used as a carbon source by a pure bacterial culture. Transformation of 4,4'-dibromodiphenyl ether did occur yielding 4-bromophenol

and 4-bromocatechol. The specific rate of oxidation of 4,4'-dibromodiphenyl ether was 19 nmol of O_2 per minute per mg of protein.

No other information was found in the literature about the transformation and degradation processes for PBDEs in water.

6.3.2.3 Sediment and Soil

Polybrominated Biphenyls. Information on the fate of PBBs in soil is limited. A pure culture of microorganism isolated from soil biodegraded 2-bromobiphenyl via the 2-bromobenzoic acid pathway (Takase et al. 1986). There is little evidence that the higher brominated biphenyls biodegrade in soil under aerobic conditions for an incubation period of #1 year (Griffin and Chou 1981a, 1981b; Jacobs et al. 1976). Some degradation of an undefined congener of pentabromobiphenyl was observed when incubated in soil, but this degradation could not be definitely attributed to biodegradation (Jacobs et al. 1976). As discussed in Section 6.3.2.2, higher brominated PBBs may biodegrade in an anaerobic region of river sediment and possibly soil polluted with PCBs and PBBs to form lower brominated products. Biodegradation of the photolysis products of hexa- and heptabromobiphenyl in soil (which produces lower brominated products) was only minor (. 3% in 1 year) since the photodegradation products were bound to soil (Jacobs et al. 1978).

Degradation of PBBs present in a contaminated soil from a manufacturing site in Michigan was significant (Hill et al. 1982). For example, 2,2',4,4',5,5'-hexabromobiphenyl, the principal component of FireMaster (54–68% in FireMaster) was reduced to 26% of the total PBBs when exposed to a field soil for several years. In two other soils, where the original concentrations of PBBs were much lower, the rate of degradation was much lower. Principal degradation products were 2,3',4,4',5-pentabromobiphenyl, 2,2',4,4',5-pentabromobiphenyl, and two unidentified tetrabromobiphenyls. The degradation was attributed to photochemical reactions. On the other hand, no significant photodegradation of FireMaster was observed after 1 year in contaminated manure spread in field soil from Michigan (Jacobs et al. 1978). The authors provided no explanation for the difference in photoreactivity of PBBs in soils with and without manure. It is important to point out that, due to attenuation and scattering of light, sunlight will not penetrate most soil beyond the surface layer. Therefore, it can be concluded from these studies that although photolysis may be the only viable degradative process for PBBs in soil, photolysis will be limited to the surface layer of soil, and the rate of photolysis will be very slow. PBBs incorporated into

thermoplastics, which were eventually buried at waste sites are not likely to absorb much light and undergo photolytic degradation.

Analysis (Morris et al. 1993) of sediments from a PBB-contaminated river in Michigan (Pine River) indicates that little degradation of PBBs has occurred since the 1970s. Although microorganisms capable of debrominating PBBs were not present in regions of highest contamination, they were found in sediments downstream from the area of highest contamination. The investigators (Morris et al. 1993) suggest that high levels of contaminants including PBBs may be inhibiting the microbial degradation of PBBs in this river.

Polybrominated Diphenyl Ethers. Information on the transformation and degradation of PBDEs in soil is limited. PBDEs may undergo debromination by direct photolysis in soils and sediment. The extent to which PBDEs photodegrade in soils and sediment is unknown in the environment. If the photodegradation process is significant, it could result in the formation of lower brominated BDEs, which are known to bioaccumulate. Studies indicate that DeBDE is debrominated by UV radiation and sunlight forming lower brominated PBDEs (Norris et al. 1973, 1975a; Watanabe and Tatsukawa 1987). The photolysis half-lives for DeBDE in sediment were 53 and 81 hours for UV and sunlight exposure, respectively. TeBDE appeared at the longest exposure time (244 hours). In sand, the half-life of DeBDE exposed to UV radiation was between 12 and 37 hours. Lower PBDEs and other compounds (not specified) were found after UV radiation (Sellström et al. 1998). In a laboratory study of soil treated with DeBDE and exposed to UV light, a photolysis half-life of 185 hours for DeBDE was measured. The debromination process was the same as that seen for other studies.

No other information was found in the literature about the transformation and degradation processes for PBDEs in soils and sediment.

6.3.2.4 Other Media

No other information was found in the literature about the transformation and degradation processes for PBBs or PBDEs in other media.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Evaluation of the potential for human exposure to PBBs or PBDEs depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Comparisons among various studies are complicated by the fact that authors may report PBB or PBDE concentrations as technical mixtures, as homologs, or as congeners. For PBDEs, it is common to determine the concentration of individual congeners. However, only a limited number of standards are available. Total PBDEs, the definition of what constitutes total PDBEs (i.e., how many and which congeners are summed), is often not the same in the various studies. Chemical analysis procedures are discussed in greater detail in Chapter 7. Recent monitoring data for PBBs are very limited. Historical monitoring data indicate that environmental PBB concentrations are confined to areas near former manufacturing facilities and regions of Michigan effected by the farm catastrophe of the early 1970's (see Section 6.1). Monitoring studies indicate that PBDEs are transported globally. Atmospheric, water, and biota levels of PBDEs tend to be dominated by lower brominated congeners (e.g., BDE-47). Sediments tend to be dominated by higher brominated congeners (e.g., BDE-209). Biota monitoring studies indicate that PBDE concentrations have increased since the late 1970s, with lower brominated congeners (e.g., BDE-47) being preferentially bioconcentrated. Studies indicate that PBDE concentrations increase with respect to trophic level; organisms that reside higher on the food chain tend to have higher concentrations of PBDEs.

6.4.1 Air

Polybrominated Biphenyls. Historically, PBBs were released to the atmosphere during three stages of the manufacturing process, and an estimate of the maximum amount of PBBs expected to be lost to the air during the manufacture of PBBs in the United States is available (see Section 6.2.1) (Neufeld et al. 1977). Monitoring data on the ambient air levels of PBBs are very limited. The concentration of hexabromobiphenyl in air samples collected downwind and crosswind from the White Chemical Company plant in Bayonne, New Jersey was 0.06 ng/m^3 (DeCarlo 1979).

Polybrominated Diphenyl Ethers. Atmospheric concentrations of PBDEs tend to be dominated by lower brominated congeners (e.g., BDE-47 and -99). The concentrations of PBDEs in air samples are summarized in Table 6-2. Air samples sampled from urban (Chicago, Illinois), rural (Sleeping Bear Dunes, Michigan and Sturgeon Point, New York), and remote (Eagle Harbor, Michigan) shorelines of the

U.S. Great Lakes all contained quantifiable levels of BDE-47, -99, -100, -153, and -154 (Dodder et al. 2000a; Strandberg et al. 2001). The most significant congeners were BDE-47 and BDE-99. The concentration of total PBDEs ranged from 6.9 to 77 pg/m^3 for all samples; the highest levels were observed near Chicago, Illinois (BDE-47, 48 pg/m^3). Throughout the year of 1997, air samples were taken from a rural site in southwestern England called Stokes Ferry and a semirural site in northwestern England called Hazelrigg and analyzed for PBDEs (Peters et al. 1999). Tri- and heptaBDEs were detected; the combined concentrations of BDE-47, -99, and -100 ranged from 7 to 69 pg/m^3 at Hazelrigg and from 6 to 58 pg/m^3 at Stoke Ferry (de Wit 2002). PBDEs have also been measured in air samples taken from remote stations in the Arctic (e.g., Alert, North West Territory, Canada; Dunai Island, eastern Siberia, Russia) between January 1994 and January 1995 (de Wit 2002). The total concentration of several di- to hexaBDEs ranged from 1 to 4 pg/m^3 at Alert the majority of the year; however, in July 1994, the concentration was 28 pg/m^3. At Dunai, the major congeners found were BDE-47 and BDE-99. In Sweden during 1990–1991, air samples collected from Ammarnäs in the northern mountains and Hoburgen on the southern tip of Gotland in the Baltic Sea, had measurable amounts of BDE-47, -99, and -100 (de Wit 2002). Total PBDE levels were approximately 1 and 8 pg/m^3, respectively. The concentration of BDE-47 was found to be highest in the gas phase, while BDE-99 and BDE-100 were highest in the particulate phase. No DeBDE was found, although the limit of detection limit for DeBDE is much higher than for the lower BDEs.

Table 6-2. Concentrations (in pg/m^3) of Several PBDEs in Air Samples

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	Reference
Air	Ammararnäs	6.3	1.6	0.4	8.3	de Wit 2000, 2002
Air	Hobburgen	0.7	0.35	0.07	1.1	de Wit 2000, 2002
Air	Stoke Ferry, United Kingdom	4.7–50	5.5–13	1.1–3.9	6.7–58	Peters et al. 1999
Air	Hazelrigg, United Kingdom	3.2–61	3.1–22	0.62–5.4	4.1–69	Peters et al. 1999
Air	Alert, Canada	No data	No data	No data	1-28	Alaee et al. 1999
Air	Dunai Island, Russia	No data	No data	No data	1-8*	Alaee et al. 1999
Air	Urban, United States	48	25	3.0	77*	Dodder et al. 2000
Air	Rural, United States	6.2–9.2	4.3–5.0	0.6–0.9	2–4.8*	Dodder et al. 2000
Air	Remote, United States	3.7	2.6	0.33	6.9*	Dodder et al. 2000

[a]3PBDEs is the sum of BDE-47, BDE-99, and BDE-100, but if more congeners are included, this is marked with an asterisk (*).

Source: de Wit (2002)

6.4.2 Water

Polybrominated Biphenyls. The concentrations of PBBs in effluents discharged from the Michigan Chemical Corporation plant in St. Louis, Michigan, to the Pine River during 1974–1977 ranged from <0.01 to 150 μg/L (Hesse and Powers 1978). The concentrations of PBBs in effluents from White Chemical Company, Bayonne, New Jersey, and Hexcel Chemical Corporation, Sayerville, New Jersey, ranged from <0.2 to 210 μg/L (DeCarlo 1979). The concentrations of PBBs in the Pine River #12 miles downstream from the Michigan Chemical Corporation plant in 1974 were 0.01–3.2 μg/L (Hesse and Powers 1978; Neufeld et al. 1977). 2,2',5,5'-Tetra- and 3,3',5,5'-tetrabromobiphenyl were qualitatively detected in water from Lake Ontario, and hexabromobiphenyl (unspecified congeners) was qualitatively detected in water from Lakes Ontario and Huron (Great Lakes Water Quality Board 1983). The concentrations of PBBs in test wells within a PBB landfill site in Michigan ranged from 0.4 to 26.0 μg/L, although the concentrations of PBBs in test wells outside the landfill ranged from <0.1 to 4.4 μg/L (Shah 1978). No other information was located about the concentrations of PBBs in water.

Polybrominated Diphenyl Ethers. In 1999, the concentration of PBDEs in Lake Ontario surface waters ranged between 4 and 13 pg/L with ~90% in the dissolved phase (Luckey et al. 2001). BDE-47 and BDE-99 were the most abundant congeners, together making up >70% of the total PBDEs. No other information was located about the concentrations of PBDEs in water.

6.4.3 Sediment and Soil

Polybrominated Biphenyls. Soil samples from the bagging and loading areas of the Michigan Chemical Corporation plant in St. Louis, Michigan, contained PBBs at concentrations of 3,500 and 2,500 mg/kg, respectively (Di Carlo et al. 1978). PBBs (mostly decabromobiphenyl, but some lower brominated biphenyls down to hexabromobiphenyl) in soil near the Hexcel Chemical Corporation plant in New Jersey and the White Chemical Company plant in New Jersey ranged from 40 to 4.6 mg/kg and from 1.14–4.25 mg/kg, respectively (DeCarlo 1979). PBB levels in surface soil samples from seven dairy farms in Michigan that spread contaminated manure on the fields ranged from 35 to 1,260 μg/kg, while the concentrations in surface soil of control farms (that did not use contaminated manure) were <25 μg/kg (Fries and Jacobs 1980).

Concentrations of PBBs in sediments upstream from the Michigan Chemical Corporation plant were below the detection limit (100 μg/kg) with the exception of one sample (Hesse and Powers 1978). The

concentration of PBBs in sediment from one upstream sample was 350 µg/kg. Hesse and Powers (1978) explained that this higher value was due to contamination by upstream currents during periods of water level regulation at the St. Louis dam. The concentrations of PBBs in near shore sediment near the Michigan Chemical Corporation plant sewer outfall were #77.0 mg/kg. PBB concentrations in Pine River sediments downstream from the plant showed a gradual decrease from a maximum value of 9.2 mg/kg to a value of 0.1 mg/kg at a location 29 miles downstream from the plant outfall (Hesse and Powers 1978). Similarly, PBB concentrations in sediment samples from swamps and marshes adjacent to the White Chemical Company and Hexcel Chemical Corporation plants in New Jersey ranged from <10 µg/kg to 4.6 mg/kg (DeCarlo 1979). A sludge sample from the discharge treatment plant of the White Chemical Company contained 431 mg/kg of PBBs (DeCarlo 1979).

Polybrominated Diphenyl Ethers. Sediment concentrations of PBDEs tend to be dominated by higher brominated congeners (e.g., BDE-209) (deWit 2002). Temporal trends suggest that concentrations of PBDEs in sediments are increasing. No information was located on the concentration of PBDEs in soils.

Levels of PBDEs in sediments from the United States were not located. The concentrations of PBDEs in sediment samples from other countries are summarized in Table 6-3. Tetra-, penta-, hexa-, and decaBDEs have been observed in river sediments from Japan (Watanabe et al. 1986, 1987, 1995). The combined concentrations of tetra- and pentaBDEs ranged from 21–59 ng/g dry weight. The concentration of DeBDE ranged from <25 to 11,600 ng/g (dry weight) (deWit 2002). In 1999, sediment samples from several locations in the Netherlands contained BDE-47, -99, and -209 (de Boer et al. 2000). Concentrations ranged from 0.3 to 7.1 ng/g (dry weight) for BDE-47, not detected to 5.5 ng/g (dry weight) for BDE-99, and not detected to 510 ng/g (dry weight) for BDE-209. The concentration of PBDEs in suspended particulate matter ranged from not detected to 9 ng/g (dry weight) for BDE-47, not detected to 23 ng/g (dry weight) for BDE-99, and not detected to 4,600 ng/g (dry weight) for BDE-209 (de Boer et al. 2000). The concentration of several brominated flame retardants was measured in sediments collected from the mouths of major European rivers (de Wit 2002). Elevated levels of BDE-47 and BDE-99 were found in Humber and Mersey rivers (Great Britain). In two rivers of the Netherlands, the sum of BDE-47 and BDE-99 ranged 1.61 to 13.1 ng/g (dry weight). The highest hexaBDE levels (as BDE-153) were found in the river Seine (France), three rivers in the Netherlands, and the rivers Schelde (Belgium), Forth (Great Britain) and Ems (Germany); the concentration of

Table 6-3. Concentrations (in ng/g Ignition Loss) of Several PBDEs in Sediment and Suspended Particulate Samples

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs	BDE-209	Reference
Sediment	Japan	No data	No data	No data	21–59 (dw)	<25–11,600	Watananbe et al. 1986, 1987, 1995
Sediment	Baltic Sea	ND–3.4	ND–2.4	ND–1.3	ND–5.4	ND	Nylund et al. 1992
Sediment	Upstream plastics plant	3.7	8.8	1.6	14.1	No data	Sellström and Jansson 1995
Sediment	Downstream plastics plant	780	1,200	270	2,250	No data	Sellström and Jansson 1995
Sediment	River Viskan, upstream and downstream textile industries	<2–50	<1–53	<0.4–19	ND–120	ND–16,000	Sellström et al. 1998a
Sediment	22 European river mouths	<0.17–6.2 (dw)	<0.19–7.0 (dw)	No data	No data	<0.51–1,800	de Wit 2002
Sediment	Seven rivers, Great Britain	<0.3–368 (dw)	<0.6–898 (dw)	No data	No data	<0.6–3,190	Allchin et al. 1999
Sediment	Netherlands, several sites	0.3–7.1 (dw)	<0.2–9 (dw)	No data	No data	<4–510 (dw)	de Boer et al. 2000b
Suspended particulates	Netherlands, several sites	<2–9 (dw)	<0.1–23 (dw)	No data	No data	<9–4,600 (dw)	de Boer et al. 2000b

Source: de Wit (2002)

dw = dry weight; ND = not detected

BDE-153 ranged from 0.013 to 0.056 ng/g (dry weight) in these sediments. The concentrations of DeBDE were highest in sediment from the Seine, ranging from 2.4 to 3.9 ng/g (dry weight). The concentrations of DeBDE in River Mersey (Great Britain), Schelde and River Liffey (Ireland) ranged from 34 to 1,800 ng/g (dry weight). In the southern Baltic Sea (Bornholm Deep), the upper layer of sediment was analyzed for BDE-47, -99, and -100; the combined concentration of these three congeners was 0.52 ng/g (dry weight) (Nylund et al. 1992).

A well-studied sediment core collected from the southern part of the Baltic Sea proper was analyzed for PBDEs and a number of organochlorine contaminants (Nylund et al. 1992). The analysis revealed a retrospective temporal trend from 1939 to 1987 and showed that the PBDE levels (i.e., sum of BDE-47, -99, and -100) have increased, with a sharp increase after 1980. The PBDE level in the sample from 1989 was 2.9 ng/g (Nylund et al. 1992). Measurable amounts of BDE-28, -47, -66, -99, and -100 were found in sediment cores from a freshwater lake in Germany, the Wadden Sea (the Netherlands), and Drammenfjord (Oslo Fjord, Norway) (Zegers et al. 2000). Samples from the Drammenfjord and freshwater lake also contained BDE-153 and BDE-154, and the Wadden Sea and freshwater lake samples contained BDE-209. The lower brominated PBDEs appear in the 1960s, and BDE-209 appears about 10 years later. The Drammenfjord sediment core shows increasing levels of BDE-47 starting in the 1940s (range, 0.02–0.18 ng/g dry weight) and increasing levels of BDE-99 (range, 0.5–0.28 ng/g dry weight), BDE-100 (range, not detected–0.07 ng/g dry weight), and BDE-154 (range, not detected–0.06 ng/g dry weight) beginning in the 1950s up to 1999. In the sediment core from Lake Woserin, lower brominated BDE congeners are detected beginning in the late 1950s, increase until the late 1970s, and then level off when BDE-209 first appears. A similar leveling-off trend is also observed in the Wadden Sea core (Zegers et al. 2000).

6.4.4 Other Environmental Media

Polybrominated Biphenyls. Although the agriculture episode in Michigan involving contaminated feed occurred in May 1973, PBBs were not identified as the causative factor until April 1974 (Fries 1985b). PBB-containing meats, milk, butter, eggs, and cheese entered the human food chain for almost a year before the PBBs were identified. Concentrations of PBBs (on a fat basis) in milk samples collected from contaminated farms soon after PBB was identified ranged from 2.8 to 595 mg/kg (Cordle et al. 1978; Kay 1977). Concentrations of PBBs in other products processed from the contaminated milk were as follows: butter, 1–2 mg/kg; cheese, 1.4–15.0 mg/kg; and canned milk, 1.2–1.6 mg/kg (Cordle et al. 1978). In 1974, the levels of PBBs in eggs from contaminated farm premises were as high as 59.7 mg/kg (Kay

1977). The levels of PBBs in poultry and cattle tissues from the contaminated farm collected in 1974 were 4,600 mg/kg and up to 2,700 mg/kg, respectively (Kay 1977). With the seizure and destruction of the contaminated farm animals and products, the levels of PBBs in consumer products showed a steady decline. For example, in 1975, among 18 milk samples, 13 cheese samples, and 14 butter samples taken in Michigan, only 3 butter samples exceeded the FDA guidelines of 0.3 mg/kg fat (Di Carlo et al. 1978). In 1975, PBBs were detected in 245/2,040 meat samples collected in Michigan, with only 24 samples containing levels >0.3 mg/kg fat (Di Carlo et al. 1978). Although 95% of 1,430 meat samples collected in Michigan in 1976 contained detectable PBBs, only 1 sample contained >0.6 mg/kg, and a market basket survey in Michigan showed detectable PBBs in only 1/102 meat samples (Di Carlo et al. 1978).

No PBBs were detected in several varieties of fish (carp, white sucker, Northern pike, bullhead, and bass) from the Alma Reservoir, which is upstream from the Michigan Chemical Corporation plant and above a dam that prevents fish from moving upstream (Hesse and Powers 1978). On the other hand, tissue samples from fish collected from the Pine River, #29 miles downstream from the plant, contained up to 1.33 mg PBBs/kg (wet weight in skinless fillets). There was no apparent change in PBB concentrations in fish between 1974 and 1976 (Hesse and Powers 1978). PBBs could be detected in fish from Pine River and other embayments and tributaries of Lake Huron in 1983. PBB concentrations in carp and other sedentary fish from embayments and tributaries of Lake Huron (including Pine River) and Lake Superior were determined (Great Lakes Water Quality Board 1989; Jaffe et al. 1985). PBBs were detected in the concentration range of 15–15,000 μg/kg (fat basis) in fish from embayments and tributaries of Lake Huron, but not from Lake Superior.

PBB concentrations in whole (with skin) and skinless ducks collected within 2 miles of the Michigan Chemical Corporation plant in 1974–1977 ranged from not detected to 2.70 mg/kg and not detected to 1.8 mg/kg, respectively (Hesse and Powers 1978). Three bottlenose dolphins (*Tursiops truncatus*) collected during 1987–1988 from the U.S. mid-Atlantic contained PBBs at concentrations of 14–20 μg/kg (lipid basis) (Kuehl et al. 1991). The source of the PBBs in the dolphins was not given. The median concentrations of PBBs in 10 specimens of carcass and brain of bald eagles collected from 29 states in 1977 were 0.07 and 0.05 mg/kg, respectively (Kaiser et al. 1980). Twenty-two other specimens did not contain detectable levels (<0.03 mg/kg) of PBBs. The concentrations of PBBs in eggs of fish-eating birds (common tern, little gull, herring gull, and red-breasted mergansers) collected during 1975–1980 from nesting islands in northwestern Lake Michigan and Green Bay contained PBBs in the concentration range of 0.02–0.25 mg/kg (wet weight) (Heinz et al. 1983, 1985).

White-tailed sea eagles collected from the Baltic Sea contained 280 ng PBBs/g lipid weight (Jansson et al. 1987). The concentration of PBBs in common guillemots (*Uria aalge*) collected in 1979–1981 from the Baltic Sea was 160 ng/g lipid (Jansson et al. 1987). Brunnich's guillemot (*Uria lomvia*), collected from Svalbard in the Arctic, contained 50 ng PBBs/g lipid (Jansson et al. 1987).

In German rivers, elevated levels of nona and octaBBs were present in fish. HexaBB was predominant in fish from the North Sea and Baltic Sea. BB-169 was found at a maximum concentration of 36 mg/kg fat in samples from the Baltic Sea. However, BB-169 was not found in waters from the North Sea or rivers. In Baltic marine fish, the concentrations of BB-153 ranged from 0.2–4.2 mg/kg lipid (de Boer et al 2000a).

In 1981, female ringed seals from Svalbard in the Swedish Arctic contained 4 ng PBBs/g lipid (Jansson et al. 1987). The level of PBBs in Baltic Sea harbor seal (*Phoca vitulina*) was 20 ng/g lipid; North Sea harbor seal contained 3 ng PBBs/g lipid (Jansson et al. 1987). The concentration of hexaBB ranged from 13–61 μg/kg wet weight from harbor seals collected from the North Sea (decaBB <1 μg/kg wet weight). In whitebeaked dolphins from the North Sea, the concentration of hexa-, penta-, and deca-BBs were 13, 8.3, and <0.9 μg/kg wet weight, respectively. Tetra-, penta-, and deca-BBs concentration ranges were 1.1–1.9, 0.4–0.9, and <0.5 μg/kg wet weight, respectively, in sperm whales from the Atlantic Ocean (de Boer et al 1999).

The quantitative determination of the concentrations of PBBs in blood, serum, adipose tissue, milk, and other body tissues or fluids is important in determining the human body burden of these chemicals. Fat is the largest repository of PBBs in the body, and concentrations in fat can provide an index of body burdens and exposure. It is simpler and less invasive to collect samples of serum or breast milk than body fat. However, the collection of milk and serum for the estimation of possible body burden has limitations. Breast milk can be obtained from limited segments of the population. Also the concentration of PBBs in breast milk can show considerable fluctuations because the breast is emptied only periodically (Brilliant et al. 1978; Willett et al. 1988). Serum, however, has lower PBB concentrations than body fat (see Section 3.5.1).

Hexabromobiphenyl was detected (detection limit 6.6 μg/kg) at a frequency of 8–57% in human adipose tissue samples from six Canadian Great Lakes municipalities in 1984 (Williams et al. 1988). The concentration of 2,2',4,4',5,5'-hexabromobiphenyl in adipose tissue samples pooled from tissues of the general population of the conterminous Unites States ranged from 1 to 2 μg/kg (Lewis and Sovocool 1982). PBB levels in the adipose tissues of 15 quarantined dairy farm residents in mid-Michigan (where

the mix-up involving FireMaster BP-6 occurred) ranged from 0.104 to 174 mg/kg (Humphrey and Hayner 1975).

In the fall of 1993, the serum levels of BB-167 (2,2',4,4',5,5'-hexaBB) in 32 subjects, approximately 10 of whom consumed sport fish from the Great Lakes, were measured (Anderson et al. 1998). When the data were stratified by lake, on average, the Lake Huron fish consumers had the highest levels of PBBs (0.6 ppb) and Lake Erie fish consumers had the lowest (0.2 ppb). When the data were then stratified by state of residence, on average, Great Lake sport fish consumers who live in Michigan had the highest PBB level (0.7 ppb) and residents of Wisconsin had the lowest level (0.05 ppb).

In Michigan after the agriculture contamination episode in 1973–1974, the median PBB concentrations in blood of exposed adults and children in farms were 0.014 and 0.035 mg/kg (14 and 35 ppb), respectively, compared to corresponding median concentrations of 0.003 and 0.006 mg/kg (3 and 6 ppb) in a control group (Humphrey and Hayner 1975). PBB levels in the blood of quarantined farm workers in Michigan were also higher than in nonquarantined farm residents and the general population of Michigan (Cordle et al. 1978; Kimbrough 1987; Lambert et al. 1990; Landrigan et al. 1979). The concentration ratio of PBBs in adipose tissue over blood plasma for 13 paired specimens was 175 to 1 (Humphrey and Hayner 1975).

A cross-section of the population of Michigan was studied in 1978, 5 years following the agriculture episode involving FireMaster BP-6, to determine the levels of PBBs in human tissues. Levels of PBBs were highest in the part of state in which the episode occurred (median: adipose tissue, 500 μg/kg; serum, 1.7 μg/L) and were lowest in the upper peninsula (median: adipose tissue, 15 μg/kg; serum, 0.2 μg/L), farthest from the source of contamination. Levels in the rest of the state were in between (median: adipose tissue, 240 μg/kg; serum, 0.9 μg/L) (Wolff et al. 1982). The estimated concentration ratio of PBBs in adipose tissue over serum was near 300 among 31 Michigan dairy farm residents (Wolff et al. 1979a). The ratio of adipose tissue to serum PBB concentration was 363 to 1 for the general population and 100 to 1 in lactating women (Brilliant et al. 1978). The kinetics of fat metabolism in lactating women seems to alter PBB partitioning. The ratios of adipose tissue to serum PBB concentration for nonpregnant females and male chemical workers, farm workers and other males, and pregnant females in 3,683 Michigan residents with varying degrees of exposure were 190–260 to 1, 325–329 to 1, and 107–119 to 1, respectively (Eyster et al. 1983). The PBB ratios for cord to serum and placenta to serum in pregnant females were 0.10–0.14 to 1 and 0.10–0.17 to 1, respectively (Eyster et al. 1983). The PBB ratios for feces to serum and bile to serum in farm and chemical workers were 0.53–0.71 to 1 and 0.45–0.63 to 1, respectively (Eyster et al. 1983). The detection of PBBs in bile and feces indicates

transfer into the intestinal tract. However, the concentration of PBBs in feces represented a minor proportion of the total body burden, indicating a slow rate of excretion (Eyster et al. 1983).

The concentrations of PBBs in the breast milk of females from the lower peninsula of Michigan (exposed area) were generally higher than in breast milk of females from the upper peninsula (farthest from the sources) (Brilliant et al. 1978). PBB levels in breast milk of five females from the exposed farms were 0.21–92.7 mg/kg (Cordle et al. 1978; Humphrey and Hayner 1976). In a cohort of Michigan residents, the ratio of PBBs in breast milk to maternal serum was 107–122 to 1 and in adipose tissue to breast milk was 1.1–1.5 to 1 (Eyster et al. 1983; Landrigan et al. 1979). The concentrations of PBBs found in human tissues and body fluids are given in Table 6-4. Recent levels of PBBs in human breast milk (i.e., 1990 to present) were not located (WHO 1994b).

In an attempt to determine the metabolites of PBBs, whole milk of lactating cows from contaminated areas of Michigan was analyzed for monohydroxy metabolites, but none were found (Gardner et al. 1976). In a later study, the feces of dogs fed FireMaster BP-6 in corn oil was found to contain a metabolite identified as 6-hydroxy-2,2',4,4',5,5'-hexabromobiphenyl (Gardner et al. 1979). However, the hydroxy compound decomposed into two pentabromodibenzofurans inside a gas chromatographic column heated to 230–260 EC.

The effects of processing cow's milk containing PBBs also has been studied (Murata et al. 1977; Zabik et al. 1978). Spray-drying reduced PBB levels in whole and skim milk, whereas pasteurization, freeze-drying, aging of cheese, and condensation were not effective in reducing the level of PBBs in milk products. Pressure cooking meat containing PBBs reduced the level of PBBs in the cooked meat (Zabik et al. 1978).

Table 6-4. Tissue Levels of PBBs in Michigan Residents

Tissue	Subject(s)	Mean/median concentration[a]	Year	Reference
Serum	Exposed farm workers	14 μg/L	1976	Stross et al. 1979
	Chemical workers	48 μg/L	No data	Stross et al. 1981
	Chemical workers	1.1–$1,000 μg/L	1976	Anderson et al. 1978d
	Exposed farm workers	BDL to $1,000 μg/L	1976	Anderson et al. 1978d
	Residents from quarantined farms	26.9 μg/L	1976–1977	Landrigan et al. 1979
	Residents from nonquarantined farms	3.5 μg/L	1976–1977	Landrigan et al. 1979
	Farm product consumers	17.1 μg/L	1976–1977	Landrigan et al. 1979
	Chemical workers and families	43.0 μg/L	1976–1977	Landrigan et al. 1979
	Control group	3.5 μg/L	1976–1977	Landrigan et al. 1979
	General population (lower peninsula)	1.9 μg/L	1978	Wolff et al. 1982
	General population (upper peninsula)	0.2 μg/L	1978	Wolff et al. 1982
	General population (remainder of state)	0.9 μg/L	1978	Wolff et al. 1982
	Chemical workers	25.4 μg/L	No data	Eyster et al. 1983
	Farm and other workers	5.4 μg/L	No data	Eyster et al. 1983
	Mothers in lower peninsula	26.2 μg/L	1976–1977	Landrigan et al. 1979
	Exposed mothers from farms	3.4 μg/L	No data	Eyster et al. 1983
	Nonpregnant women from exposed farms	3.1 μg/L	No data	Eyster et al. 1983
Cord serum	Exposed mothers in lower peninsula	3.2 μg/L	1976–1977	Landrigan et al. 1979
	Mothers in lower peninsula	<1.0 μg/L	No data	Eyster et al. 1983
Blood plasma	Workers from quarantined farms	14 μg/L	1974	Humphrey and Hayner 1975
	Children from quarantined farms	35 μg/L	1974	Humphrey and Hayner 1975
	Adults from nonquarantined farms	3 μg/L	1974	Humphrey and Hayner 1975
	Children from nonquarantined farms	6 μg/L	1974	Humphrey and Hayner 1975
Placenta	Exposed mothers	<1 μg/L	No data	Eyster et al. 1983

Table 6-4. Tissue Levels of PBBs in Michigan Residents *(continued)*

Tissue	Subject(s)	Mean/median concentration[a]	Year	Reference
Breast milk	Exposed mothers	370 μg/kg (fat basis)	No data	Eyster et al. 1983
	Exposed mothers in lower peninsula	3,614 μg/kg (fat basis)	1976–1977	Landrigan et al. 1979
	Mothers from lower peninsula	68 μg/kg (fat basis)	1976	Brilliant et al. 1978
	Mothers from upper peninsula	<44 μg/kg (fat basis)	1976	Brilliant et al. 1978
Adipose tissue	Population of lower peninsula	500 μg/kg	1978	Wolff et al. 1982
	Population of upper peninsula	15 μg/kg	1978	Wolff et al. 1982
	Population of rest of the state	240 μg/kg	1978	Wolff et al. 1982
	Chemical workers	9,330 μg/kg	No data	Brown et al. 1981
	Farm residents in lower peninsula	3,940 μg/kg	No data	Brown et al. 1981
	Farm residents in lower peninsula	3,260 μg/kg	1976	Stross et al. 1979
	Chemical workers	12,820 μg/kg	No data	Stross et al. 1981
	Workers from quarantined dairy farms	12,500 μg/kg	1974	Humphrey and Hayner 1975
	Pregnant females from lower peninsula	400 μg/kg	No data	Eyster et al. 1983
	Chemical workers	5,290 μg/kg	No data	Eyster et al. 1983
	Farm and other workers in lower peninsula	1,650 μg/kg	No data	Eyster et al. 1983

[a]When both mean and median values are available, the former values have been used in the table. In some cases, when neither value is available, the range is given in the table.

BDL = below detection limit

Polybrominated Diphenyl Ethers. Information about the concentrations of PBDEs in food stuffs is very limited. Recently, Ohta et al. (2002) determined the concentration of total PBDEs in vegetables and meat samples from Japan. The concentrations of PBDEs in spinach, potato, and carrot were 134, 47.6, and 38.4 pg/g fresh weight, respectively. The highest concentrations of total PBDEs and BDE-47 were found in spinach. Interestingly, different congener patterns were found among the vegetables analyzed. Compared to root vegetables, which had high concentrations of BDE-153, spinach (representing a leafy vegetable) might be strongly influenced by PBDE contamination in air. The concentration of PBDEs in pork, beef, and chicken were 63.6, 16.2, and 6.25 pg/g fresh weight, respectively. PBDE concentrations were highest in pork samples; however, the reason for this is unknown (Ohta et al. 2002). Four types of commercial fish oils sold in Sweden were found to contain PBDEs (0.2-28.1 ng/g lipid weight) (Haglund et al. 1997). The highest concentration of PBDEs was found in the cod liver oil. These oils were from products marketed as dietary supplements for humans.

The concentrations of PBDEs in biosolids (sewage sludge) and effluent samples are summarized in Table 6-5. PBDEs were detected in biosolids from four different regions of the United States (Pardini et al. 2001). The total concentrations of PeBDE in biosolids ranged from 1,100 to 2,290 µg/kg dry weight; the levels of PeBDE were high and consistent, regardless of the region of origin. The concentration of DeBDE (BDE-209) varied widely among biosolids from different regions; the concentration of BDE-209 ranged from 84.8 to 4,890 µg/kg dry weight in the biosolid samples. Sewage sludge samples from 13 waste water treatment plants in Germany were sampled (Hagenmaier et al. 1992). The mean concentration of tri- to hepta-BDEs was 8.37 ng/g with tri-, tetra-, penta-, hexa-, and heptaBDE at concentrations of 0.65, 3.06, 3.02, 0.49, and 0.22 ng/g, respectively. Levels of penta- and hexaBDEs were highest in these samples.

Monitoring data indicated that the levels of PBDEs are increasing in freshwater aquatic organisms with higher concentrations near point sources. The congener profiles show the highest levels for BDE-47. The presence of PBDEs in freshwater aquatic organisms taken from remote regions suggests that diffuse sources of PBDEs are also important. The concentrations of PBDEs in freshwater fish samples are summarized in Table 6-6. Fish were sampled from two U.S. lakes, Hadley Lake, Indiana near a possible PBDE point source, and Lake of the Ozarks, Missouri, with no known sources (Dodder et al. 2000a). Mean total PBDE concentrations (sum of BDE-47, -99, -100, -153, and -154) were higher in crappie (*Poxomis annularis*) and bluegill (*Lepomis macrochiras*) from Hadley Lake (1,500 and 1,900 ng/g lipid weight, respectively) than from Lake of the Ozarks (340 and 390 ng/g lipid, respectively). BDE-47, -99,

Table 6-5. Concentrations (in ng/g Dry Weight) of Several PBDEs in Biosolids (Sewage Sludge) and Effluent Samples

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Sewage sludge	Gothenburg	15	19	3.5	38	No data	Nylund et al. 1992
Sewage sludge	Klippan	22	18	5.4	45.4	No data	Sellström 1999; Sellström and Jansson 1995
Sewage Sludge	Rimbo	53	53	13	119	No data	Sellström 1999; Sellström and Jansson 1995
Sewage sludge	Three plants, Stockholm	39–91	48–120	11–28	98–239	140–350	Sellström et al. 1999
Sewage sludge	Germany	No data	No data	No data	04–15*	No data	Hagenmaier et al 1992
Sewage treatment plant effluent residues	Netherlands, several sites	11–35	<1	No data	11–35	310–920	de Boer et al. 2000b

[a]3PBDEs is the sum of BDE-47, BDE-99, and BDE-100, but if more congeners are included, this is marked with an asterisk (*).

Source: de Wit (2002)

Table 6-6. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Freshwater Fish Samples

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Whitefish	Lake Storvindeln	15	7.2	3.9	26	No data	Sellström et al. 1993
Arctic char	Lake Vättern	400	64	51	520	No data	Sellström et al. 1993
Pike	Lake Bolmen, 1993	65	42	19	130	No data	Kierkegaard et al. 1993
Pike	Dalslands canal	94–98	60–79	25–36	180–210	No data	Sellström et al. 1993
Pike	River Viskan, upstream and downstream	<46–2,000	<37–1,600	<14–1,000	<130–4,600	Trace	Sellström et al 1998a
Trout	Dalslands canal	120–460	130–590	33–150	280–1,200	No data	Sellström et al. 1993
Carp	United States	No data	No data	No data	13–22* (fw)	No data	Loganathan et al. 1995
Steelhead trout	Lake Michigan, United States	1,700	600	360	3,000*	No data	Asplund et al. 1999b
Lake trout	Lake Ontario, United States	No data	No data	No data	540*	No data	Alaee et al. 1999
Lake trout	Lake Huron, United States	No data	No data	No data	240*	No data	Alaee et al. 1999
Lake trout	Lake Superior, United States	No data	No data	No data	140*	No data	Alaee et al. 1999

Table 6-6. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Freshwater Fish Samples *(continued)*

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Lake trout	Lake Erie, United States	No data	No data	No data	117*	No data	Alaee et al. 1999
Crappie	Hadley Lake, Indiana	250	430	150	1,500*	No data	Dodder et al. 2000
Bluegill	Hadley Lake, Indiana	420	320	240	1,900	No data	Dodder et al. 2000
Crappie	Lake of the Ozarks, Missouri	190	78	59	340*	No data	Dodder et al. 2000
Bluegill	Lake of the Ozarks, Missouri	200	91	59	390	No data	Dodder et al. 2000
Eels	Netherlands	<20–1,400	No data	No data	<50–1,700	No data	de Boer 1990
Bream	Netherlands (several sites)	0.2–130 (dw)	Not detected	No data	No data	No data	de Boer et al. 2000b
Several fish species	Germany	No data	No data	No data	19–983*	No data	Krüger 1988
Osprey	Sweden	1,800	140	200	2,140	No data	Sellström et al. 1993

[a]3PBDEs is the sum of BDE-47, BDE-99, and BDE-100, but if more congeners are included, this is marked with an asterisk (*).

Source: de Wit (2002)

dw = dry weight; fw = fresh weight

-153, and -154 were primary congeners. From the Lake of Ozarks, BDE-47 was the dominant congener in fish. The total PBDE concentrations in smelt (*Osmerus mordax*) from Lakes Superior and Ontario were 150±9 and 240±30 ng/g lipid, respectively (Dodder et al. 2002). The dominate congeners in these fish were BDE-47 and -99. An analysis of fish tissue samples from selected locations in Washington State showed that total PBDE concentrations ranged 29 ng/g lipid in rainbow trout from a remote spring-fed stream (Douglas Creek, Washington) to 19,000 ng/g lipid in rainbow trout from the urbanized Spokane River, Washington (Johnson and Olson 2001). The tetra- and pentaBDE isomers were the major compounds present. TeBDE to hexaBDE were found in carp (*Cyprinus carpio*) from the Buffalo River (New York), a polluted area around the Great Lakes (Loganathan et al. 1995). TeBDEs dominated the congener pattern with 94–96% of total PBDEs. TeBDE and PeBDE concentrations ranged from 13 to 22 ng/g fresh weight. Asplund et al. (1999a) found tri- to hexaBDEs in steelhead trout (*Oncorhynchus mykiss*) sampled in 1995 from Lake Michigan. The combined concentration of BDE-47, -99, -100, -153, and -154 was 3,000 ng/g lipid weight (Asplund et al. 1999b). Lake trout (*Salvelinus manaycush*) from Lakes Ontario, Huron, and Superior were also found to have di- to heptaBDEs with combined concentrations of 545, 237, and 135 ng/g lipid weight, respectively (Alaee et al. 1999). Lake trout from Lake Erie had 117 ng/g lipid weight (Luross et al. 2000). Variations in local sources, combined with atmospheric transport, may explain differences that were seen in congener profiles for the different lakes. A retrospective temporal study for the years 1978, 1983, 1988, 1993, and 1998 using archived trout samples from Lake Ontario show a dramatic increase in total PBDE concentrations over time (Luross et al. 2000). At 50 fresh water sites in Virginia, muscle samples from 253 fish samples were collected and analyzed for PBDEs (Hale et al. 2000, 2001). Approximately 85% of the samples contained BDE-47, the predominant congener, at measurable concentrations. Concentrations were >1,000 ng/g lipid weight at 9 of 50 sites. The highest combined PBDE concentrations (up to 57,000 ng/g lipid weight) were observed in carp downstream of textile and furniture facilities. BDE-47 levels were greater than PCB-153 concentrations in 58% of the samples analyzed.

Between 1986 and 1988, levels of BDE-47, -99, and -100 were measured in whitefish (*Coregonus spp*.) from a remote mountain lake in Northern Sweden (Lake Storvindeln), Arctic char (*Salvelinus alpinus*) from a heavily populated lake (Lake Vättern) in south-central Sweden with numerous municipal and industrial point sources, and in trout (*Salmo trutta*) and pike (*Esox lucius*) from several sites along Dalslands Canal in west central Sweden (Jansson et al. 1993). No point sources of PBDEs were identified from these sites. Whitefish from the remote lake contained the lowest levels (26 ng/g lipid weight) of PBDEs, whereas the Arctic char, from a heavily populated lake, contained 520 ng/g lipid weight PBDEs. In both samples, BDE-47 was the predominant congener. PBDE concentration levels in pike and trout from the Dalslands Canal ranged from 180 to 210 ng/g lipid weight and from 280 to

1,200 ng/g lipid weight, respectively. The congener pattern in these samples was similar to the technical mixture, Bromkal 70-5DE, with equal quantities of both BDE-47 and BDE-99. The levels in pike and trout are of the same order of magnitude as in the Arctic char, indicating the spread of PBDEs from diffuse sources (de Wit 2002). In 1979 and 1980, high levels of tri- to hexaBDEs (range, 950–27,000 ng/g lipid weight in muscle tissues) were measured in fish sampled along a river in Sweden (Viskan) where numerous textile industries are located (Andersson and Blomkvist 1981). These textile industries have used PBDEs in the production of textiles. BDE-47 was the predominant congener at 70–80% of the total PBDEs. In 1977, the PBDEs were not detected in fish sampled at the same sites. The elevated levels of BDE-47, -99, and -100 were later confirmed in a follow-up study where fish were caught from approximately the same locations (Sellström et al. 1993). In the current study, BDE-47 was the predominant congener at 65–96% of total PBDEs. Several fish species were sampled (pike, perch, bream, eel, tench, and sea trout) in these studies. In 1995, fresh samples of pike and sediments were collected at four of eight sites along River Viskan in order to search for point sources of contaminants. The combined concentrations of BDE-47, -99, and -100 ranged from not detected to 4,600 ng/g lipid weight, with BDE-47 being the predominant congener (50–90% of total). BDE-209 was found in a few fish at trace amounts. The lowest levels of the PBDEs were found upstream of the industries. The concentrations of PBDEs increased further downstream as more industries were passed (Sellström et al. 1998). Levels of BDE-47 ranged from <20 to 1,700 ng/g lipid in eels (*Anguilla anguilla*) from Dutch rivers and lakes (at 10 locations); BDE-47 comprised 70% of the total PBDEs (de Boer 1990). Bream (*Abramais brama*) sampled from several sites in the Netherlands had concentrations of BDE-47 ranging from 0.2 to 130 ng/g dry weight (de Boer et al. 2000). BDE-99 was below the detection limits. BDE-153 ranged from <0.04 to 4.1 ng/g dry weight. Allchin et al. (1999) conducted a study of PBDEs in plaice (*Pleuronectes platessa*), flounder (*Platichys flesus*), and dab (*Limanada limanada*) collected in the estuaries of rivers in the United Kingdom. Suspected sources of PBDEs in the estuaries include a manufacturer of PeBDE and OBDE, several industries using PeBDE, and several landfills receiving wastes suspected to contain PBDEs. Levels of BDE-47, BDE-99, PeBDE (as technical mixture DE-71), and OBDE (as technical mixture DE-79) in fish ranged from not detected to 9,500 ng/g lipid weight, not detected to 370 ng/g lipid weight, 47 to 1,200 ng/g lipid weight, and not detected to 1,200 ng/g lipid weight. The highest levels were at Tees Bay downstream from a manufacturing plant on the River Tees. These results are similar to the situation found in Sweden along the River Viskan (Andersson and Blomkvist 1981; Sellström et al. 1993).

Freshwater mussels (*Dreissena polymorpha*) were collected at several locations in the Netherlands and analyzed for BDE-47, -99, -153, and -209 (de Boer et al. 2000). Concentration ranges for the congeners

were 0.7–17, 0.4–11, and <0.1–1.5 ng/g dry weight for BDE-47, -99, and -153, respectively. BDE-209 was below the detection limit.

No identifiable temporal or spacial trends were found for PDBE levels in marine aquatic species. The congener profiles show the highest levels for BDE-47. The levels of several PBDEs in marine aquatic species are summarized in Table 6-7. Fall-caught herring (*Clupea harengus*) muscle from five sites along the Swedish coast was analyzed from BDE-47, -99, and -100; the combined concentration of these three congeners ranged from 17 to 61 ng/g lipid, with BDE-47 being the dominate congener (Sellström et al. 1993). Likewise, the concentration of BDE-47 in Baltic herring ranged from 3.2 to 27 ng/g lipid in different age groups; the combined concentration of BDE-47, -99, and -100 ranged from 3.2 to 32 ng/g lipid (Haglund et al. 1997); 2-year-old herring had the lowest levels and 5-year-old herring had the highest levels. Similarly, Strandman et al. (1999) observed increasing concentrations with age of BDE-47, -99, and -153 in Baltic sprat (*Sprattus sprattus*, age 3–13 years). However, this trend was not seen for herring. BDE-47 was the primary congener with levels ranging from 7.6 to 24 ng/g lipid weight for 1- to 3-year-old sprat, 17–140 ng/g lipid weight for 3- to 13-year-old sprat, and 7.6–24 ng/g lipid weight in herring. The concentrations of BDE-47, -99, and -100 in whole-body composites of herring were 6.21, 0.62, and 0.81 ng/g lipid, respectively; in sprat, the concentrations were 4.32, 0.71, and 0.80 ng/g lipid, respectively (Burreau et al. 1999). Baltic sea herring had similar levels of BDE-47 (46.3 ng/g lipid) compared to 8.4–100 ng/g lipid of BDE-47 found by de Boer (1990) for herring collected from three regions of the North Sea. BDE-47, -99, and -153 concentrations in Baltic salmon (*Salmo salar*) muscle were 167, 52, and 4.2 ng/g lipid, respectively (Haglund et al. 1997). BDE-47, -99, and -100 levels were 47, 7.2, and 6.3 ng/g lipid, respectively, in whole-body composites (Burreau et al. 1999). In another study, the levels of BDE-47, -99, and -100 were determined in muscle, ripe eggs, and blood plasma from Baltic salmon (Asplund et al. 1999a). The mean concentrations of PBDEs in tissues from Baltic salmon (ng/g lipid weight) were as follows: BDE-47 (muscle, 190; ripe eggs, 64; blood, 190), BDE-99 (muscle, 52; ripe eggs, 16; blood, 55), and BDE-100 (muscle, 46; ripe eggs, 18; blood, 59). Cod (*Gadus morhua*) liver samples at three locations of the North Sea had combined levels of BDE-47 and BDE-99 of 1.9–360 ng/g lipid (de Boer 1989). From several sites in the Netherlands, BDE concentrations in flounder were 0.6–20 ng/g dry weight for BDE-47 and <0.01–4.6 ng/g dry weight for BDE-99 (de Boer et al. 2000); concentrations of BDE-153 and BDE-209 were below the detection limit. In 1996, de Boer et al. (2001) measured the levels of two BDE congeners in flounder liver samples from

Table 6-7. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Marine Aquatic Species

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Herring	Baltic Sea	19–38	7.8–17	3.4–6	30–61	No data	de Wit 2002 Sellström et al. 1993
Herring	Baltic Sea	3.2–27	ND–2.9	1.3–1.9	3.2–32	No data	Haglund et al. 1997
Herring	Baltic Sea	7.6–24	4.3–3.9	No data	12.9–28.3*	No data	Strandman et al. 1999
Herring	Baltic Sea	6.3	0.6	0.8	12*	No data	Burreau et al. 1999
Herring	Kattegatt	12	3.4	1.6	17	No data	de Wit 2002; Sellström et al. 1993
Herring	North Sea	8.4–100	No data	No data	No data	No data	de Boer 1990
Sprat (different age groups)	Baltic Sea	17.5–140.8	1.9–9.5	No data	21–149*	No data	Strandman et al. 1999
Sprat	Baltic Sea	4.3	0.7	0.8	8.4*	No data	Burreau et al. 1999
Cod liver	North Sea	170	No data	No data	1.9–360	No data	de Boer 1989
Salmon	Baltic Sea	167	52	44	220	No data	Haglund et al. 1997
Salmon	Baltic Sea	190	52	46	290	No data	Asplund et al. 1999b
Salmon	Baltic Sea	46	7.3	6.4	86*	No data	Burreau et al. 1999
Several fish species	Japan	No data	No data	No data	0.1–17*	No data	Watanabe et al. 1987
Yellowfin tuna	Japan	0.5	0.4	0.25	1.9*	No data	Ohta et al. 2000
Yellowtail	Japan	17	4.5	4.0	30.5*	No data	Ohta et al .2000

Table 6-7. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Marine Aquatic Species *(continued)*

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Yellowtail (cultured)	Japan	29	3.3	5.3	44*	No data	Ohta et al. 2000
Salmon	Japan	22	8.1	5.3	46*	No data	Ohta et al. 2000
Several flatfish	Seven river estuaries, Great Britain	73–9,500	16–790	No data	No data	ND	Allchin et al. 1999
Flounder	Netherlands, several sites	0.6–20 (dw)	<0.01–4.6	No data	No data	No data	de Boer et al. 2000b

[a]3PBDEs is the sum of BDE-47, BDE-99, and BDE-100, but if more congeners are included, this is marked with an asterisk (*).

Source: de Wit (2002)

dw = dry weight; ND = not detected

the Amsterdam and Rotterdam harbors, and off the Dutch coast; BDE-47 and -99 ranged from 15 to 280 and <2 to 24 ng/g lipid weight, respectively. Olsson et al. (1999) detected BDE-47 in perch (*Perca fluviatilis*) from Latvia in a study examining environmental contamination in coastal areas of the former Soviet Union; the concentration of BDE-47 ranged from 6.4 to 10 ng/g lipid weight in the perch.

Watanabe et al. (1987) detected PBDEs in numerous marine fish and shell fish in Japan. TeBDE and PeBDE levels ranged from 0.1 and 17 ng/g fresh weight, with TeBDE being the major congener. DeBDE was also detected in a mussel sample from Osaka Bay (at 1.4 μg/kg wet weight). Recently, Japanese market fish were analyzed for PBDEs. The highest combined PBDE levels (BDE-28, -47, -99, -100, -153, and -154) were in salmon, cultured yellowtail, and wild yellowtail muscle (46, 44, and 30.5 ng/g lipid weight, respectively) and lowest levels in yellowfin tuna (1.9 ng/g lipid weight) (Ohta et al. 2000). BDE-47 was major congener in all samples. In another study, several fish species from Japan were analyzed for 15 BDE congeners (Hori et al. 2000). The PBDE levels ranged from 0.00136 to 2.1 ng/g fresh weight, with BDE-47 as the predominant congener. Seven species of marine fish (conger eel, flounder, gray mullet, horse mackerel, red sea bream, sea bass, and yellowtail) were collected from the Inland Seas of Seto, Japan (Akutsu et al. 2001). Seven PBDEs (BDE-28, -47, -66, -99, -100, -153, and -154) were detected in all samples with BDE-47 being the most abundant congener. Levels of total PBDEs in gray mullets and yellowtails were 63 and 15 ng/g lipid weight, respectively.

Marine mussels (*Mytilus edulis*) collected at several locations in the Netherlands and analyzed for BDE-47, -99, -153, and -209 (de Boer et al. 2000). Concentrations of BDE-47 and -99 ranged from 0.9 to 4.3 ng/g dry weight and from 0.3 to 1.6 ng/g dry weight, respectively. BDE-153 and BDE-209 were not detected. Di- to heptaBDE were analyzed for in hepatopancreas samples from Dungenes crab from several sites on the Strait of Georgia, British Columbia, Canada (Ikonomou et al. 1999). The primary congener detected was BDE-47. The combined concentration of BDE-47 and BDE-99 was approximately 100–350 ng/g lipid weight.

In marine animals, temporal trends show increasing levels of PBDEs with higher levels found near human populated areas. In all marine animal studies, the congeners profile show the highest levels for BDE-47. The concentrations of several PBDEs in marine animals are summarized in Table 6-8. PBDEs have been detected in several species of seal from several different sites. In the Baltic Sea, female grey seals (*Halichoerus grypus*) sampled in 1979–1985 contained 730 ng PBDE/g lipid in their blubber (sum of BDE-47, -99, and -100) (Jansson et al. 1993); male grey seals had 280 ng PBDE/g lipid weight

Table 6-8. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Marine Animals

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Galaucous gull	Bear Island, Norway (Arctic)	290–634	160	No data	No data	No data	de Wit 2002
Brunnich's guillemot	Svalbard	No data	No data	No data	130	No data	Jansson et al. 1987
Cormorant liver	Rhine delta	No data	No data	No data	28,000 (fw)	No data	de Boer 1990
Cormorant	England, United Kingdom	170–3,500	50–250	50–1,500	300–6,400*	No data	Allchin et al. 2000
Grey seal	Baltic Sea	650	40	38	730	No data	de Wit 2002; Sellström et al. 1993
Grey seal	Baltic Sea	308	54	57	419	No data	Haglund et al. 1997
Grey seal	Baltic Sea	No data	No data	No data	208	No data	Andersson and Wartanian 1992
Ringed seal	Baltic sea	256	33	61	350	No data	Haglund et al. 1997
Ringed seal	Baltic sea	No data	No data	No data	320	No data	Andersson and Wartanian 1992
Ringed seal	Svalbard	47	1.7	2.3	51	No data	de Wit 2002; Sellström et al. 1993
Ringed seal	Canadian Arctic	No data	No data	No data	25.8–50*	No data	Alaee et al. 1999
Ringed seal	Holman Island, Northwest Territories, Canada	2.8	No data	No data	2.4–4.9*	No data	Ikonomou et al. 2000
Harbor seal	Baltic Sea	No data	No data	No data	90	No data	Jansson et al. 1987

Table 6-8. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Marine Animals *(continued)*

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Harbor seal	Skagerrak	No data	No data	No data	230	No data	Andersson and Wartanian 1992
Harbor seal	North Sea	390–4,900	42–660	25–450	600–6,000	No data	de Boer et al. 1998
Harbor seal	San Francisco Bay, California	46–6,682	17–303	No data	No data	No data	She et al. 2000
Bottlenose dolphin	South Atlantic Ocean	No data	No data	No data	180–220	No data	Kuehl et al. 1991
Bottlenose dolphin	Gulf of Mexico	No data	No data	No data	8,000	No data	Kuehl and Haebler 1995
Whitebeaked dolphin	Netherlands	5,500	1,000	1,200	7,700	No data	de Boer et al. 1998
Harbor porpoise	Britsh Columbia, Canada	50–1,200	No data	No data	350–2,300*	No data	Ikononmou et al. 2000
Harbor porpoise	England and Wales, United Kingdom	227–6,790	No data	No data	440–7,670	No data	Law et al. 2000
Beluga whale	Canadian Arctic	No data	No data	No data	81–160*	No data	Alaee et al. 1999
Beluga whale	Southeast Baffin, Canada	10	0.9	1.6	15*	No data	Stern and Ikonomou 2000
Long-finned pilot whale	Faeroe Islands	410–1,780	160–600	87–280	843–3,160*	No data	Lindström et al. 1999
Long-finned pilot whale	Faeroe Islands	66–860	24–170	12–98	126–1,250*	No data	van Bavel et al. 1999

Table 6-8. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Marine Animals *(continued)*

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Minke whale	Netherlands	630	160	79	870	No data	de Boer et al. 1998
Sperm whale	Netherlands	130–250	32–64	21–35	187–349	No data	de Boer et al. 1998

[a]3PBDEs is the sum of BDE-47, BDE-99, and BDE-100, but if more congeners are included, this is marked with an asterisk (*).

Source: de Wit (2002)

fw = fresh weight

(Andersson and Wartanian 1992). Male ringed seals (*Pusa hispida*) from the Baltic Sea had 320 ng PBDE/g lipid weight (Andersson and Wartanian 1992). Baltic gray and ringed seal blubber sampled between 1981 and 1988 contained 419 and 350 ng PBDEs/g lipid (total of BDE-47, -99, and -100), respectively (Haglund et al. 1997). In 1981, female ringed seals from Svalbard in the Swedish Arctic contained 40–51 ng PBDEs/g lipid in blubber (Jansson et al. 1987, 1993; Sellström et al. 1993). Higher levels of PBDEs are generally seen in Baltic Sea ringed seals (320–350 ng/g lipid) (Andersson and Wartanian 1992; Haglund et al. 1997) compared to Arctic ringed seals (26–51 ng/g lipid) (Alaee et al. 1999; Jansson et al. 1987). The level of PBDEs in harbor seals from Skagerrak on the Swedish west coast was 230 ng PBDE/g lipid (Andersson and Wartanian 1992). She et al. (2000) analyzed the concentration of BDE-47, -99, and -153 in harbor seal from the San Francisco Bay area (She et al. 2000). Mean concentrations for BDE-47, -99, and -153 were 1,124, 107, and 50 ng/g lipid weight, respectively. Alaee et al. (1999) found that ringed seal from the Canadian Arctic had mean PBDE concentrations (sum of di- to hexaBDEs) of 25.8 ng/g lipid weight (females) and 50.0 ng/g lipid weight (males). The lower levels in female seals suggests that PBDEs are transferred to young through breast milk. On Holman Island, North West Territory, Canada (Arctic) in 1996, ringed seal had total PBDE concentrations of 2.4–4.9 ng/g lipid for males. The levels of PBDEs were found to increase with age (Ikonomou et al. 2000). In a retrospective temporal trend study, archived samples of blubber from ringed seals from Holman Island, North West Territory, Canada were analyzed for PBDE levels. The concentration of PBDE in samples collected between 1981 and 1996 increased from approximately 0.3 ng/g lipid weight in 1981 to 3.6 ng/g lipid weight in 1996 (Ikonomou et al. 2000).

The levels of PBDEs have recently been determined in harbor porpoises (*Phocaena phocaena*) from British Columbia, Canada (Ikonomou et al. 2000) and from the coasts of England and Wales (Law et al. 2000). In British Colombia (Canada) samples, the total PBDE levels (sum of tri- to hepta-congeners) were 350–2,300 ng/g lipid weight; BDE-47 was found at the highest levels in these samples (range, 50–1,200 ng/g lipid weight) (Ikononmou et al. 2000). Concentrations of total PBDEs (sum of 13 congeners) along the coast of England and Wales, ranged from 450 to 7,670 ng/g lipid weight, with BDE-47 levels ranging from 227 to 6,790 ng/g lipid weight (Law et al. 2000).

During a mass mortality event on the south Atlantic coast in 1987–1988, blubber samples were collected from three bottlenose dolphins (*Tursiops truncatus*); these samples contained 180–220 ng PBDEs/g lipid (Kuehl et al. 1991). Blubber samples, taken from stranded bottlenose dolphins from several locations around the Gulf of Mexico in 1990, contained 3,110 ng PBDEs/g lipid (Kuehl and Haebler 1995). On the Dutch coast in early 1998, de Boer et al. (1998) found PBDEs in blubber of one whitebeaked dolphin

(*Lagenorhynchus albirostris*); the levels of BDE-47, -99, and -100 were 5,500, 1,000, and 1,200 ng/g lipid weight, respectively.

The concentration of 19 PBDEs was determined in long-finned pilot whale (*Globicephala melas*) from the Faeroe Islands in the north Atlantic (Lindström et al. 1999). Young males and females had the highest levels, ranging from 3,000 to 3,160 ng/g lipid; lower levels were observed for both adult females (840–1,050 ng/g lipid) and males (1,610 ng/g lipid). The predominant isomers in all samples were BDE-47 and BDE-99, accounting for 70% of the sum of 19 congeners. van Bavel et al. (1999) also studied the levels of PBDEs in long-finned pilot whales. They observed a similar trend with young animals having higher PBDE concentrations (740 ng/g lipid weight) and adult animals having lower levels (females, 230 ng/g lipid; males, 540 ng/g lipid). In Beluga whales sampled in 1997 from southeast Baffin (Cumberland Sound), the levels of total PBDEs and BDE-47 were 15 and 10 ng/g lipid weight, respectively (Stern and Ikonomou 2000). Between 1982 and 1997, total PBDE concentrations in archived blubber samples of beluga whales from southeast Baffin Canada increased significantly. For this time period, BDE-47, -99, -100, -154, and total PBDEs increased by factors of 6.5, 10.3, 7.9, 30.6, and 6.8, respectively (Stern and Ikonomou 2000). Three sperm whales (*Pyseter macrocephalus*) and one minke whale (*Balaenaoptera acutorostrata*) found stranded on the Dutch coast in early 1998 were analyzed for PBDEs (de Boer et al. 1998a, 1998b). Exposure to PBDEs for these animals occurred in the deep Atlantic through the food web. The concentrations of PPBEs in these marine mammals were as follows: sperm whale (BDE-47, 130–250 ng/g lipid weight; BDE-99, 32–64 ng/g lipid weight; and BDE-100, 21–35 ng/g lipid weight) and minke whale (BDE-47, 630 ng/g lipid weight; BDE-99, 160 ng/g lipid weight; BDE-100, 79 ng/g lipid weight); BDE-209 (DeBDE) was below detection limits in all samples.

Increasing levels of PBDEs have been found in marine birds and eggs, with BDE-47 found at the highest levels. Di- and triBDE have been detected, but not quantified, in black skimmer (*Rynchops nigra*) tissues and eggs in the United States (Stafford 1983). Ospreys (*Pandion haliaetus*), found dead at various locations around Sweden, were pooled and analyzed for PBDEs in muscle tissues (Jansson et al. 1993; Sellström et al. 1993). The ospreys' diet was freshwater fish. The combined concentration of BDE-47, -99, and -100 was 2,100 ng/g lipid in samples collected between 1982 and 1986; BDE-47 was the primary congener (86%) in these samples (n=35). High concentrations of PBDEs may reflect biomagnification and/or fish consumption along their migratory routes. The concentrations of PBDEs in common guillemots (*Uria aalge*) collected in 1979–1981 from the Baltic and North Seas were 370 and 80 ng/g lipid, respectively (Jansson et al. 1987). As part of the Swedish National Environmental Monitoring Program, guillemot eggs (St. Karlsö, Baltic Sea) are collected yearly and placed in the Swedish Natural History Museum's Environmental Specimens Bank. The concentrations of BDE-47, -99, and -100 in

pooled egg samples from the specimen bank showed a significant increase from 1969 to the beginning of the 1990s, with highs of 1,100 ng/g for BDE-47 in 1984 and 190 ng/g for BDE-99 in 1990 (Sellström 1999; Sellström et al. 1993). Between 1992 and 1997, PBDE levels started to decrease statistically. In 1997, the PBDE level (sum of BDE-47, -99, and -100) was 190 ng/g lipid, with BDE-47 as the predominant congener.

The quantitative determination of the concentrations of PBDEs in body tissues and fluids is important in determining the human body burden of these chemicals. Increasing levels of PBDEs have been measured in blood and breast milk in temporal trend studies. Individuals who consumed fish had a somewhat higher concentration of total PBDEs in body fluids compared to individuals who ate less fish. Tables 6-9, 6-10, and 6-11 summarize the concentrations of PBDEs found in blood (serum), adipose tissue, breast milk, and other body tissues or fluids, respectively. No data were located on the levels of PBDEs in body tissues and fluids from individuals living in the United States. However, levels of PBDEs in body tissues and fluids from individuals living in the United States are expected to be similar to individuals from other regions of the world.

Six PBDE congeners (BDE-28, -47, -66, -99, -100, and -153) were quantified in 40 human blood plasma samples from Sweden. The highest concentrations in plasma were for BDE-47 and BDE-99; these congeners made up 70% of the total PBDE concentration. The mean concentration of total PBDEs were 2.1±1.4 ng/g lipid weight (Klasson Wehler et al. 1997). Whole-blood samples from a German environmental specimen bank, collected in 1985, 1990, 1995, and 1999, contained measurable quantities of BDE-28, -47, -66, -85, -99, -100, -153, and -154. An increasing temporal trend was also observed; the mean total PBDE concentration (sum of eight congeners) increased from 3.9 ng/g lipid weight in 1985 to 5.6 ng/g lipid weight in 1999. For the 1999 sample, BDE-47 was the major congener found, with a mean concentration of 3.9 ng/g lipid weight. The total PBDE concentrations were significantly lower in female blood samples (Schröter-Kermani et al. 2000). Serum samples collected from 12 U.S. blood donors in 1988 were analyzed for PBDEs, and BDE-47, -153, -183, and -209 were detected (Patterson et al. 2000; Sjödin et al. 2001). Concentrations of these congeners were similar to those found in the Sjödin et al. (1999b) study for the control group. The median concentrations and ranges of BDE-47, BDE-153,

Table 6-9. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Human Blood Samples

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Human blood	Sweden	No data	No data	No data	2.1*	No data	Klasson Wehler et al. 1997
Human blood	Sweden, computer disassembly workers	2.9 (median)	No data	No data	26*	4.8	Sjödin et al. 1999a
Human blood	Sweden, cleaning personnel/office workers	1.5–1.6 (median)	No data	No data	3.3–4.1*	<0.7 (median)	Sjödin et al. 1999a
Human blood	Sweden, high fish intake	2.1	No data	No data	No data	No data	Bergman et al. 1999; Sjödin et al. 2000
Human blood	Sweden, no fish intake	0.40	No data	No data	No data	No data	Bergman et al. 1999; Sjödin et al. 2000
Human blood	Germany	3.9	No data	No data	5.6*	No data	Schröter-Kermani et al. 2000

[a]3PBDEs is the sum of BDE-47, BDE-99, and BDE-100, but if more congeners are included, this is marked with an asterisk (*).

Source: de Wit (2002)

Table 6-10. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Human Adipose Tissue Samples

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Human adipose tissue	Sweden	8.8	1.1	1.8	11.7	No data	Haglung et al. 1997
Human adipose tissue	Sweden	3.8–16	No data	No data	No data	No data	Lindström et al. 1998
Human adipose tissue	Sweden	2.2	1.6	0.1	5*	No data	Meironyté Guvenius and Norén 1999
Human adipose tissue	United States	No data	No data	No data	No data	ND–0.7	Cramer et al. 1990; Stanley et al. 1991
Human adipose tissue	Finland	7.3	2.3	No data	6.2–22*	No data	Strandman et al. 1999
Human adipose tissue	Spain	1.36	0.42	No data	No data	No data	Meneses et al. 1999
Human adipose tissue	Northern California, United States	7.0–28	3.1–7.3	No data	No data	No data	She et al. 2000

[a]3PBDEs is the sum of BDE-47, BDE-99, and BDE-100, but if more congeners are included, this is marked with an asterisk (*).

Source: de Wit (2002)

ND = not detected

Table 6-11. Concentrations (in ng/g Lipid Weight) of Several PBDEs in Human Breast Milk Samples

Sample type	Location	BDE-47	BDE-99	BDE-100	3PBDEs[a]	BDE-209	Reference
Human breast Milk	Germany	No data	No data	No data	0.6–11*	No data	Krüger 1988
Human breast milk	Sweden	2.3	0.5	0.4	4*	No data	Norén and Meironyté 1998, 2000
Human breast milk	Sweden	2.5	0.7	0.5	4.4*	No data	Darnerud et al. 1998
Human breast milk	Finland	1.31	0.39	No data	No data	No data	Strandman et al. 2000
Human breast milk	Quebec and Ontario, Canada	3.4	1.2	0.44	5.8*	No data	Ryan and Patry 2000
Human breast milk	Martimes, Canada	No data	No data	No data	19*	No data	Ryan and Patry 2000
Human breast milk	Quebec, Canada	No data	No data	No data	18.8*	No data	Ryan and Patry 2000
Human breast milk	Ontario, Canada	No data	No data	No data	2.8*	No data	Ryan and Patry 2000
Human breast milk	Prairies, Canada	No data	No data	No data	5.7*	No data	Ryan and Patry 2000
Human breast milk	Canada, wide	No data	No data	No data	16.2	No data	Ryan and Patry 2000
Human breast milk	Japan	0.18–0.57	0.09–0.13	0.07–0.18	0.65–1.48*	No data	Ohta et al. 2000

[a]3PBDEs is the sum of BDE-47, BDE-99, and BDE-100, but if more congeners are included, this is marked with an asterisk (*).

BDE-183, BDE-209, and total PBDEs (sum of four congeners) were 0.63 (<0.4–24); 0.35 (0.08–2.0); 0.17 (0.09–1.3); <1 (<1–34); and 2.2 ng/g lipid weight, respectively (Sjödin et al. 2001). In a study of the influence of diet on concentrations of PBDEs, BDE-47 was measured in blood serum from persons with high fish intake and no fish intake (Bergman et al. 1999; Sjödin et al. 2000). High fish intake groups of Swedish and Latvian men had median BDE-47 concentrations of 2.2 and 2.4 ng/g lipid weight, respectively, whereas the no fish intake groups had median concentrations of 0.4 and 0.26 ng/g lipid weight, respectively (Sjödin et al. 2000).

BDE-47, -153, -154, -183, and -209 were measurable in blood plasma from three groups of workers (i.e., workers at a computer disassembly plant, workers in a computerized office, and a control group) (Sjödin et al. 1999b). The median concentrations (sum of five congeners) were highest for the computer disassembly plant workers (26 ng/g lipid weight); the office workers had a median concentration of 4.1 ng/g lipid weight and the control group had a median concentration of 3.3 ng/g lipid weight. The congener patterns for the control group and office workers were similar, with BDE-47 having the highest levels. For the computer disassembly plant workers, the median concentrations of BDE-183, -153, -154, -47, and -209 were 7.8, 4.5, 1.2, 2.9, and 4.8 ng/g lipid weight, respectively. Blood serum samples from 19 full-time computer technicians were analyzed (Hagmar et al. 2000). The serum concentrations of BDE-153, -183, and -209 in these samples were found to be approximately 5 times higher than the control and office workers in the Sjödin et al. (1999b) study. The median concentration for total PBDEs (for the sum of five congeners) was 10.6 pmol/g (7.0 ng/g) lipid weight. The highest concentrations were seen for BDE-153. Two OBDE congeners and one NoBDE congener were also detected. Connections were observed between fish consumption and serum concentrations for congeners BDE-47, -153, and -183, and between worktime at the computer and congeners BDE-153 and -183.

DeBDE, as well as hexa- through NoBDE, has been found in composite samples from the 1987 National Human Adipose Tissue Survey repository (Cramer at al 1990; Stanley et al. 1991). The concentrations ranged from not detected to 1 ng/g fat for HexaBDE, 0.001–2 ng/g fat for HeptaBDE and not detected to 8 ng/g fat for OBDE. NoBDE concentrations were estimated to be >1 ng/g fat; DeBDE was estimated to range between not detected and 0.7 ng/g fat. In the late 1990s, breast adipose samples collected in northern California contained quantifiable amounts of BDE-47, -99, and -153 (She et al. 2000). Mean concentrations were 18 ng/g lipid weight for BDE-47, 4.9 ng/g lipid weight for BDE-99, and 2.2 ng/g lipid weight for BDE-153. In the adipose tissue of a 74-year-old Swedish male, the BDE-47 concentration was 8.8 ng/g lipid weight (Haglund et al. 1997). Adipose and liver tissue from two Swedish males were examined for several PBDEs (BDE-28, -47, -85, -99, -100, -153, and -154) (Meironyté Guvenius and Norén 1999). The distribution of congener concentrations in the adipose and liver tissues for each

individual were similar. BDE-47, -99, and -153 were the predominant congeners with adipose BDE-47 concentrations ranging from 2 to 2.4 ng/g lipid weight, BDE-99 concentrations of 1.6 ng/g lipid weight, BDE-100 concentrations of 0.1 ng/g lipid weight, and BDE-153 concentrations ranging from 1 to 1.3 ng/g lipid weight. The total PBDE concentration (i.e., the sum of the seven congeners) in adipose tissue was 5 ng/g lipid weight. Human liver and adipose tissues from one woman and four men autopsied in Sweden in 1994, were analyzed form PBDEs containing 3–6 bromine atoms (Meironyté Guvenius and Norén 2001). PBDEs were found in all of the tissue samples. The sums of nine congeners (BDE-17, -28, -47, -66, -100, -99, -85, -154, and -153) were 5–18 and 4–8 ng/g lipids in liver and adipose tissue, respectively. The PBDE congeners BDE-47, -99, and -153 occurred at the highest levels and constituted 87–96 and 84–94% of the total sum in liver and adipose tissue, respectively. Strandman et al. (1999) measured the concentration of BDE-47, -99, and -153 in adipose tissue samples from 10 randomly selected individuals in Finland. Mean concentrations were 7.3 ng/g fat for BDE-47, 2.2 ng/g fat for BDE-99, and 2.3 ng/g fat for BDE-153. Levels of PBDEs were measured in adipose tissue samples from 13 individuals (3 women, 10 men) from Tarragona, Spain; the mean concentrations of BDE-47, -99, and -153 were 1.36, 0.42, and 1.83 ng/g lipid weight, respectively. The mean concentrations of PeBDE and HexaBDE were 0.93 and 1.83 ng/g lipid weight, respectively (Meneses et al. 1999).

Norén and Meironyté (1998, 2000) examined the temporal trends of PBDE concentrations in pooled breast milk samples from mothers in Stockholm, Sweden. Between 1972 and 1997, the concentration of PBDEs in human breast milk increased, with a doubling rate of 5 years. In the 1997 sample, the concentration of PBDEs (sum of eight congeners) was 4 ng/g lipid, whereas the 1972 sample contained 0.07 ng/g lipids (Meironyté et al. 1999). The authors suggest that the current exposure of humans to PBDEs may not be only diet; other exposure routes may result from the presence of PBDE in both work or home environments. PBDE levels were studied in breast milk obtained from mothers pregnant for the first time (n=39, ages 22–36 years old) from Uppsala County, Sweden (Darnerud et al. 1998). The mean value of total PBDEs (sum of eight congeners) was 4.4 ng/g fat; the major congener was BDE-47, comprising ca. 55% of the total PBDEs. In human breast milk from 25 German mothers, the levels of PBDEs ranged from 0.6 to 11 ng/g lipid (de Wit 2002). In 1992, the mean concentration of total PBDEs (sum of BDE-28, -47, -99, -100, -153, and -183) was 5.8 ng/g lipid weight for samples (n=6) from mothers from Ontario and Quebec, Canada (Ryan and Patry 2000). Combined samples from 1992 representing four regions of Canada and one representing all Canadian provinces had total PBDE concentrations ranging from 2.6 to 19 ng/g lipid weight; the highest concentrations were observed in the New Brunswick, Nova Scotia, and Prince Edward Island. Breast milk samples from Finland, collected between 1994 and 1998, had concentrations of total PBDEs (sum of BDE-28, -47, -99, and -153) ranging from 0.88 to 5.9 ng/g lipid weight (Strandman et al. 2000). In Japan, breast milk samples had total PBDE

concentrations (sum of BDE-28, -47, -99, -100, -153, and -154) ranging from 0.66 to 2.8 ng/g lipid weight (Ohta et al. 2002). Women who consumed fish had a somewhat higher concentration of total PBDEs (range, 1.4–2.8 ng/g lipid weight) compared to women who ate less fish (range, 0.67–0.87 ng/g lipid weight). BDE-47 was the major congener in most of the samples; BDE-153 levels were analogous to BDE-47 levels in some samples (Ohta et al. 2002).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Polybrominated Biphenyls. PBB are no longer produced or used in the United States. Thus, the general population exposure to PBBs will only be from historical releases. For people residing in the lower peninsula of Michigan, especially in the immediate vicinity of the PBB contaminated areas of this region, exposure to PBBs may still be occurring today. However, environmental levels have decreased since the 1970s and current exposure, if any, will be at low levels. For other regions of the United States, the levels of exposure will either be very low or none.

In the past, the general population may have been exposed to PBBs by inhaling contaminated air, ingesting contaminated water and food, and using consumer products containing PBBs. Other than in air in the vicinity of PBB production plants (see Section 6.1), no current or historical data exist that would indicate that PBBs might be present in ambient air. There are no current or historical data on the direct exposure of humans to PBBs from water. The general population may have been exposed to low levels of PBBs from the consumption of contaminated foods, but no estimate is available that quantitated this exposure. Historical monitoring and body burden data indicate that low level exposures to PBBs were limited to the population within the state of Michigan (see Section 6.4 and Table 6-4). The level of exposure to PBBs was slightly higher for the people residing in the lower peninsula of Michigan and highest among people residing in the immediate vicinity of the contaminated dairy farms, where people consumed contaminated meat, eggs, and dairy products (see Section 6.4 and Table 6-4). Consumer exposure in the past (plastics containing PBBs may not be in circulation anymore since PBB production ceased in the 1970s) from using PBB-containing plastics (e.g., typewriters, calculators, projector housings, and movie equipment cases) is expected to be very low since the PBBs were incorporated into the plastic and their mobilization could only have occurred under conditions such as combustion (Di Carlo et al. 1978).

Workers involved in the historical production of PBBs, PBB-containing plastics, and PBB-containing plastic products could have been exposed to PBBs via inhalation of dust and vapor and/or dermal contact.

Both workplace environmental monitoring and body burden monitoring data of workers (see Table 6-4) (Hesse and Powers 1978; Humphrey and Hayner 1975; Wolff et al. 1979b) indicated that workers in PBB industries were exposed to higher concentrations of PBBs than the general population. Although no evidence has been reported, workers in facilities that combusted or incinerated PBB-containing plastics might have been exposed to higher levels of PBBs.

Polybrominated Diphenyl Ethers. PBDEs are ubiquitous in the environment. Body burden data indicate that there are low-level exposures to PBDEs for the general population. Humans are primarily exposed to PBDEs by inhalation of ambient or contaminated air and ingestion of contaminated food. Dermal exposure to PBDEs could occur by contact with products containing PBDEs such textiles or polymers. However, little information is known about the potential exposure from this route.

In the United States, widespread exposure is evident by the levels of PBDEs found in tissues from individuals from all areas of the country and in all age groups (see Section 6.4.4). OBDE ranged from not detected to 8,000 ng/kg in adipose tissue samples collected for the National Human Adipose Tissue Survey (NHATS) in 1987 (Cramer et al. 1990; Stanley et al. 1991). HeptaBDE (1–2,000 ng/kg) was also found in the adipose tissue (Stanley et al. 1991). Analysis of adipose tissue samples from subjects of various ages and geographic locations within the United States showed that levels of HexaBDE and HeptaBDE were generally higher for ages 15–44 and 45+ years, whereas levels of OBDE were generally higher for ages 0–14 and 15–44 years. In studies of the general populations of other countries, it has also been shown that exposure to the general population is widespread (Haglund et al. 1997; Meneses et al. 1999).

The concentration of PBDEs in outdoor air ranges from 2 (rural) to 77 (urban) pg/m^3 in the United States (Dodder et al. 2000a), which indicates low levels of exposure to the general population. In Sweden, indoor air concentrations of PBDEs in lecture halls, computerized indoor environments, and rooms with electronic devices (e.g., televisions) have low levels of PBDEs (Lindström 1999). Point sources may result in increased concentrations of PBDEs in indoor air. For example, OBDE has been found in indoor areas that contain electronic products containing PBDEs (e.g., televisions and computers) (Bergman et al. 1997). The release of PBDEs from polymers is dependant on the migration ability of the PBDE molecule through the polymer matrix to the polymer surface where emission is possible (Danish EPA 1999). Because PBDEs are large molecules, migration is expected to occur slowly. No experimental studies were located on the emission rate of PBDEs from plastics. Based on worst case emission factors, the estimated emission of deca-, octa-, and pentaBDEs from plastics are 0.038, 0.054, and 0.39% per year, respectively (Danish EPA 1999).

Consumption of food is expected to be the major route of exposure in humans (Lindström 1999). Consumption of fish has been associated with elevated levels of PBDEs in tissues from the Swedish population (Bergman et al. 1999). In Sweden, fish consumption is about 30 g/day; this translates to an estimated 0.1 μg of PeBDE and 0.3 μg of total PBDEs from fish that is ingested by humans daily (WHO 1994a). The fish of greatest concern to humans are bottom feeders like carp and catfish. Like PCBs, there may be a higher risk of exposure to PBDEs in Native Americans that reside in the Arctic region who consume whale and seal blubber (Jaret 2000).

Workers involved in the production and manufacture of PBDE-containing plastics and plastic products are exposed to PBDEs. Body burden data indicate higher levels for workers exposed to PBDEs than for the general population. Occupational exposure to PBDEs also occurs in workers at plants that dismantle electronic equipment, computer monitor repair technicians, and automobile drivers, as well as other professions (Lindström 1999). Occupational exposure occurs primarily by inhalation. Inhalation of vapor phase PBDEs is expected to be low due to the low vapor pressures of PBDEs (see Table 4-6); however, the inhalation of particulate phase PBDEs is possible during plastic reprocessing where grinding or shredding of polymers with PBDEs occurs. Air samples were taken from an electronics dismantling plant, an office with computers, and outdoors and then analyzed for PBDEs (Sjödin et al. 1999a, 2001a). The electronics dismantling plant had the highest concentrations of PBDEs, with mean concentrations of 2.5 pmol/m^3 (1,250 pg/m^3) for BDE-47, 4.6 pmol/m^3 (2,600 pg/m^3) for BDE-99, 6.1 pmol/m^3 (3,930 pg/m^3) for BDE-153, 26 pmol/m^3 (18,800 pg/m^3) for BDE-183, and 38 pmol/m^3 (36,500 pg/m^3) for BDE-209 (Sjödin et al. 1999a, 2001a). Air samples were found to be 4–10 times higher in PBDE concentrations near a plastic shredder when compared to other locations in the plant (range, 0.42–200 ng/m^3). Concentrations of PBDEs in the office (range, <0.002– 0.09 ng/m^3) were 400–4,000 times lower than in the plant, and PBDEs were not detected in outside air (Sjödin et al. 1999a, 2001a).

BDE-47, -153, -154, -183, and -209 were measurable in blood plasma from three groups of workers (i.e., workers at a computer disassembly plant, workers in a computerized office, and a control group) (Sjödin et al. 1999b). The median concentrations (sum of five congeners) were highest for the computer disassembly plant workers (26 ng/g lipid weight); the office workers had a median concentration of 4.1 ng/g lipid weight and the control group had a median concentration of 3.3 ng/g lipid weight. The congener patterns for the control group and office workers were similar, with BDE-47 having the highest levels. For the computer disassembly plant workers, the median concentrations of BDE-183, -153, -154, -47, and -209 were 7.8, 4.5, 1.2, 2.9, and 4.8 ng/g lipid weight, respectively. Blood serum samples from 19 full-time computer technicians were analyzed (Hagmar et al. 2000). The serum concentrations of

BDE-153, -183, and -209 in these samples were found to be approximately 5 times higher than the control and office workers in the Sjödin et al. (1999b) study. The median concentration for total PBDEs (for the sum of five congeners) was 10.6 pmol/g (7.0 ng/g) lipid weight. The highest concentrations were seen for BDE-153. Two OBDE congeners and one NoBDE congener were also detected.

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 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).

Polybrominated Biphenyls. Infants who consume breast milk may have had a higher exposure to PBBs than children who drink formula milk, especially children exposed during the Michigan episode (see Section 6.4.4). No additional information was found in the literature about the exposure of children to PBBs (WHO 1994b).

Polybrominated Diphenyl Ethers. Infants who consume breast milk may have a higher exposure to PBDEs than children who drink formula milk (see Section 6.4.4). Exposure of neonates is evident due to the presence of PBDEs in breast milk of women from around the world as well as one study indicating the presence of PBDEs in placental tissue. The PBDEs detected in breast milk are the tri- to hexaBDEs, but not the hepta- to decaBDEs (LaKind and Berlin 2000), which are the same congeners found in bioaccumulation studies with fish and other mammals. Levels of PBDEs in the breast milk of Swedish women shows an exponentially increasing trend in exposure since the 1970s, with concentrations of PBDEs in breast milk doubling every fifth year (Lindström 1999). The concentrations of PBDEs in breast milk are increasing exponentially from about 300 pg/g lipid in 1976 to about 4,000 pg/g lipid in 1997 in Swedish women (Norön and Meironyté 2000). The sum of four PBDE congeners (BDE-28, BDE-47, BDE-99, and BDE-209) was between 0.88 and 5.89 ng/g lipid in breast milk and between

1.00 and 4.40 ng/g lipid in placental tissue of 11 Finnish women (Strandman et al. 2000). The four highest concentrations of PBDEs were found in nulliparous women. No additional information was found in the literature about the exposure of children to PBDEs (WHO 1994a).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Polybrominated Biphenyls. The production of PBBs ceased in 1979, and the usable life of the plastics containing PBBs has expired. Therefore, these plastics are probably no longer in circulation. At the present time and in the near future, populations potentially exposed to low levels of PBBs are those living near hazardous waste sites in which the PBB-containing plastics have been disposed and the residents in and around the contaminated farms in Michigan. The lifetime of PBBs in soil is on the order of years (Jacobs et al. 1978), and the levels of PBBs in fish caught in contaminated waters have declined slowly (Hesse and Powers 1978). Therefore, concentrations of residual PBBs in soil and streams in the vicinity of PBB-containing hazardous waste sites, PBB production facilities, and contaminated farm areas are expected to remain above background levels for many years. The sources of potential exposure to PBBs for residents in these areas are consumption of contaminated meat and dairy products obtained from herds grazing over contaminated soil and consumption of fish from nearby contaminated streams. PBB contamination has triggered the issuance of one human health advisory in the state of Michigan. As of September 30, 1993, recreational and subsistence fishermen who consume appreciably higher amounts of fish caught in the Pine River downstream from St. Louis in Gratiot and Midland Counties (RTI 1993) may be exposed to higher levels of PBBs associated with dietary intake (EPA 1993). The body burden for PBBs in residents of contaminated areas has been higher than in the general population (Brilliant et al. 1978; Cordle et al. 1978; Eyster et al. 1983; Humphrey and Hayner 1975; Kimbrough 1987; Lambert et al. 1990; Landrigan et al. 1979; Wolff et al. 1982). Therefore, babies breast fed by exposed mothers in the contaminated areas may also be at higher risk (Jacobson et al. 1989).

Polybrominated Diphenyl Ethers. Subsistence fisherman who consume PBDE contaminated fish and Native Americans that reside in the Arctic region who consume whale and seal blubber may have a higher risk of exposure to PBDEs (WHO 1994a). No other information was located that identified specific populations with higher exposure levels to PBDEs.

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 PBBs and PBDEs are 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 PBBs and PBDEs.

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.

Polybrominated Biphenyls. Many of the relevant physical and chemical properties of the PBBs are not available (see Table 4-3). More data on the physical and chemical properties of hexabromobiphenyl are available relative to octabromo- and decabromobiphenyl. Even in the case of hexabromobiphenyl, not all relevant data are available, and the quality of data are questionable because the properties of FireMaster BP-6 have been reported as the properties of hexabromobiphenyls. More importantly, very limited data are available on the physical and chemical properties for the individual congeners of hexabromo-, octabromo-, and decabromobiphenyl. The absence of such important data as K_{oc}, vapor pressure, and Henry's law constant, is a major impediment in the prediction of the environmental fate and transport of PBBs.

Polybrominated Diphenyl Ethers. Many of the relevant physical and chemical properties of the PBDEs are not available (see Table 4-4). Very limited data are available on the physical and chemical properties for the individual congeners. Important data, such as K_{oc}, vapor pressure, and Henry's law constant, are necessary for the prediction of the environmental fate and transport of PBDEs.

Production, Import/Export, Use, Release, and Disposal.

Polybrominated Biphenyls. The production of all PBBs in the United States stopped in 1979 (IARC 1986). Data on the past production, import/export, and use of PBBs are available (Neufeld et al. 1977). In the past, PBB-containing plastic was used in consumer products, but the useful life of these products may have ended (Di Carlo et al. 1978; Neufeld et al. 1977), and these products are probably no longer in circulation. In the workplace, the environmental media contaminated by PBBs were air, water, and soil (DeCarlo 1979). Outside of the workplace, soil is expected to be the medium with significant contamination due to disposal of solid waste from production plants and disposal of PBB-containing plastics in landfills (Neufeld et al. 1977). Although it is known that PBB-containing plastics may have been disposed in landfills (Di Carlo et al. 1978), the amount that may have been incinerated is not known. No data were located from studies that determined the efficiency of incineration as a method of disposal of PBBs present in the neat form in industrial wastes or in plastics. Environmental regulations regarding the manufacture and disposal of PBBs have been established (EPA 1988a). According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory

(TRI), which contains this information for 1999, became available in 2002. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Polybrominated Diphenyl Ethers. Production and use data are available. More information for PBDEs is needed on import/export, release, and disposal. Soil is expected to be the medium with significant contamination due to disposal of PBDE-containing plastics in landfills. Although it is known that PBDE-containing plastics are disposed in landfills, the amount that is incinerated is not known.

Environmental Fate.

Polybrominated Biphenyls. Information regarding the environmental fate of PBBs in air was not located in the literature. The data about the fate of PBBs in air are important for the prediction of transport characteristics of these compounds in air. Photolysis of the PBBs will produce debrominated products in proton donating organic solvents (Ruzo and Zabik 1975; Ruzo et al. 1976), but there is less certainty about the importance of photolysis of PBBs in water (Norris et al. 1973; Ruzo et al. 1976). PBBs will partition from aquatic phase to sediment and suspended solids in water (Hesse and Powers 1978). PBBs will bioconcentrate in aquatic organisms, but the BCF may decrease as the bromine substitution exceeds six (Gobas et al. 1989; Opperhuizen et al. 1985; Zitko 1979; Zitko and Hutzinger 1976). However, the difference in the reported BCF values for hexabromobiphenyl among different investigators is vast (Gobas et al. 1989; Hesse and Powers 1978; Opperhuizen et al. 1985; Veith et al. 1979). PBBs will remain strongly sorbed to soil (Filonow et al. 1976; Griffin and Chou 1981a, 1981b) and will persist in soil because of the lack of suitable degradation pathways (Jacobs et al. 1978). The translocation of PBBs from soil to upper parts in plants was not observed, and the transfer of PBBs from soil to carrot roots was found to be minor (Jacobs et al. 1976, 1978). A recent article by de Boer et al. (1998) found PBBs in deep ocean marine mammals, which suggests that PBBs may be transported globally. More monitoring data for PBBs in the environment are needed to verify the possible global transport of PBBs. Since the toxicity and the environmental fate of PBBs depends on specific PBBs congeners, development of more data regarding congener-specific fate and transport of PBBs in the environment are needed.

Polybrominated Diphenyl Ethers. There is a lack of quantitative data on the photodegradation potential of PBDEs in air, water, and soil in the presence of natural sunlight. No extensive, systematic studies have been done on biodegradation of PBDEs in the environment, especially studies investigating dehalogenation mechanisms. Since the toxicity and the environmental fate of PBDEs depend on specific

PBDEs congeners, development of more data regarding congener-specific fate and transport of PBDEs in the environment are needed.

Bioavailability from Environmental Media.

Polybrominated Biphenyls. Available information regarding the rate of absorption of PBBs following inhalation, oral, or dermal contact is discussed in the Toxicokinetics Section (Section 3.4). Although no data on the bioavailability of PBBs from inhalation of contaminated air, or ingestion of or dermal contact with water, or inhalation of or dermal contact with soil are available, the bioavailabilities from these routes of exposure are expected to be far less than 100% because these compounds strongly sorb to particulate matter and soil. The estimated bioavailability of higher brominated biphenyls are expected to be even lower than the less brominated biphenyls due to stronger sorption characteristics of the former compounds. The estimated bioavailability of PBBs by farm animals from ingestion of contaminated soil was 56–65% (Fries 1985a).

Polybrominated Diphenyl Ethers. The absorption and distribution of PBDEs as a result of inhalation, ingestion, and dermal exposure are discussed in Sections 3.3.1, 3.3.2, and 3.3.3. Studies that describe the bioavailability of PBDEs from ambient air, surface water, and groundwater, or soil do not exist. Studies determining the effect of particle size and organic matter content on the bioavailability of PBDEs from soil and the role of microparticle-sorbed PBDEs on the bioavailability of PBDEs from drinking water are needed. Such studies would be useful in assessing the health effects of PBDEs on people living near hazardous waste sites.

Food Chain Bioaccumulation.

Polybrominated Biphenyls. PBBs do not readily translocate from soil to plants via root uptake (Jacobs et al. 1976, 1978). Therefore, PBBs may not bioconcentrate in plants. However, plant uptake data are limited, and it will be helpful to develop additional plant uptake data. Brominated biphenyls with bromine substitution 6 or less will bioconcentrate in aquatic organisms (Gobas et al. 1989; Norris et al. 1973; Opperhuizen et al. 1985; Zitko 1979; Zitko and Hutzinger 1976). PBBs are preferentially stored in the adipose tissue of animals (Kimbrough 1987). Although PBBs have been detected in fish-eating birds and predatory animals from the consumption of contaminated food (Heinz et al. 1983, 1985; Hesse and Powers 1978), no systematic study was located that analyzed the biomagnification potential in predators resulting from consumption of contaminated food.

Polybrominated Diphenyl Ethers. The limited existing data indicate that PBDEs bioaccumulate in aquatic and terrestrial food chains and biomagnify in predators due to consumption of contaminated prey. More information on bioaccumulation and biomagnification of PBDE and its congeners is needed in assessing human health risks.

Exposure Levels in Environmental Media.

Polybrominated Biphenyls. Only limited data on the levels of PBBs in ambient air are available (DeCarlo 1979). Data are available on the levels of PBBs in effluent water from manufacturing plants, in river water, stream sediment, and soil in the vicinity of the plants, in sludge of a waste treatment plant, and in groundwater of a landfill site (Hesse and Powers 1978; Shah 1978). No data on the level of PBBs in drinking water from the contaminated sites were located. No estimate on the human intake of PBBs from any of the various environmental media was located in the literature.

Reliable monitoring data for the levels of PBBs in contaminated media at hazardous waste sites are needed so that the information obtained on levels of PBBs in the environment can be used in combination with the known body burden of PBBs to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Polybrominated Diphenyl Ethers. Information on the relative importance of different routes of exposure to PBDEs is limited. Data on the concentrations of PBDEs in foods, collected using a market-basket approach, are needed to determine concentrations of PBDEs in foods consumed by the general population. Data on the PBDE concentrations in foods grown in contaminated areas, particularly in the vicinity of hazardous waste sites, are also needed. Data on congener-specific PBDE analysis of food, especially plant products, would be useful. More monitoring data on the concentrations of total PBDEs as well as congeners in air in remote, rural, urban, and areas near hazardous waste sites and incinerators are needed. Data on PBDE concentrations in finished drinking water nationwide would be helpful.

Exposure Levels in Humans.

Polybrominated Biphenyls. Body burden data indicate that low-level exposures to PBBs have occurred for people in the state of Michigan. No recent information about average daily intake of PBBs was located. The levels of PBBs in human tissue and body fluids, such as blood, serum, adipose tissue, breast milk, feces, cord blood, biliary fluid, and placenta, of people in the state of Michigan have been

extensively studied (Brilliant et al. 1978; Cordle et al. 1978; Eyster et al. 1983; Humphrey and Hayner 1975; Lambert et al. 1990; Landrigan et al. 1979; Wolff et al. 1982). However, no recent data are available. Data on the levels of PBBs in tissues and body fluids of residents who live in the vicinity of sites of industrial discharge of PBB wastes were not located. Updated information would be useful to understand current exposure levels of people in the state of Michigan to PBBs. This information is necessary for assessing the need to conduct health studies on these populations.

Polybrominated Diphenyl Ethers. Body burden data indicate that there are low-level exposures to PBDEs for the general population. Information about the average daily intake of PBDEs is limited to populations living in Sweden (Bergman et al. 1999; Lindström 1999; WHO 1994a). PBDE levels are reported in the current literature for blood, breast milk, and adipose tissue of the general population and occupationally exposed individuals (WHO 1994a). However, no surveys have ever been conducted in the United States to evaluate the trend of PBDE concentrations in human tissues over the years. It would be helpful to develop a database of information on congener-specific PBDE 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 PBDEs 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.

Polybrominated Biphenyls. Children may be exposed to PBBs by a variety of exposure pathways. Levels will be highest for children living in the vicinity of the area affected by the Michigan contamination episode. The most important pathway appears to be consumption of contaminated mother's milk (see Section 6.4.4). More data are needed on the levels of PBB exposure in nursing women from consumption of fish and 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. Information related to the exposure of children living near hazardous waste sites is also needed. In particular, information is needed that is related to the potential for children to be exposed to PBBs 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 PBBs 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. Infants and young children consume a greater amount of food per kilogram of body weight and, therefore, may have a proportionately greater exposure to PBBs than adults.

Polybrominated Diphenyl Ethers. Children may be exposed to PBDEs by a variety of exposure pathways. The most important pathway appears to be consumption of contaminated foods, particularly fish (Bergman et al. 1999; Lindström 1999; WHO 1994a). Children can also be exposed to PBDEs from mother's milk (LaKind and Berlin 2000; Lindström 1999; Norön and Meironyté 2000; Strandman et al. 2000; WHO 1994a). More data are needed on the levels of PBDEs exposure in nursing women from occupational situations or consumption of fish and 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 is needed that is related to the potential for children to be exposed to PBDEs 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 PBDEs 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 PBDEs than adults.

Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries.

Polybrominated Biphenyls. The Michigan Department of Community Health (MDCH), together with the Centers for Disease Control and Prevention (CDC) and three other federal agencies, began a major study to assess the health effects of PBBs after the Michigan contamination episode. A health questionnaire and blood samples were collected from people affected by the feed contamination incident. MDCH had

the responsibility to analyze several thousand samples for PBB from 1975 to 1978. MDCH continues contact with this cohort, updates health questionnaires, and collects blood samples to be analyzed (MDCH 2002).

Polybrominated Diphenyl Ethers. No exposure registries for PBDEs 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 exposure to this substance.

6.8.2 Ongoing Studies

Polybrominated Biphenyls. A search in Federal Research in Progress (FEDRIP 2002) did not identify ongoing research studies for PBBs.

Polybrominated Diphenyl Ethers. A search in Federal Research in Progress (FEDRIP 2002) did not identify ongoing research studies for PBDEs.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring polybrominated biphenyls and polybrominated diphenyls ethers, their metabolites, and other biomarkers of exposure and effect to polybrominated biphenyls and polybrominated diphenyls ethers. 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.

Polybrominated biphenyl (PBBs) and polybrominated diphenyl ether (PBDEs) are analyzed in environmental and biological samples by methods quite similar to those used for polychlorinated biphenyls (PCBs) (de Kok et al. 1977; Fries 1985b; Pomerantz et al. 1978). The analysis methodology includes several steps: sample collection and storage, extraction, cleanup, and determination. 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, PBBs and PBDEs may be concentrated from water onto sorbents. PBBs and PBDEs are typically separated from the biological and environmental media by extraction with organic solvents. Cleanup steps are necessary to remove compounds that may interfere with the determination. Lipids (e.g., oils and fats) are removed with concentrated sulfuric acids. Chromatography (e.g., gel permeation, silica gel, Florisil) is used to remove other matrix interferences and to fractionate samples. The identification and quantitation of PBBs and PBDEs 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 PBBs and PBDEs 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 brominated compounds. The mass spectrometer (MS) detectors have sensitivities somewhat lower than ECD, and they have even greater selectivity for PBBs and PBDEs and can distinguish and individually measure homologs that may coelute on a particular HRGC column. A recent method of detection is electron capture negative ionization (ECNI) as an ionization technique in combination with GC-MS analysis (de Boer et al 2000). This method is advantageous because it offers a high sensitivity for

compounds with four or more bromine atoms. The sensitivity is approximately 10 times higher than with the use of the ECD. The small number of certified reference standards that are available for individual PBB and PBDE congeners poses a problem for analysis, since comparative analysis is often based on technical mixture equivalents rather than by comparison of individual congeners.

de Kok et al. (1979) described several analysis methods for analysis of commercial PBDEs such as GC-MS, high-performance liquid chromatography (HPLC), reversed-phase thin layer chromatography, and ultraviolet (UV) spectrometry.

7.1 BIOLOGICAL MATERIALS

Methods for the determination of organobromine compounds such as PBBs and PBDEs generally consist of the following steps: extraction of the analyte from the sample matrix; clean-up to remove interfering compounds; and analysis (separation and quantitation). The primary method of analysis is GC coupled with ECD or MS. Analytical methods have been developed for the determination of PBBs and PBDEs in blood or serum, urine, feces, adipose tissue, liver, and breast milk. The methods for determining PBB and PBDE residues in biological samples are given in Tables 7-1 and 7-2, respectively.

Polybrominated Biphenyls. Residues in biological samples can be extracted using hexane/ether, petroleum ether/diethyl ether, toluene/ethyl acetate, or methylene chloride (Burse et al. 1980; Domino et al. 1980; Fawkes et al. 1982; Fehringer 1975b; Wolff et al. 1979b). Elution of samples on a florisil column, which is used for the cleanup of extracts with petroleum ether, separates PBBs from interfering substances (Pomerantz et al. 1978). As in the case of PCBs, the solvent(s) used for the extraction of a sample and the method used for the cleanup of an extract is dependent on the sample matrix (Pomerantz et al. 1978). Quantitation is usually done by GC. The major difference between the methods for the determination of PCBs and PBBs arises from the lower volatility of PBBs compared to PCBs. Due to the lower volatility of PBBs, the GC method is performed at a higher temperature and low liquid phase load of the stationary phase. Capillary columns are required for the separation of the individual congeners in a mixture (Robertson et al. 1983b). However, decabromobiphenyl is so nonvolatile that a very short capillary column and high carrier gas linear velocity are required, which reduces the advantage of the capillary column over the packed column (Farrell 1980). Peaks from individual congeners of PBBs are detected and quantified with the ECD (Robertson et al. 1983b). In general, retention time in gas chromatographic columns and response of ECD increase with increasing bromination. PBB residues in a sample can be confirmed by thin layer chromatography, photochemical alteration method, halogen-

Table 7-1. Analytical Methods for Determining PBBs in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Serum	Extract denatured sample with hexane-ethyl ether; clean up by Florisil column chromatography	GC-ECD	1 μg/L	100.6–106.8 at 100 μg/L	Burse et al. 1980
Serum	Extract denatured sample with hexane-ether; clean up by Florisil column chromatography	GC-ECD	1 μg/kg	86–92	Wolff et al. 1979
Plasma	Extract denatured sample with petroleum ether-ethyl ether; clean up by Florisil and silica gel column chromatography	GC-ECD	1.0 μg/L (for hexa)	102 (for hexa)	Willet et al. 1978
Whole blood	Extract denatured sample with petroleum ether-ethyl ether; clean up by Florisil column chromatography	GC-ECD	0.7 μg/kg	90–96	Domino et al. 1980
Feces	Extract sample with petroleum ether-ethyl ether; clean up by Florisil and silica gel column chromatography	GC-ECD	1.4 μg/kg (for hexa)	61 (for hexa)	Willet et al. 1978
Bile	Extract denatured sample with petroleum ether-ethyl ether; clean up by Florisil and silica gel column chromatography	GC-ECD	0.08 μg/kg (for hexa)	92 (for hexa)	Willet et al. 1978
Milk	Extract denatured sample with petroleum ether-ethyl ether; clean up by Florisil and silica column chromatography	GC-ECD	1.4 μg/L (for hexa)	108 (for hexa)	Willet et al. 1978
Milk, human	Extract with potassium oxalate, ethanol/diethyl ether, or hexane	GC-ECD	1 μg/kg	No data	Eyster et al. 1983
Liver	Extract sample with methanol-chloroform; clean up by acidic silica column chromatography	GC-ECD	No data	70 (for hexa)	Fawkes et al. 1982
Adipose tissue	Extract sample with methylene chloride; clean up by acidic silica gel column chromatography	GC-ECD	No data	80	Fawkes et al. 1982
Adipose tissue (exposed workers)	Toluene/ethyl acetate (1+3); clean up using GPC/Bio beads	GC-ECD	0.5 μg/kg	98	Wolff et al. 1979

Table 7-1. Analytical Methods for Determining PBBs in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human tissues (post-mortem)	Extract with hexane; clean up using Florisil column	GC-ECD	0.5 ng/g	No data	Micelli et al. 1985

EC = electron capture detection; GC = gas chromatography; GPC = gel permeation chromatography; hexa = hexabrominated biphenyl; PBBs = polybrominated biphenyls; SIM = selected ion monitoring

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Table 7-2. Analytical Methods for Determining PBDEs in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Animal tissues (muscle, fat, and egg)	Extraction with sulfuric acid; clean up with GPC/silca column/carbon column	GC-MS (NCI)	No data	No data	Sellström et al. 1993
Human adipose tissue	Soxhlet extraction; clean up using 2 solid-phase extraction cartridges	Capillary GC-EILR-MS	0.05–0.30 ng/g lipid	81–103%	Covaci et al. 2002
Human adipose tissue	Extraction with methylene chloride; evaporate; clean up on silica gel followed by clean up on alumina and on a carbon/silica gel column	HRGC/HRMS	0.73–120 ng/kg	No data	Cramer et al. 1990
Human liver/adipose tissue	Extract with 2-propanol/hexane; clean up with Lipidex 5000, column chromatography/GPC	GC-MS (NCI)	5 pg/g lipids	83% (54–116%) liver 71% (51–95%) adipose	Meironyte Guvenius et al. 2001
Human milk	Extract with potassium oxalate/ethanol/diethyl ether/pentane; GPC; clean up on Florisil; elute with hexane	GC/MS (NCI/SIM)	<0.6 ug/kg fat	No data	WHO 1994a
Human milk	Extract by column chromatography using hexane/dichloromethane/ hexane; clean up using GPC	GC-MS (SIM)	5 pg/g lipids	86–102%	Meironyté et al. 1999a, 1999b
Human milk	Extract with n-hexane; clean up using multi-layer column	HRGC-LRMS or LRGC-HRMS (EI-SIM)	No data	>80%	Ohta et al. 2002
Human plasma	Extract with formic acid, 2-propanol, and water on a SPE column; derivatized using diazomethane	GC-MS (NCI)	1–10 pg/g plasma	72%	Thomsen et al. 2001b

Table 7-2. Analytical Methods for Determining PBDEs in Biological Materials *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human serum	Extraction with hexane/MTBE (1:1); clean up silica gel/surfuric acid column	GC-ECD; GC-MS (NCI)	0.7 ng/g lipid weight	69–104% (low spike); 77–104% (high spike)	Sjödin et al. 1999a

ECD = electron capture detection; EI = electron input; EILR = electron impact low-resolution; GC = gas chromatography; GPC = gel permeation chromatography; HRGC = high resolution gas chromatography; HRMS = high resolution mass spectrometry; LRGC = low resolution gas chromatography; LRMS = low resolution mass spectrometry; MS = mass spectrometry; MTBE = methyl-tert-butyl either; NCI = negative chemical ionization; PBDEs = polybrominated diphenyl ethers; SIM = secondary ion measurement; SPE = solid phase extraction

specific gas chromatographic detection, or MS (de Kok et al. 1977; Erney 1975; Pomerantz et al. 1978). High recoveries (80–90%) of PBB residues are obtained by the available analytical methods. Typically, the limit of quantitation for PBB residues is about 1 μg/kg in blood serum, 1 μg/kg in human milk, and 0.5 μg/kg in adipose tissue (Eyster et al. 1983; Wolff et al. 1979a). An interlaboratory study is available that validates the precision and accuracy of PBB residue determination in human serum by a commonly used method (Burse et al. 1980).

Polybrominated Diphenyl Ethers. Residues in biological samples can be extracted using sulfuric acid, 2-propanol/hexane, methylene chloride, n-hexane, formic acid/2-propanol/water, or hexane/methyl *t*-butyl ether (Cramer et al. 1990; Meironyte Guvenius et al. 2001; Ohta et al. 2002; Sellström et al. 1993; Sjödin et al. 1999; Thomsen et al. 2001b). Samples are cleaned up to remove interferences using Florosil, silica gel, alumina or activated charcoal column chromatography, gel permeation chromatography (GPC), and/or liquid chromatography (LC) (Sellström et al. 1993; Cramer et al. 1990; Meironyte Guvenius et al. 2001; Sjödin et al. 1999). Most techniques are based on analysis by GC with ECD, or, coupled with MS (WHO 1994a). Capillary columns and temperature programming allow the separation of the different PBDE congeners. High recoveries (69–104%) of PBDE residues are obtained by the available analytical methods. Typically, the limit of quantitation for PBDE residues is about 0.7 ng/g lipid in blood serum, 5 pg/g lipid in human milk, and 0.3 ng/g lipid in adipose tissue (Covaci et al. 2002; Meironyté et al. 1999a, 1999b; Sjödin et al. 1999).

7.2 ENVIRONMENTAL SAMPLES

Most environmental analyses have been performed using multiresidue methods involving solvent extract of the analytes from the sample matrix, clean-up to remove interfering compounds, determination by GC with ECD, and confirmation using an ancillary method such as MS. New methods and technologies are evolving, and this has resulted in lower detection limits. For example, detection limits for PBBs are in the low ppb to ppt range for water matrices and in the low ppm to ppb range for food; for PBDEs, detection limits are in the low ppb range for water matrices and in the low ppb to ppm range for fish tissues. Analytical methods for the determination of PBBs and PBDEs in environmental samples are given in Tables 7-3 and 7-4, respectively.

Polybrominated Biphenyls. Residues in environmental samples can be extracted using hexane-ether, petroleum ether-ether, toluene-ethyl acetate, or methylene chloride (Burse et al. 1980; Domino et al.

Table 7-3. Analytical Methods for Determining PBBs in Environmental Samples

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Commercial	Sample dissolved in benzene FireMaster BP-6	GC-ECD	1.6 ng (EC) GC-PED	Not applicable 2.8 ng (PED)	Mulligan et al. 1980
Soil	Extract sample with hexane-acetone; clean up by Florisil column chromatography	GC-ECD	0.1 μg/kg	74.2–83.2 (for hexa)	Jacobs et al. 1976, 1978
Soil	Extraction using hexane/acetone; clean up using Florisil column	GC-FID/ECD	No data	No data	Hill et al. 1982
Plant tissue	Extract macerated sample with hexane-acetone; clean up by Florisil column chromatography	GC-ECD	0.3 μg/kg	No data	Jacobs et al. 1978
Effluent and river water	Extract sample with hexane-ethyl ether	GC-ECD	0.1 μg/kg	90	Hesse and Powers 1978
Sediment	Extract sample with hexane-acetone	GC-ECD	No data	No data	Hesse and Powers 1978
Sediment	Pressurized hot water extraction coupled with clean up by LC	LC-GC-MS/FID	0.71 ng/g	No data	Kuosmanen et al. 2002
Fish	Extract homogenized sample with hexane-water; clean up by acidic and basic silica columns	GC-ECD	No data	98 (for hexa)	Gobas et al. 1989
Fish	Extract homogenized sample with hexane-methylene chloride; clean up by gel permeation and silica gel chromatography	HRGC-HRMS	No data	No data	Kuehl et al. 1991
Fish	Extract homogenized sample with hexane-acetone; clean up by gel permeation chromatography	HRGC-MS/NCI and HRGC-ECD	No data	No data	Jaffe et al. 1985
Terrestrial, fresh water, and marine samples	Extraction with diethyl ether/hexane; hydrolysis with 98% sulfuric acid/bio beads/silica gel/activated charcoal	MS (NCI)	No data	No data	Jansson et al. 1991, 1993
Dolphin fat	Soxhlet extraction using hexane-methylene chloride; clean up using GPC, silica gel	MS	No data	No data	Kuehl et al. 1991
Animal feeds	Elute ground sample containing celite with methylene chloride; clean up by Florisil column chromatography	GC-ECD	8 μg/kg (for hexa)	98 (for hexa)	Fehringer 1975b
Dairy products	Fat extracted by methanol/ether; clean up by GPC, 25% toluene in ethyl acetate	GC-ECD	7 μg/kg	No data	Fehringer 1975

Table 7-3. Analytical Methods for Determining PBBs in Environmental Samples *(continued)*

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plants	Cut, extracted with hexane/acetone; clean up with Florisil column	GC-ECD	0.3 μg/kg wet basis	No data	Chou et al. 1978

EC = electron capture detection; FID = flame ionization detector; GC = gas chromatography; hexa = hexabrominated biphenyl; HRGC = high resolution gas chromatography; HRMS = high resolution mass spectrometry; LC = liquid chromatography; MS = mass spectrometry; NCI = negative chemical ionization; PED = plasma emission detection; PBBs = polybrominated biphenyls

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Table 7-4. Analytical Methods for Determining PBDEs in Environmental Samples

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Air pumped through glass fiber filter and adsorbent trap; filters and adsorbants are Soxhlet extracted with acetone/hexane; cleaned-up by column chromatography	GC/MS	No data	No data	Dodder et al. 2000a
Water	Clean up by disk-type C18 solid-phase extraction	Capillary GC-ECD	0.12 ng/mL	103±8.6% (river water) 87±10.7% (sea water)	Yamamoto et al. 1997
Sewage	Extract with chloroform; evaporate and dissolve residue in ethanol	GC/MS	0.06 mg/kg	No data	WHO 1994a
Sediment	Clean up by cartridge-type Florosil extraction	Capillary GC-ECD	9.7 ng/g	91±6.3%	Yamamoto et al. 1997
Sediment	Pressurized hot water extraction coupled with clean up by LC	LC-GC-MS/FID	0.71 ng/g	No data	Kuosmanen et al. 2002
Sediment	Extract with acetone; clean up on Florisil	NAA GC/EC	<5 μg/kg <5 μg/kg	No data	Watanabe et al. 1987
Fish	Extract with acetone-hexane + hexane-ethyl ether; treatment with sulfuric acid or clean up on alumina; chromatography on silica gel	GC/EC; GC/MS	0.1 mg/kg fat	No data	Anderson and Blomkvist 1981
Fish	Extract with dichloromethane on chromatography column; clean-up using GPC; fractionation using silica gel column	GC-HRMS (NCI)	5–93 pg/g	No data	Alaee et al. 2001
Fish	Extract clean up with GPC and mini-column chromatography; concentration	GC-MS (NCI)	0.01–0.2 ng/g lipid	88–128%	Akutsu et al. 2001

Table 7-4. Analytical Methods for Determining PBDEs in Environmental Samples

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Animal tissues	Homogenize; extract with n-hexane-acetone; treatment with sulfuric acid; GPC; chromatography or silica gel chromatography or activated charcoal	GC/MS (NCI)	10 ng/kg	No data	Jansson et al. 1991

ECD = electron capture detection; GC = gas chromatography; GPC = gel permeation chromatography; HRMS = high resolution mass spectrometry; LC = liquid chromatography; MS = mass spectrometry; NAA = neutron activation analysis; NCI = negative chemical ionization; PBDEs = polybrominated diphenyl ethers

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1980; Wolff et al. 1979b; Fawkes et al. 1982; Fehringer 1975b). As for biological samples, quantitation of environmental samples is also usually done by GC. Capillary columns are required for the separation of the individual congeners in a mixture (Robertson et al. 1983b). High recoveries (74–98%) of PBB residues in environmental samples are obtained by the available analytical methods. Typically, the limit of quantitation for PBB residues is about 0.1 μg/kg in soil and 0.7 μg/kg in sediment (Jacobs et al. 1976, 1978; Kuosmanen et al. 2002).

Polybrominated Diphenyl Ethers. Like PCBs, air samples containing PBDEs 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, respectively (Dobber et al 2000a; Hillery et al 1997). The filters and adsorbants are then Soxhlet extracted with acetone/hexane, and the extracts are cleaned-up and analyzed by high resolution GC techniques.

Residues in environmental samples can be extracted using chloroform, acetone, acetone-hexane, hexane-acetone, and hexane-ether (Anderson and Blomkvist 1981; Jansson et al. 1991; Watanabe et al. 1987; WHO 1994a). Samples are cleaned up to remove interferences using Florosil, silica gel, alumina or activated charcoal column chromatography, GPC, and/or LC (Akutsu et al. 2001; Alaee et al. 2001; Anderson and Blomkvist 1981; Jansson et al. 1991; Watanabe et al. 1987; Yamamoto et al. 1997). As for biological samples, quantitation of environmental samples is also usually done by GC. Capillary columns are required for the separation of the individual congeners in a mixture (WHO 1994a). High recoveries (88–128%) of PBDE residues in environmental samples are obtained by the available analytical methods (Akutsu et al. 2001). Typically, the limit of quantitation for PBDE residues is about 0.12 ng/mL in water, 9.7 μg/kg in sediment, and 0.2 μg/kg lipid in fish (Akutsu et al. 2001; Yamamoto et al. 1997). The first interlaboratory study on PBDEs in environmental samples showed that there is good agreement for quantification of BDE-47 and BDE-100 congeners. However, improved methods are required for analysis of BDE-99, -153, -154, and -209 congeners (de Boer 2000).

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 PBBs and PBDEs 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 PBBs and PBDEs.

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.

Exposure. Methods used as biomarkers for exposure to PBBs and PBDEs are available (Brilliant et al. 1978; Covaci et al. 2002; Eyster et al. 1983; Landrigan et al. 1979; Meironyté et al. 1999a, 1999b; Sjödin et al. 1999; Wolff et al. 1982). Analytical methods of sufficient precision and accuracy are presently available for the determination of PBBs and PBDEs in adipose tissue, serum, and breast milk (Burse et al. 1980; Covaci et al. 2002; Domino et al. 1980; Fawkes et al. 1982; Fehringer 1975a; Meironyté et al. 1999a, 1999b; Sjödin et al. 1999; Willet et al. 1978; Wolff et al. 1979a, 1979b). Addition congener standards are needed for PBB and PBDEs analysis. Only 30–40 congener standards are currently available for identification and quantification of PBDEs (Eljarrat et al. 2002; Sjödin et al. 1998). Metabolites are also important biomarkers for exposure to PBBs and PBDEs. However, these compounds are mostly unknown, and standards are not available.

Effect. No known effect of PBB or PBDE exposure can be quantitatively correlated with PBB or PBDE exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods of sufficient sensitivity are presently available for the determination of PBBs and PBDEs in environmental samples (Akutsu et al. 2001; Anderson and Blomkvist 1981; Fehringer 1975b; Hesse and Powers 1978; Jacobs et al. 1976, 1978; Yamamoto et al. 1997).

It would be helpful to develop data determining the detection limit and accuracy of PBB determinations in fish and other aquatic animals (e.g., seals) and in sediment (Gobas et al. 1989; Jaffe et al. 1985; Kuehl

et al. 1991). Analytical methods for determining lower brominated PBBs in environmental samples are available (Morris et al. 1992). An analytical method to determine PBB metabolites in fish would be helpful. A method for determining of 6-hydroxy-2,2',4,4',5,5'-hexabromobiphenyl, a metabolite of 2,2',4,4',5,5'-hexabromobiphenyl, in dog feces is available (Gardner et al. 1979). Photochemical degradation leads to the formation of lower brominated products, which are the only environmental degradation products identified for PBBs. Analytical methods are presently available for the determination of these compounds in environmental samples (De Kok et al. 1977; Hill et al. 1982; Robertson et al. 1983b). There is no evidence in the literature of detectable biodegradation of PBBs in the environment under aerobic conditions (Griffin and Chou 1981a, 1981b), but the compounds may biodegrade to debrominated products under anaerobic conditions in polluted environments (Morris et al. 1992).

It would be helpful to develop data determining the accuracy of PBDE determinations (e.g., percent recovery) in environmental samples. Methods for determining degradation products and metabolites of PBDE are needed. There is no information in the literature of detectable biodegradation of PBDEs in the environment under aerobic or anaerobic conditions. The analysis of PBDE pyrolysis degradation products, such as polybrominated dibenzo-*p*-dioxins and dibenzofurans (PBDD/Fs), is often disturbed by the presence of PBDEs. Ebert et al. (1999) demonstrated that by using a Florisil column in a sample clean-up process, almost complete separation of PBDEs and PBDD/Fs is achieved before analysis by GC-MS.

7.3.2 Ongoing Studies

Two ongoing studies regarding analytical methods for determining PBB and PBDE residues or metabolites were located. This information is presented in Table 7-5, and was found as a result of a search of the Federal Research in Progress Database (FEDRIP 2002).

Table 7-5. Ongoing Studies on Analytical Methods for PBBs and PBDEs

Investigator	Affiliation	Subject	Sponsor
Huwe JK et al.	Agricultural Research Service, Fargo, North Dakota	Dioxins and other environmental contaminants in foods	USDA
Robertson LW	University of Kentucky Medical Center	Synthesis	National Institute of Environmental Health Sciences

Source: FEDRIP 2002

PBBs = polybrominated biphenyls; PBDEs = polybrominated diphenyl ethers; USDA = U.S. Department of Agriculture

8. REGULATIONS AND ADVISORIES

Table 8-1 summarizes international, national, and state regulations and guidelines on human exposure to PBBs and PBDEs.

ATSDR has derived an MRL of 0.01 mg/kg/day for acute-duration oral PBB exposure. The MRL is based on a NOAEL for thyroid effects in rats (Allen-Rowland et al. 1981). Intermediate- and chronic-duration oral MRLs were not derived because serious developmental effects (fetal abortion and stillbirths) were observed in monkeys that had been exposed to PBBs for durations that spanned the intermediate and chronic categories at the lowest dose tested in the database. This dose, 0.012 mg/kg/day, caused increased menstrual cycle duration and implantation bleeding after 6–7 months of exposure and fetal deaths after1 year of exposure in monkeys, with surviving infants having decreased birth weight and decreased postnatal weight gain and weight loss also occurring in maternal animals (Allen et al. 1978, 1979; Lambrecht et al. 1978). The reproductive effects are less serious, but concern for serious developmental toxicity following exposures of >1 year precludes deriving an MRL for intermediate-duration exposure. Derivation of an MRL for chronic oral exposure is precluded by the serious developmental effects that occurred following exposures exceeding 1 year in duration.

ATSDR has derived an MRL of 0.03 mg/kg/day for acute-duration oral exposure to PBDEs. The acute oral MRL is based on a NOAEL of 1 mg/kg/day for reduced serum levels of thyroid T_4 hormone in fetal rats that were exposed to octabromodiphenyl ether on days 4–20 of gestation (Zhou et al. 2002). ATSDR also derived an MRL of 0.007 mg/kg/day for intermediate-duration oral exposure to PBDEs. The intermediate oral MRL is based on a minimal LOAEL of 2 mg/kg/day for liver effects in rats that were exposed to pentabromodiphenyl oxide for 90 days (WIL Research Laboratories 1984).

IARC (1987) has classified decabromobiphenyl, hexabromobiphenyl, and octabromobiphenyl in Group 2B, possibly carcinogenic to humans. NTP (2002) has classified decabromobiphenyl, octabromo-biphenyl, and polybrominated biphenyl as reasonably anticipated to be human carcinogens. EPA (IRIS 2002) has classified decabromodiphenyl ether in Group D, as a possible human carcinogen, and nona-bromodiphenyl ether, octabromodiphenyl ether, hexabromodiphenyl ether, pentabromodiphenyl ether, tetrabromodiphenyl ether, tribromodiphenyl ether, *p,p'*-dibromodiphenyl ether, and *p*-bromodiphenyl ether in Group D, not classifiable as to human carcinogenicity.

Reference doses (RfDs) for decabromodiphenyl ether, octabromodiphenyl ether, and pentabromodiphenyl ether are $1x10^{-2}$, $3x10^{-3}$, and $2x10^{-3}$ mg/kg/day, respectively (IRIS 2002).

PBDEs including decabromodiphenyl ether, octabromodiphenyl ether, and pentabromodiphenyl ether are required to report health and safety data under the Toxic Substances Control Act (TSCA) (EPA 2002).

No regulations were located for PBBs and PBDEs for occupational safety and health standards, water quality, and food safety.

Table 8-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a]

Agency	Description	Information	Reference
INTERNATIONAL Guidelines:			
IARC	Carcinogenicity classification		IARC 1987
	Decabromobiphenyl	Group 2B[b]	
	Decabromodiphenyl ether	Group 3[c]	
	Hexabromobiphenyl	Group 2B[b]	
	Octabromobiphenyl	Group 2B[b]	
NATIONAL Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	No data	
NIOSH	REL (10-hour TWA)	No data	
OSHA	PEL (8-hour TWA)	No data	
b. Water			
EPA	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring for *p*-bromodiphenyl ether		EPA 2002e 40CFR264, Appendix IX
	Suggested EPA method	8270	
	PQL	10 μg/L	
c. Food			
FDA	Indirect food additives; substances for use only as components of adhesives		FDA 2001 21CFR175.105 (c)(5)
	Hexabromo-1,1'-biphenyl		
d. Other			
EPA	Carcinogenicity classification		IRIS 2002
	Decabromodiphenyl ether	Group C[d]	
	Nonabromodiphenyl ether	Group D[e]	
	Octabromodiphenyl ether	Group D[e]	
	Hexabromodiphenyl ether	Group D[e]	
	Pentabromodiphenyl ether	Group D[e]	
	Tetrabromodiphenyl ether	Group D[e]	
	Tribromodiphenyl ether	Group D[e]	
	p,p'-Dibromodiphenyl ether	Group D[e]	
	p-Bromodiphenyl ether	Group D[e]	

Table 8-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a] *(continued)*

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
EPA	Oral reference dose (RfD)			IRIS 2002
	Decabromodiphenyl ether	$1x10^{-2}$ mg/kg/day		
	Octabromodiphenyl ether	$3x10^{-3}$ mg/kg/day		
	Pentabromodiphenyl ether	$2x10^{-3}$ mg/kg/day		
	Chemical substances subject to proposed or final TSCA rules or orders	Regulated under TSCA section(s)		EPA 1998
	Decabromobiphenyl	5(a)(2)		
	Decabromodiphenyl ether	4		
	Hexabromo-1,1'-biphenyl	5(a)(2)		
	Octabromobiphenyl	5(a)(2)		
	Octabromodiphenyl ether	4		
	p-Bromodiphenyl ether	5(a)(2)		
	Pentabromodiphenyl ether	4		
	EPCRA Section 313; toxic chemical			EPA 2001
	Decabromodiphenyl ether			
	Identification and listing of hazardous waste; commercial chemical products, manufacturing chemical intermediates, or off-specification commercial chemical products are identified as toxic wastes; EPA hazardous waste number			EPA 2002b 40CFR261.33(f)
	p-Bromodiphenyl ether	U030		
	Land disposal restrictions; universal treatment standards			EPA 2002c 40CFR268.48(a)
	p-Bromodiphenyl ether			
	Wastewater standard	0.055 mg/L		
	Nonwastewater standard	15 mg/kg		
	Municipal solid waste landfills; hazardous constituent	Suggested methods	PQL	EPA 2002a 40CFR258, Appendix II
	p-Bromodiphenyl ether	8110	25 µg/L	
		8270	10 µg/L	
	Radiation protection; health and environmental protection standards for uranium and thorium mill tailings; listed constituent			EPA 2002d 40CFR192, Appendix I
	p-Bromodiphenyl ether			

Table 8-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a] *(continued)*

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
EPA	CERCLA hazardous substance under Section 307(a) of the Clean Water Act and RCRA Section 3001; reportable quantity			EPA 2002f 40CFR302.4
	p-Bromodiphenyl ether	100 pounds		
	Chemicals subject to the Prior Informed Consent Procedure: International right-to-know			EPA 2002g
	Decabromobiphenyl			
	Hexabromobiphenyl			
	Octabromobiphenyl			
	Toxic chemical release reporting; community right-to-know; effective date for reporting			EPA 2002h 40CFR372.65(c)
	Decabromodiphenyl ether	01/01/87		
	Polybrominated biphenyls	01/01/87		
	TSCA; chemical information rules; manufacturers and importers must submit a Preliminary Assessment Information Manufacturers' Report for each site at which they manufacture or import each substance by the reporting date shown			EPA 2002i 40CFR712.30(d)
	Decabromodiphenyl ether	03/12/90		
	Octabromodiphenyl ether	03/12/90		
	Pentabromodiphenyl ether	03/12/90		
	TSCA; chemical substances required to be tested			EPA 2002j 40CFR766.25 (a)(1)
	Decabromodiphenyl ether	Chemical substances known to be manufactured between 01/01/84 and date of promulgation		
	Octabromodiphenyl ether			
	Pentabromodiphenyl ether			
	TSCA; health and safety data reporting[f]	Effective date	Sunset date	EPA 2002l 40CFR716.120 (a)
	Decabromodiphenyl ether	01/11/90	06/30/98	
	Octabromodiphenyl ether	01/11/90	06/30/98	
	Pentabromodiphenyl ether	01/11/90	06/30/98	

Table 8-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a] *(continued)*

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	TSCA; reporting requirements including deadline for submitting the protocols		EPA 2002k 40CFR766.35
	Decabromodiphenyl ether	01/31/91	
	Octabromodiphenyl ether	01/31/91	
	Pentabromodiphenyl ether	02/06/95	
	TSCA; significant new uses subject to reporting of *p*-bromodiphenyl ether	Significant new use includes manufacturing, importing, or processing of 10,000 pounds or more per year per facility for any use	EPA 2002m 40CFR721.3430
	TSCA; significant new uses subject to reporting of polybrominated biphenyl		EPA 2002n 40CFR721.1790
	Decabromodiphenyl Hexabromo-1,1'-biphenyl Octabromobiphenyl	The significant new use is *any use*.	
	Voluntary children's chemical evaluation program		EPA 2002o
	Decabromodiphenyl ether Octabromodiphenyl ether Pentabromodiphenyl ether		
NTP	Carcinogenicity classification		NTP 2002
	Decabromobiphenyl Octabromobiphenyl Polybrominated biphenyl	Reasonably anticipated to be human carcinogens	
STATE Regulations and Guidelines:			
a. Air		No data	
b. Water			
Florida	Drinking water guideline *p*-Bromodiphenyl ether	10 µg/L	HSDB 2002
c. Food		No data	

Table 8-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a] *(continued)*

Agency	Description	Information	Reference
STATE *(cont.)*			
d. Other			
Florida	Toxic substance Polybrominated biphenyl		BLR 2002
Massachusetts	Hazardous substances requires the labeling of containers of toxic substances in the workplace Decabromobiphenyl Decabromdiphenyl ether Hexabromobiphenyl Hexabromo-1,1'-biphenyl Octabromobdiphenyl *p*-Bromodiphenyl ether Polybrominated biphenyl	 Extraordinary hazardous[g] Extraordinary hazardous[g] Extraordinary hazardous[g] Extraordinary hazardous[g]	BLR 2002
Michigan	Critical materials register; requires all businesses discharging waste products into the water or any sewer system to report the annual amount *p*-Bromodiphenyl ether		BLR 2002
Minnesota	Hazardous substance Decabromodiphenyl ether Hexabromo-1,1'-biphenyl		BLR 2002
New Jersey	Hazardous substance; requires SIC employers to submit Community Right-to-Know survey listing environmental hazardous substances present at their facilities in quantities that exceed 500 pounds Decabromodiphenyl ether		BRL 2002
New York	Hazardous substance *p*-Bromodiphenyl ether Reportable quantity (air) Reportable quantity (land)	 100 pounds 100 pounds	BLR 2002

Table 8-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a] *(continued)*

Agency	Description	Information	Reference
STATE *(cont.)*			
Pennsylvania	Hazardous substance; requires employers to complete the Hazardous Substance Survey Form annually		BLR 2002
	Decabromodiphenyl ether	Environmental hazard	
	p-Bromodiphenyl ether	Environmental hazard	
	Polybrominated biphenyl	Special hazard	

[a]Polybrominated biphenyls category includes: decabromobiphenyl (CAS# 13654-09-6); decabromodiphenyl ether (CAS# 1163-19-5); hexabromobiphenyl (CAS# 59080-40-9); hexabromo-1,1'-biphenyl (CAS# 36355-01-8); hexabromodiphenyl ether (CAS# 36483-60-0); nonabromodiphenyl ether (CAS# 63936-56-1); octabromobiphenyl (CAS# 27858-07-7); octabromobiphenyl (CAS# 61288-13-9); octabromodiphenyl ether (CAS# 32536-52-0); *p*-bromodiphenyl ether (CAS# 101-55-3); *p,p'*-dibromodiphenyl ether (CAS# 2050-47-7); pentabromodiphenyl ether (CAS# 32534-81-9); polybrominated biphenyl (CAS# 59536-65-1); polybrominated biphenyl mixture (CAS# 67774-32-7); tetrabromodiphenyl ether (CAS# 40088-47-9); and tribromodiphenyl ether (CAS# 49690-94-0).
[b]Group 2B: possibly carcinogenic to humans
[c]Group 3: not classifiable as to its carcinogenicity to humans
[d]Group C: possible human carcinogen
[e]Group D: not classifiable as to human carcinogenicity
[f]Health and safety data reporting: the listed chemical substances are subject to all provisions of 40CFR716. Manufacturers, importers, and processors of a listed substance are subject to the reporting requirements of Subpart A for that substance.
[g]Extraordinary hazardous and designated carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; BRL = Business & Legal Reports, Inc.; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; EPCRA = Emergency Planning and Community Right-to-Know Act; FDA = Food and Drug Administration; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limits; RCRA = Resource Conservation Recovery Act; REL = recommended exposure limit; RfD = oral reference dose; SIC = Standard Industrial Classification; TLV = threshold limit value; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average

9. REFERENCES

*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.

Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Federal Register 54(174):37618-37634.

Agency for Toxic Substances and Disease Registry. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems. Subcommittee on Biomarkers of Organ Damage and Dysfunction, Atlanta, GA.

*Agency for Toxic Substances and Disease Registry. 1994. Toxicological profile for chlorodibenzofurans. U.S. Department of Health and Human Services. Atlanta, GA.

*Agency for Toxic Substances and Disease Registry. 1998. Toxicological profile for chlorinated dibenzo-p-dioxins. U.S. Department of Health and Human Services. Atlanta, GA.

*Agency for Toxic Substances and Disease Registry. 2000. Toxicological profile for Polychlorinated biphenyls. U.S. Department of Health and Human Services. Atlanta, GA.

*Ahmadizadeh M, Kuo C-H, Echt R, et al. 1984. Effect of polybrominated biphenyls, B-napthoflavone and phenobarbital on arylhydrocarbon hydrolase activities and chloroform-induced nephrotoxicity and hepatotoxicity in male C57BL/6J and DBA/2J mice. Toxicology 31:343-352.

*Akoso BT, Sleight SD, Aust SD, et al. 1982a. Pathologic effects of purified polybrominated biphenyl congeners in rats. J Am Coll Toxicol 1:1-21.

*Akoso BT, Sleight SD, Nachreiner RF, et al. 1982b. Effects of purified polybrominated biphenyl congeners on the thyroid and pituitary glands in rats. J Am Coll Toxicol 1:23-36.

*Akutsu K, Obana H, Okihashi M, et al. 2001. GC/MS analysis of polybrominated diphenyl in fish collected from the inland sea of Seto, Japan. Chemosphere 44:1325-1333.

Alaee M. 2001. Levels and trends of PBDEs in North American environment. BFR:131-134.

*Alaee M, Sergeant DB, Ikonomou MG, et al. 2001. A gas chromatography/high-resolution mass spectrometry (GC/HRMS) method for determination of polybrominated diphenyl ethers in fish. Chemosphere 44(6):1489-1895.

*Alaee M, Sergeant DB, Muir DCG, et al. 1999. Distribution of polybrominated diphenyl ethers in the Canadian environment. Organohalogen Compounds 40:347-350.

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*Cited in text

Alcock RE, Jones KC. 1999. New directions "new" organic compounds in the environment. Atmos Environ 33(10):1645-1646.

*Allchin CR, Law RJ, Morris S. 1999. Polybrominated diphenylethers in sediments and biota downstream of potential sources in the UK. Environ Pollut 105:197-207.

*Allchin CR, Morris S, Law RJ, et al. 2000. Polybrominated diphenyl ether residues in cormorant (*Phalocrocorax L.*) livers from England, UK. Organohalogen Compounds 47:190-193.

*Allen JR, Barsotti DA, Lambrecht LK, et al. 1979. Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. Ann N Y Acad Sci 320:419-424.

*Allen JR, Lambrecht LK, Barsotti DA. 1978. Effects of polybrominated biphenyls in nonhuman primates. J Am Vet Med Assoc 173:1485-1489.

*Allen-Rowlands CF, Castracane VD, Hamilton MG, et al. 1981. Effect of polybrominated biphenyls (PBB) on the pituitary - thyroid axis of the rat. Proc Soc Exp Biol Med 166:506-514.

*Altman PL, 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.

*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. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

Anderson BE, Zeigler E, Shelby MD, et al. 1990. Chromosome aberration and sister chromatid exchange test results with 42 chemicals. Environ Mol Mutagen 16(18):55-137.

*Anderson H, 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.

*Anderson HA. 1985. Utilization of adipose tissue biopsy in characterizing human halogenated hydrocarbon exposure. Environ Health Perspect 60:127-131.

*Anderson HA, Holstein EC, Daum SM, et al. 1978a. Liver function tests among Michigan and Wisconsin dairy farmers. Environ Health Perspect 23:333-339.

*Anderson HA, Lilis R, Selikoff IJ, et al. 1978b. Unanticipated prevalence of symptoms among dairy farmers in Michigan and Wisconsin. Environ Health Perspect 23:217-226.

*Anderson HA, Rosenman KD, Snyder J. 1978c. Carcinoembryonic antigen (CEA) plasma levels in Michigan and Wisconsin dairy farmers. Environ Health Perspect 23:193-197.

*Anderson HA, Wolff MS, Fischbein A, et al. 1978d. Investigation of the health status of Michigan Chemical Corporation employees. Environ Health Perspect 23:187-191.

*Anderson HA, Wolff MS, Lilis R, et al. 1979. Symptoms and clinical abnormalities following ingestion of polybrominated-biphenyl-contaminated food products. Ann N Y Acad Sci 320:684-702.

9. REFERENCES

*Andersson O, Blomkvist G. 1981. Polybrominated aromatic pollutants found in fish in Sweden. Chemosphere 10(9):1051-1060.

*Andersson O, Wartanian A. 1992. Levels of polybrominated camphenes toxaphene chlordane compounds and polybrominated diphenyl ethers in seals from Swedish waters. Ambio 21(8):550-552.

Andersson PL, Wagman N, Berg H, et al. 1999. Biomagnification of structurally matched polychlorinated and polybrominated diphenylethers (PCDE/PBDE) in zebrafish (*Danio rerio*). Organohalogen Compounds 43:9-12.

*Andres J, Lambert I, Robertson L, et al. 1983. The comparative biologic and toxic potencies of polychlorinated biphenyls and polybrominated biphenyls. Toxicol Appl Pharmacol 70:204-215.

Anliker R, Moser P, Poppinger D. 1988. Bioaccumalation of dyestuffs and organic pigments in fish. Relationships to hydrophobicity and steric factors. Chemosphere 17:1631-1644.

Anonymous. 1981. Workplace environmental exposure level guide- decambromodiphenyl oxide. Am Ind Hyg Assoc J 12(4):A-76-77.

Anonymous. 1998. Swedish research spotlights brominated flame retardant risks. ENDS Rep 276:6.

Anonymous. 2000. TV makers battle with bromine barons over fire safety. ENDS Rep 309:30-31.

*Argus Research Laboratories. 1984. Dosage-range embryo/fetal toxicity & teratogenic potential of Saytex 115 administered orally via gavage to Crl: CONB CD (SD) BR presumed pregnant to rats. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0522189.

*Argus Research Laboratories. 1985a. Embryo/fetal toxicity and teratogenic potential study of Saytex® 115 administered orally via gavage to Crl: COBS® CD® (SD) BR presumed pregnant rats. Submitted to U.S. EPA under TSCA Section 8E, Fiche no. OTS0000973.

*Argus Research Laboratories. 1985b. Embryo/fetal toxicity and teratogenic potential study of Saytex® 115 administered orally via gavage to Crl: COBS® CD® (SD) BR presumed pregnant rats. Submitted to U.S. EPA under TSCA Section 8E, Fiche no. OTS0509725.

Arneric SP, McCormack KM, Braselton WE, et al. 1980. Altered metabolism of progesterone by hepatic microsomes from rats following dietary exposure to polybrominated biphenyls. Toxicol Appl Pharmacol 54:187-196.

Ashby J, Tennant RW. 1988. Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. Mutat Res 204:17-115.

Ashby J, Tennant RW. 1991. Definitive relationships among chemical structure carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP. Mutat Res 257:229-306.

Asplund L, Athanasiadou M, Sjodin A, et al. 1999a. Organohalogen substances in muscle, egg and blood from healthy Baltic salmon (*Salmo salar*) and Baltic salmon that produced offspring with the M74 syndrome. Ambio 28(1):67-76.

*Asplund L, Hornung M, Peterson RE, et al. 1999b. Levels of polybrominated diphenyl ethers (PBDEs) in fish from the Great Lakes and Baltic Sea. Organohalogen Compounds 40:351-354.

*Atkinson R. 1987a. Estimation of OH radical reaction rate constants and atmospheric lifetimes for polychlorobiphenyls, dibenzo-p-dioxins, and dibenzofurarans. Environ Sci Technol 21:305-307.

*Atkinson R. 1987b. A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. Int J Chem Kinet 19:779-828.

*Atlas E, Giam CS. 1987. Ambient concentration and precipitation scavenging of atmospheric organic pollutants. Water Air Soil Pollut 38:19-36.

*Aulerich RJ, Ringer RK. 1979. Toxic effects of dietary polybrominated biphenyls on mink. Arch Environ Contam Toxicol 8:487-498.

Aust SD. 1984. On the mechanism of anorexia and toxicity of TCDD and related compounds. Banbury Rep 18:309-318.

*Aust SD, Dannan GA, Slieght SD et al. 1981. Toxicology of polybrominated biphenyls. In: Khan MAQ, Stanton RH, eds. Toxicology of halogenated hydrocarbons: Health and ecological effects. Oxford, NY Pergaman Press, 73-96.

Babish JG, Stoewsand GS. 1977. Polybrominated biphenyls: Inducers of hepatic microsomal enzymes and type A cytochrome P450 in the rat. J Toxicol Environ Health 3:673-682.

*Babish JG, Stoewsand GS, Lisk DJ. 1978. Effect of diet on the hepatotoxicity of polybrominated biphenyls (FireMaster PB-6). Environ Health Perspect 23:133-137.

*Bahn AK, Mills JL, Snyder PJ, et al. 1980. Hypothyroidism in workers exposed to polybrominated biphenyls. N Engl J Med 302(1):31-33.

*Ballschmiter K, Zell M. 1980. Baseline studies of the global pollution: Occurrence of organohalogensin pristine European and Antarctic aquatic environments. Int J Environ Anal Chem 8:15-25.

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, Biegel L, Davis D, et al. 1989. 6-Methyl-1,3,8-trichlorodibenzofuran (MCDF) as a 2,3,7,8-tetrachlorodibenzo-p-dioxin antagonist in C57BL/6 mice. Toxicology 54:139-150.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Barontini F, Cozzani V, Cussola A, et al. 2001. Investigation of hexabromocyclododene thermal degradation pathways by gas chromatography/mass spectrometry. Rapid Commun Mass Spectrom 15(9):690-698.

*Barr M. 1980. Pediatric aspects of the Michigan polybrominated biphenyl contamination. Environ Res 21:255-274.

*Beaudoin AL. 1977. Teratogenicity of polybrominated biphenyls in rats. Environ Res 14:81-86.

*Beaudoin AR. 1979. Embryo toxicity of polybrominated biphenyls. Adv Study Birth Defects 2:211-222.

*Bekesi JG, Anderson HA, Roboz JP, et al. 1979. Immunologic dysfunction among PBB-exposed Michigan dairy farmers. Ann N Y Acad Sci:717-728.

*Bekesi JG, Holland JF, Anderson HA, et al. 1978. Lymphocyte function of Michigan dairy farmers exposed to polybrominated biphenyls. Science 199:1207-1209.

*Bekesi JG, Roboz J, Fischbein A, et al. 1985. Immunological, biochemical, and clinical consequences of exposure to polybrominated biphenyls. In: Dean JH, Luster MI, Munson AE, et al., eds. Immunotoxicology and Immunopharmacology. New York, NY: Raven Press, 393-406.

*Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. Endometriosis: Advanced management and surgical techniques. New York, NY: Springer-Verlag.

Bergman A. 2000. Brominated flame retardants-a burning issue. Organohalogen Compounds 47:35-40.

*Bergman A, Athanasiadou M, Wehler EK, et al. 1999. Polybrominated environmental pollutants. Human and wildlife exposures. Organohalogen Compounds 43:89-92.

Bergman A, Oestman C, Nybom R, et al. 1997. Flame retardants and plasticizers on particulates in the modern computerized indoor environment. Organohalogen Compounds 1987:414-419.

Bernert JT, Groce DF. 1984. Acute response of rat liver microsomal lipids, lipid peroxidation, and membrane anisotropy to a single oral dose of polybrominated biphenyls. J Toxicol Environ Health 13:673-687.

*Bernert JT, Groce DF, Kimbrough RD. 1983. Long-term effects of a single oral dose of polybrominated biphenyls on serum and liver lipids in rats. Toxicol Appl Pharmacol 68:424-433.

*Berry DL, DiGiovanni J, Juchou 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 N Y Acad Sci 320:405-414.

Betts KS. 2002. Rapidly rising PBDE levels in North America. Environ Sci Technol 36(3):50A-52A.

Beutler B, Cerami A. 1987. Cachectin: More than a tumor necrosis factor. N Engl J Med 316(7):379-385.

*Bieniek D, Bahadir M, Korte F. 1989. Formation of heterocyclic hazardous compounds by thermal degradation of organic compounds. Heterocycles 28(2):719-722.

Blake BW, Enslein K, Gombar VK, et al. 1990. Salmonella mutagenicity and rodent carcinogenicity: quantitative structure-activity relationships. Mutat Res 241(3):261-271.

Bleavins MR, Aulerich RJ. 1987. Feed consumption and food passage time in mink (*Mustela vison*) and European ferrets (*Mustela putorius furo*). Lab Anim Sci 31:268-269.

*Bleavins MR, Aulerich MR, Ringer RK. 1980. Placental and mammary transfer of polychlorinated and polybrominated biphenyls in the mink and ferret. ASTM Spec Tech Publ 757:121-131.

*BLR. 2002. Book of chemical lists on CD-Rom. Business & Legal Reports, Inc. Old Saybrook, CT.

*Booij K, Zegers BN, Boon JP. 2000. Levels of some polybrominated diphenyl ether (PBDE) flame retardants along the Dutch Coast as derived from their accumulation in SPMDs and Blue mussels (*Mytilus edulis*). Organohalogen Compounds 47:89-92.

*Borlakoglu JT, Wilkins JP. 1993. Metabolism of di-, tri- and tetrabromobiphenyls by hepatic microsomes isolated from control animals and animals treated with Aroclor 1254, a commercial mixture of polychlorinated biphenyls (PCBs). Comp Biochem Physiol C 105(1):107-112.

*Brenner KS, Knies H. 1993. Workplace of PBDFs abd PBDDs during extrusion production and injection modeling of a polybutyleneterephthalate (PBTP) glass fiber/tetrabromo-bisphenol A carbonate oligomer (BC52)/Sb2O3-resin; part II. Chemosphere 26(11):1953-1963.

*Breslin WJ, Kirk HD, Zimmer MA. 1989. Teratogenic evaluation of a polybromodiphenyl oxide misture in New Zealand white rabbits following oral exposure. Fundam Appl Toxicol 12(1):151-157.

*Brilliant LB, Van Amburg G, Isbister J, et al. 1978. Breast-milk monitoring to measure Michigan's contamination with polybrominated biphenyls. Lancet: Sept:643-646.

*British Industrial Biological Research Association. 1977. The acute oral toxicity of pentabromodiphenylether to rats. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS052287.

Brouwer A. 1998. Structure-dependent multiple interactions of polyhalogenated aromatic hydrocarbons with the thyroid hormone system. Organohalogen Compounds 37:225-232.

*Brown GG, Nizon R. 1979. Exposure to polybrominated biphenyls. Some effects on personality and cognitive functioning. JAMA 242:523-527.

*Brown GG, Preisman RC, Anderson MD, et al. 1981. Memory performance of chemical workers exposed to polybrominated biphenyls. Science 212:1413-1415.

*BSEF. 2002. An introduction to brominated flame retardants. Bromine Science and Environmental Forum. Brussels, Belgium, 1-28.

*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.

*Burreau S, Broman D, Zebuhr Y. 1999. Biomagnification quantification of PBDEs in fish using stable nitrogen isotopes. Organohalogen Compounds 40:363-366.

*Burreau S, Axelman J, Brogman D, et al. 1997. Dietary uptake in pike (*Esox incius*) of some polychlorinated biphenyls, polychlorinated naphthalenes and polybrominated diphenyl ethers administered in natural diets. Environ Toxicol Chem 16:2508-2513.

9. REFERENCES

*Burreau S, Zeb HR, Ishaq R, et al. 2000. Comparison of biomagnification of PBDEs in food chains from the Baltic Sea and the North Atlantic Sea. Organohalogen Compounds 47:253-255.

*Burse VW, Needham LL, Liddle JA, et al. 1980. Interlaboratory comparison for polybrominated biphenyls in human serum. J Anal Toxicol 4:22-26.

*Buser HR. 1986. Polybrominated dibenzofurans and dibenzo-p-dioxins: Thermal reaction products of polybrominated diphenyl ether flame retardants. Environ Sci Techol 20:404-408.

*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 21:520-527.

*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.

*Cabe PA, Tilson HA. 1978. Hind limb extensor response: A method for assessing motor dysfunction in rats. Pharmacol Biochem Behav 9:133-136.

*Cagen SZ, Preache MM, Gibson JE. 1977. Enhanced disappearance of drugs from plasma following polybrominated biphenyls. Toxicol Appl Pharmacol 40:317-325.

*Carlson GP. 1980a. Induction of xenobiotic metabolism in rats by brominated diphenyl ethers administered for 90 days. Toxicol Lett 6:207-212.

*Carlson GP. 1980b. Induction of xenobiotic metabolism in rats by short-term administration of brominated phenyl ethers. Toxicol Lett 5(1):19-26.

*Castracane VD, Allen-Rowlands CF, Hamilton MG, et al. 1982. The effect of polychlorinated biphenyl (PBB) on testes, adrenal, and pituitary function in the rat. Proc Soc Exp Biol Med 169:343-347.

CDC/ATSDR. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems: Centers for Disease Control/Agency for Toxic Substances and Disease Registry. Atlanta, GA.

*Chanda JJ, Anderson HA, Glamb RW, et al. 1982. Cutaneous effects of exposure to polybrominated biphenyls (PBBs): The Michigan PBB incident. Environ Res 29:97-108.

Chen E. 1979. An American tragedy prentice. Englewood Cliffs, NJ: Prentice-Hall Inc.

*Chen G, Konstantinov AD, Chittim BG, et al. 2001. Synthesis of polybrominated diphenyl ethers and their capacity to induce CYPIA by the Ah receptor mediated pathway. Environ Sci Technol 35(18):3749-3756.

Chen LC, Berberian I, Koch B, et al. 1992. Polychlorinated and polybrominated biphenyl congners and retinol levels in rat tissues: Structural-activity relationships. Toxicol Appl Pharmacol 114(1):47-55.

Chessells M, Hawker DW, Connell DW. 1992. Influence of solubility in lipid on bioconcentration of hydrophobic compounds. Ecotoxicol Environ Saf 23:260-273.

*Chhabra RS, Bucher JR, Hasman JK, et al. 1993. Comparative carcinogenicity of polybrominated biphenyls with or without perinatal exposure in rats and mice. Fundam Appl Toxicol 21(4):451-460.

Choudhry GG, Sundstrom G, Ruzo LO, et al. 1977. Photochemistry of chlorinated diphenyl ethers. J Agric Food Chem 25:1371-1376.

*Chou SF, Jacobs LW, Penner, D, et al. 1978. Absence of plant uptake and translocation of polybrominated biphenyls (PBBs). Environ Health Perspec 23:9-12.

*Christensen JH, Platz J. 2001. Screening of polybrominated diphenyl ethers in blue mussels, marine and freshwater sediments in Denmark. J Environ Monitor 3(5):543-547.

Chu I, Villeneuve DC, Becking GC, et al. 1980. Short-term study of the combined effects of mirex, photomirex, and Ketone with halogenated biphenyls in rat. J Toxicol Environ Health 6:421-432.

*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*Colborn T, Clement C, eds. 1992. Chemically-induced alterations in sexual and functional development: The wildlife-human connection. In: Advances in modern environmental toxicology, Vol. XX1. Princeton, NJ: Princeton Scientific Publishing.

*Colborn T, vom Saal F, Soto A. 1993. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101(5):378-384.

Collins WT, Capen CC, Garthoff LH, 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.

*Corbett TH, Beaudoin AR, Cornell RG, et al. 1975. Toxicity of polybrominated biphenyls (Firemaster BP-6) in rodents. Environ Res 10:390-396.

*Corbett TH, Simmons JL, Kawanishi H, et al. 1978. EM changes and other toxic effects of FireMaster BP-6 (polybrominated biphenyls) in the mouse. Environ Health Perspect 23:275-281.

*Cordel F, Corneliussen P, Jelinek C, et al. 1978. Human exposure to polychlorinated biphenyls and polybrominated biphenyls. Environ Health Perspect 24:157-172.

*Covaci A, de Boer J, Ryan JJ, et al. 2002. Determination of polybrominated diphenyl ethers and polychlorinated biphenyls in human adipose tissues by large-volume injection-narrow-bore capillary gas chromatograpy/electron impact low-resolution mass spectrometry. Anal Chem 74(4):790-798.

*Cramer PH, Ayling RE, Thornburg KR, et al. 1990. Evaluation of an analytical method for the determination of polybrominated dibenzo-p-dioxins/dibenzofurans (PBDD/PBDF) in human adipose. Chemosphere 20(7-9):821-827.

*Crisp TM, Clegg ED, Cooper RL, et al. 1998. Environmental endocrine disruption: An effects assessment and analysis. Environ Health Perspect 106(1):11-56.

*Dagnani MJ, Barda HJ, Benya TJ, et al. 1986. Bromine Compounds. In: Gerhartz W, ed. Ullman's encyclopedia of industrial chemistry. Baton Rouge, Louisiana, 405-417.

*Damstra T, Jurgelski W, Posner HS, et al. 1982. Toxicity of polybrominated biphenyls (PBBs) in domestic and laboratory animals. Environ Health Perspect 44:175-188.

*Danerud PO, Eriksen GS, Johannesson T, et al. 2001. Polybrominated diphenyl ethers: occurrence, dietary exposure, and toxicology. Environ Health Perspect Suppl 109:49-68.

*Danish EPA. 1999. Brominated flame retardants. Substance flow analysis and assessment of alternatives. Danish Environmental Protection Agency, 1-200.

Dannan GA, Guengerich FP, Kaminsky LS, et al. 1983. Regulation of cytochrome P-450. Immunochemical quantitation of eight isozymes in liver microsomes of rats treated with polybrominated biphenyl congeners. J Biol Chem 258(2):1282-1288.

*Dannan GA, Moore RW, Aust SD. 1978a. Studies on the microsomal metabolism and binding of polybrominated biphenyls (PBBs). Environ Health Perspect 23:51-61.

*Dannan GA, Moore RW, Besaw LC, et al. 1978b. 2,4,5,3',4',5'-hexabromobiphenyl is both a 3-methylcholanthrene- and a phenobarbital-type inducer of microsomal drug metabolizing enzymes. Biochem Biophys Res Commun 85:450-457.

*Dannan GA, Sleight SD, Fraker PJ, et al. 1982. Liver microsomal enzyme induction and toxicity studies with 2,4,5,3',4'-pentabromobiphenyl. Toxicol Appl Pharmacol 64:187-203.

*Darjono, Sleight SD, Stowe HD, et al. 1983. Vitamin A status, polybrominated biphenyl (PBB) toxicosis, and common bile duct hyperplasia in rats. Toxicol Appl Pharmacol 71:184-193.

*Darnerud PO, Sinjari T. 1996. Effects of polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PCBs) on thyroxine and TSH blood levels in rats and mice. Organohalogen Compounds 29:316-319.

*Darnerud PO, Thuvander A. 1998. Studies on immunological effects of polybrominated diphenyl ether (PBDE) and polychlorinated biphenyl (PCB) exposure in rats and mice. Organohalogen Compounds 35:415-418.

*Darnerud PO, Atuma S, Aune M, et al. 1998. Polybrominated diphenyl ethers (PBDEs) in breast milk from primiparous women in Uppsala county, Sweden. Organohalogen Compounds 35:411-414.

*Darnerud PO, Eriksen GS, Johannesson T, et al. 2001. Polybrominated diphenyl ethers: Occurrence, dietary exposure, and toxicology. Environ Health Perspect 109:49-64.

*Daston GP, Gooch JW, Breslin WJ, et al. 1997. Environmental estrogens and reproductive health: A discussion of the human and environmental data. Reprod Toxicol 11(4):465-481.

*de Boer J. 1989. Organochlorine compounds and bromodiphenylethers in livers of Atlantic cod (Gadus morhua) from the North Sea, 1977-1987. Chemosphere 18(11/12):2131-2140.

*de Boer J. 1990. Brominated diphenyl ethers in Dutch freshwater and marine fish. Organohalogen Compounds 2:315-318.

*de Boer J. 2000. First worldwide interlaboratory study on polybrominated diphenyl ethers (PBDEs). Organohalogen Compounds 45:118-121.

de Boer J, Korytar P. 2001. Analysis of brominated flame retardants- Methodological issues. BFR:45-49.

*de Boer J, de Boer K, Boon JP. 2000a. Polybrominated biphenyls and diphenylethers. Handbook of Environmental Chemistry 3(K):61-95.

*de Boer J, Larry R, Dettmer LW, et al. 1998a. Polybrominated diphenyls in human adipose tissue and relation with watching television. A case study. Organohalogen Compounds 35:407-410.

*de Boer J, Van der Horst A, Wester PG. 2000b. PBDEs and PBBs in suspended particulate matter, sediments, sewage treatment plant in- and effluent and biota from The Netherlands. Organohalogen Compounds 47:85-88.

de Boer J, van der Zande TE, Pieters H, et al. 2001. Organic contaminants and trace metals in flounder liver and sediment from the Amsterdam and Rotterdam harbours and off the Dutch coast. J Environ Monitor 3(4):386-393.

*de Boer J, Wester PG, Klamer HJ, et al. 1998b. Do flame retardants threaten ocean life? Nature 394(6688):28-29.

de Boer J, Wester PG, Pastor RD, et al. 1998c. Polybrominated biphenyls and diphenylethers in sperm whales and other marine mammals. A new threat to ocean life? Organohalogen Compounds 35:383-386.

*Decarlo VJ. 1979. Studies in brominated chemicals in the environment. Ann N Y Acad Sci 320:678-681.

*De Kok JJ, De Kok A, Brinkman UA, et al. 1977. Analysis of polybrominated biphenyls. J Chromatogr 142:367-383.

*De Kok JJ, De Kok A, Brinkman UA. 1979. Analysis of polybrominated aromatic ethers. J Chromatogr 171:269-278.

*Denison MS, Fisher JM, Whitlock JP. 1989. Protein-DNA interactions at recognition sites for the dioxin-Ah receptor complex. J Biol Chem 264:16478-16482.

*Dent JG. 1978. Characteristics of cytochrome P-450 and mixed function oxidase enzymes following treatment with PBBs. Environ Health Perspect 23:301-307.

*de Wit CA. 2000. Levels and trends of BFRs in the European environment. BFR:135-138.

*de Wit CA. 2002. An overview of brominated flame retardants in the environment. Chemosphere 46(5):583-624.

*Dicarlo FJD, Seifter J, De Carlo VJ. 1978. Assessment of the hazards of polybrominated biphenyls. Environ Health Perspect 23:351-365.

*Dixon D, Sleight SD, Aust SD, et al. 1988. Tumor-promoting, initiating, and hepatotoxic effects of 3,4,3',3'-tetrabromobiphenyl (34-TBB) in rats. J Am Coll Toxicol 7(5):687-697.

*Dodder NG, Strandberg B, Hites RA. 2000. Concentrations and spatial variations of polybrominated diphenyl ethers in fish and air from the northeastern United States. Organohalogen Compounds 47:69-72.

Dodder NG, Strandberg B, Hites RA. 2002. Concentrations and spatial variations of polybrominated diphenyl ethers and several organochlorine compounds in fishes from the northeastern United States. Environ Sci Technol 36(2):146-151.

*Domino EF, Wright DD, Domino SE. 1980. GC-EC analysis of polybrominated biphenyl constituents of Firemaster FF-1 using tetrabromobiphenyl as an internal standard. J Anal Toxicol 4:299-304.

*Domino LE, Domino SE, Domino EF. 1982. Toxicokinetics of 2,2',4,4',5,5'-hexabromobiphenyl in the rat. J Toxicol Environ Health 9:815-833.

*Dow Chemical Company. 1971. Results of 30 day dietary feeding studies on octabromodiphenyl SA-1902 and decabromodiphenyl oxide SA-1892.1. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0522265.

*Dow Chemical Company. 1975. Results of a reproduction study in rats maintained on diets containing decabromodiphenyl oxide. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0522252.

*Dow Chemical Company. 1985. Decabromodiphenyloxide: A summary of an oral teratology study in Sprague-Dawley rats. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. 0522284 .

*Doucette WJ, Andren AW. 1988. Estimation of octanol/water partition coefficients: Evaluation of six methods for highly hydrophobic aromatic hydrocarbons. Chemosphere 17:345-359.

*Dumler R, Lenoir D, Thoma H, et al. 1990. Thermal formation of polybrominated bibenzofurans and dioxins from decamromodiphenyl ether flame retardants influence of antimony-III oxide and the polymer matrix. Chemosphere 20(10-12):1867-1874.

*Dumler R, Lenoir HTD, Hutzinger O. 1989a. OBDF and PBDD from the combustion of bromine containing flame retarded polymers: A survey. Chemosphere 19(12):2023-2031.

Dumler R, Thoma H, Lenoir D, et al. 1989b. Thermal formation of polybrominated dibenzodioxins (PBDD) and dibenzofurans (PBDF) from bromine containing flame retardants. Chemosphere 19(1-6):305-308.

Dumler-Gradl R, Tartler D, Thoma H, et al. 1995. Detection of polybrominated diphenylethers (PBDE), dibenzofurans (PBDF) and dibenzodioxins (PBDD) in scrap of electronics and recycled products. Organohalogen Compounds 24:101-104.

*Dunckel AE. 1975. An updating on the polybrominated biphenyl disaster in Michigan. J Am Vet Med Assoc 167:838-841.

Dungey S. 2001. Environmental risk assessment of octa-and decambrodiphenyl ether. BFR:37-39.

*Durst HI, et al. 1977. Effects of polybrominated biphenyls on health and performance of pregnant holstein heifers. J Dairy Sci 60:1294-1299.

Easton MDL, Luszniak D, Von der Geest E. 2002. Preliminary examination of contaminant loadings in farmed salmon, wild salmon and commercial salmon feed. Chemosphere 46(7):1053-1074.

*Ebert J, Lorenze W, Bahadir M. 1999. Optimization of the analytical performance of polybrominated dibenzo-p-dioxins and dibenzofurans (PBDD-F). Chemosphere 39(6):977-986.

Ecobichon DJ, Hansell MM, Safe S. 1977. Halogen substituents at the 4- and 4'-positions of biphenyl: Influence on hepatic function in the rat. Toxicol Appl Pharmacol 42:359-366.

Ecobichon DJ, Hansell MM, Safe S. 1979. Isomerically pure bromobiphenyl congeners and hepatic mono-oxygenase activities in the rat: Influence of position and degree of bromination. Toxicol Appl Pharmacol 47:341-352.

*Ecobichon DJ, Hidvegi S, Comeau AM, et al. 1983. Transplacental and milk transfer of polybrominated biphenyls to perinatal guinea pigs from treated dams. Toxicology 28:51-63.

Egginton J. 1980. The poisoning of Michigan. New York, New York: WW Norton & Company.

*Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15(1):30-38.

*el Dareer SM, Kalin JR, Tillery KF, et al. 1987. Disposition of decabromobiphenyl ether in rats dosed intravenously or by feeding. J Toxicol Environ Health 22(4):405-415.

*Elferink CJ, Whitlock JPJ. 1990. 2,3,7,8-Tetrachlorodibenzo-p-dioxin-inducible, Ah receptor-mediated bending of enhancer DNA. J Biol Chem 265(10):5718-5721.

*Eljarrat E, Lacorte S, Barcelo D. 2002. Optimization of congener-specific ananlysis of 40 polybrominated diphenyl ethers by gas chromatography/mass spectrometry. J Mass Spectrom 37(1):76-84.

EPA. 1977. Market input/output studies. Task IV. Polybrominated biphenyls. U.S. Environmental Protection Agency. EPA-560/6-77-017.

EPA. 1981. Development of test for determining anaerobic biodegradation potential: Washington, DC. U.S. Environmental Protection Agency.

EPA. 1988a. Polybrominated biphenyl. Code of Federal Regulation: Washington, DC: U.S. Environmental Protection Agency 704.195.

EPA. 1988b. U.S. Environmental Protection Agency: Part 372. Toxic chemical release reporting: community right-to-know. 40 CFR Ch 1 (7-1-88-ed.).

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Criteria and Assessment Office. EPA 600/8-90/066A.

*EPA. 1995. Toxic chemical release inventory. Reporting form R and instructions. Washington DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA 745-K-95-051.

*EPA. 1997. 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.

*EPA. 1997. Automated Form R for Windows: User's guide (RY97). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics.

*EPA. 1998. Instructions for reporting for the 1998 partial updating of the TSCA chemical inventory data base. U.S. Environmental Protection Agency. Office of Prevention, Pesticides and Toxic Substances. EPA 749-B-98-001.

*EPA. 2001a. List of lists. Consolidated list of chemicals subject to the Emergency Planning and Community Right-to-Know Act (EPCRA) and Section 112(r) of the Clean Air Act. U.S. Environmental Protection Agency. Office of Solid Waste and Emergency Response. EPA 550-B-98-003.

*EPA. 2002a. Criteria for municipal solid waste landfills. List of hazardous inorganic and organic constituents. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 258, Appendix II. http://ecfr.access.gpo.gov/otcgi/cfr/otfilter. April 19, 2002.

*EPA. 2002b. Identification and listing of hazardous waste. Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33(f). http://ecfr.access.gpo.gov/otcgi/cf. April 19, 2002.

*EPA. 2002c. Land disposal restrictions. Universal treatment standards. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268.48(a). http://ecfr.access.gpo.gov/otcg. April 19, 2002.

*EPA. 2002d. Radiation protection program. Health and environmental protection standards for uranium and thorium mill tailings. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 192, Appendix I. http://ecfr.access.gpo.gov/otcg. April 19, 2002.

*EPA. 2002e. Standards for owners and operators of hazardous waste treatment, storage, and disposal facilities. Ground-water monitoring list. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix IX. http://ecfr.access.gpo.gov/otcgi/cfr/otfilter. April 19, 2002.

*EPA. 2002f. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notification. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. http://ecfr.access.gpo.gov/otcgi/cfr/otfilter. April 19, 2002.

*EPA. 2002g. The prior informed consent (PIC) procedure: International right-to-know. U.S. Environmental Protection Agency. Office of Pesticide Programs. http://www.epa.gov/oppfod01/international/pic.htm. April 19, 2002.

*EPA. 2002h. Toxic chemical release reporting: Community right-to-know. Chemicals and chemical categories to which this part applies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65(c). http://ecfr.access.gpo.gov/otcgi/cf. April 18, 2002.

*EPA. 2002i. Toxic Substances Control Act. Chemical information rules. Chemical lists and reporting periods. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 712.30(d). http://ecfr.access.gpo.gov/otcgi/cfr/otfil. April 19, 2002.

*EPA. 2002j. Toxic Substances Control Act. Dibenzo-para-dioxins/dibenzofurans. Chemical substances for testing. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 766.25(a)(1). http://ecfr.access.gpo.gov/otcg. April 19, 2002.

*EPA. 2002k. Toxic Substances Control Act. Dibenzo-para-dioxins/dibenzofurans. Reporting requirements. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 766.35. http://ecfr.access.gpo.gov/otcgi/cfr/otfilter. April 19, 2002.

*EPA. 2002l. Toxic Substances Control Act. Health and safety data reporting. Substances and listed mixtures to which this subpart applies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 716.120. http://ecfr.access.gpo.gov/otcgi/cfr/otfilter. April 19, 2002.

*EPA. 2002m. Toxic Substances Control Act. Significant new uses of chemical substances. 4-Bromophenyl phenyl ether. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 721.3430. http://ecfr.access.gpo.gov/otcg. April 19, 2002.

*EPA. 2002n. Toxic Substances Control Act. Significant new uses of chemical substances. Polybrominated biphenyls. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 721.1790. http://ecfr.access.gpo.gov/otcg. April 18, 2002.

*EPA. 2002o. Voluntary children's chemical evaluation program. U.S. Environmental Protection Agency. Office of Pollution Prevention and Toxics. http://www.epa.gov/chemrtk/childhlt.htm. April 19, 2002.

Eriksson J, Jakobsson E, Marsh G, et al. 2001. Photo decomposition of brominated diphenylethers in methanol/water. BFR:203-206.

Eriksson P, Anakarberg E, Viberg H, et al. 2001. Neonatal exposure to toxicants defined critical period: altered adult susceptibility. Neurotoxicology 22(4):510.

*Eriksson P, Jakobsson E, Fredriksson A. 1998. Developmental neurotoxicity of brominated flame-retardants, polybrominated diphenyl ethers, and tetrabromo-bis-phenol A. Organohalogen Compounds 35:375-377.

*Eriksson P, Jakobsson E, Fredriksson A. 2001. Brominated flame retardants: a novel class of developmental neurotoxicants in our environment. Environ Health Perspect 109(9):903-908.

*Eriksson P, Viberg H, Jakobsson E, et al. 1999. PBDE 2,2', 4,4', 5-pentabromodiphenyl ether, causes permanent neurotoxic effects during a defined period of neonatal brain development. Organohalogen Compounds 40:333-336.

Eriksson P, Viberg H, Jakobsson E, et al. 2002. A brominated retardant, 2,2'4,4',5-pentabromodiphenyl ether: Uptake, retention, and induction of Neurobehavioral alterations in Mice during a critical phase of neonatal brain development. Toxicol Sci 67:98-103.

*Erney DR. 1975. Confirmation of polybrominated biphenyl residues in feeds and dairy products, using an ultraviolet irradiation-gas-liquid chromatographic technique. J Assoc Off Anal Chem 58(6):1202-1205.

*EU. 2001. Diphenyl ether, pentabromo derivative (pentabromodiphenyl ether). European Union Risk Assessment Report. Luxembourg: Office for Official Publications of the European Committees, 1-124.

*Evans MG, Sleight SD. 1989. Effects of simultaneous dietary exposure to 2,2',4,4',5,5'-hexa-bromobiphenyl and 3,3',4,4',4,4'-hexachlorobiphenyl on hepatic tumor promotion in rats. J Am Coll Toxicol 8(6):1201-1206.

*Eyster JT, Humphrey HEB, Kimbrough RD. 1983. Partitioning of polybrominated biphenyls (PBBs) in serum, adipose tissue, breast milk, placenta, cord blood, and biliary fluid, and feces. Arch Environ Health 38:47-53.

*Farber T, Kasza L, Giovetti A, et al. 1978. Effect of polybrominated biphenyls (Firemaster BP-6) on the immunologic system of the beagle dog. Toxicol Appl Pharmacol 45:343.

Farrar DB, Crump KS. 1988. Exact statistical tests for any carcinogenic effect in animal bioassays. Fundam Appl Toxicol 11(4):652-663.

Farrar DB, Crump KS. 1990. Exact statistical tests for any carcinogenic effect in animal bioassays. Fundam Appl Toxicol 15(4):710-721.

Farrell TJ. 1980. Glass capillary gas chromatography of chlorinated dibenzofurans, chlorinated anisoles, and brominated biphenyls. J Chromatogr Sci 18:10-17.

*Fawkes J, Albro PW, Walters DB, et al. 1982. Comparison of extraction methods for determination of polybrominated biphenyl residues in animal tissue. Anal Chem 54:1866-1871.

*FDA. 1989. Tolerances for unavoidable poisonous or deleterious substances. Food and Drug Administration. 21 CFR 109.30.

*FDA. 2001. Indirect food additives: Adhesives and components of coatings. Adhesives. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105(c)(5). http://www.accessdata.fda.gov/. April 11, 2002.

*FEDRIP. 2002. Federal Research in Progress. The Dialog Corporation: Cary, NC.

*Fehringer NV. 1975a. Determination of polybrominated biphenyl residues in dairy products. J Assoc Off Anal Chem 58(5):978-982.

Fehringer NV. 1975b. Determination of polybrominated biphenyl residues in dry animal feeds. J Assoc Off Anal Chem 58(6):1206-1210.

*Fernlof G, Gadhasson I, Podra K, et al. 1997. Lack of effects of some individual polybrominated diphenyl ether (PBDE) and polychlorinated biphenyl congeners on human lymphocyte functions in vitro. Toxicol Lett 90(2-3):189-197.

*Filonow AB, Jacobs LW, Mortland MM. 1976. Fate of polybrominated biphenyls (PBBs) in soils. Retention of hexabromobiphenyl in four Michigan soils. J Agric Food Chem 24(6):1201-1204.

*Fomon 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.

*Fomon 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.

Foureman P, Mason JM, Valencia R, et al. 1994. Chemical mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. Environ Mol Mutagen 23(3):208-227.

*Fowles JR, Fairbrother A, Baecher-Steppan L, et al. 1994. Immunologic and endocrine effects of the flame-retardant pentabromodiphenyl ether (DE-71) in C57BL/6J mice. Toxicology 86(1-2):49-61.

*Fraker PJ. 1980. The antibody-mediated and delayed type hypersensitivity response of mice exposed to polybrominated biphenyls. Toxicol Appl Pharmacol 53:1-7.

*Fraker and Aust. 1980. The effect of polybrominated biphenyls on the immune response of BALB/c mice. In: Asher IM, ed. Inadvertent modifications of the immune response: the effect of foods, drugs, and environmental contaminants. Proceedings of the 4th FDA Science Symposium. HHS Publication no. (FDA) 80-1074, 270-271.

Francis BM. 1989. Relative developmental toxicities of nine diphenyl ethers related to nitrofen. Environ Toxicol Chem 8(8):681-688.

Francis BM, Metcalf RL. 1984. Structure activity relationships in diphenyl ether teratogenicity. Teratology 29:29A.

Freeman PK, Jang J-S, Haugen CM. 1996. The photochemistry of polyhaloarenes. XIII. The photohydrodehalogenation of 3,4-dibromobiphenyl. Tetrahedron 52(25):8397-8406.

*Fries GF. 1985a. Bioavailability of soil-borne polybrominated biphenyls ingested by farm animals. J Toxicol Environ Health 16:565-579.

*Fries GF. 1985b. The PBB episode in Michigan: An overall appraisal. CRC Crit Rev Toxicol 16:105-156.

*Fries GF, Jacobs IW. 1980. Residual polybrominated biphenyl contamination: Locations, amounts and significance on dairy farms. J Dairy Sci 63:114.

Fu X, Schmitz FJ. 1999. New brominated diphenyl ether from an unidentified species of Dysidea sponge. 13C NMR data for some brominated diphenyl ethers. J Nat Prod 59(1):1102-1103.

Fu X, Schmitz FJ, Govindan M, et al. 1995. Enzyme inhibitors: New and known polybrominated phenols and diphenyl ethers from four Indo-Pacific *Dysidea* sponges.

Gallet G, Perez G, Karlsson S. 2001. Two approaches for extraction and analysis of brominated flame retardants (BFR) and their degradation products in recycled polymers and BFR containing water. BFR:177-179.

*Galloway SM, Armstrong MJ, Reuben C, et al. 1987. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 Chemicals. Environ Mol Mutagen 10:1-175.

*Gardner AM, Righter HF, Roach JAG. 1976. Excretion of hydroxylated polychlorinated biphenyl metabolites in cow's milk. J Assoc Off Anal Chem 59(2):273-277.

*Gardner AM, Warren VL, Chen JT, et al. 1979. A metabolite of polybrominated biphenyls: Its identification and decomposition to a brominated dibenzofuran in the gas chromatograph-mass spectrometer. J Agric Food Chem 27(1):116-119.

Gause EM, Ross DH, Hamilton MG, et al. 1979. Correlation of systemic and biochemical effects of PBB with behavioral efects. Neurobehav Toxicol 1:269-274.

*Geller I, Gause EM, Leal BZ, et al. 1985. Behavioral effects of drugs as a function of maternal polybrominated biphenyl body burden. Toxicol Lett 24:229-234.

*Geller I, Hartman RJ, Garcia C, et al. 1979. Effects of polybrominated biphenyl on a discrimination. Neurobehav Toxicol 1:263-267.

Gerlienke SA, Legger FF, Van Meeteren ME, et al. 1998. In vitro inhibition of thyroid hormone sulfaction by hydroxylated metabolites of halogenated aromatic hydrocarbons. Chem Res Toxicol 11(9):1075-1081.

*Getty SM, Rickert DE, Trapp AL. 1977. Polybrominated biphenyl (PBB) toxicosis: an environmental accident. CRC Crit Rev Environ Control 7:309-323.

*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(2):65-71.

Glatt H, Anklam E, Robertson LW. 1992. Biphenyl and fluorinated derivatives: liver enzyme-mediated mutagenicity deteced in Salmonella typhimurium and Chinese hamster V79 cells. Mutat Res 281(3):151-156.

*Glinoer D, De Nayer P, Bourdoux P, et al. 1990. Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab 71:276-287.

*Gobas FAPC, Clark KE, Shiu WY, et al. 1989. Bioconcentration of polybrominated benzenes and biphenyls and related superhydrophobic chemicals in fish: Elimination into the feces. Environ Toxicol Chem 8:231-245.

*Goldstein JA, Safe S. 1989. Mechanism of action and structure-activity relationships for the chlorinated dibenzo-p-dioxins and related compounds. In: Kimbrough, Jenson, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products: Elsevier Science Publishers, 239-293.

*Goldstein JA, Linko PC, Levy LA, et al. 1979. A comparison of a commercial polybrominated biphenyl mixture, 2,4,5,2',4',5'-hexabromobiphenyl and 2,3,6,7-tetrabromonaphthalene as inducers of liver microsomal drug-metabolizing enzymes. Biochem Pharmacol 28:2947-2956.

Golub MS, Chernoff GF. 1994. Issues in regulatory protection of reproductive health in the workplace. Occup Med 9(3):373-386.

Great Lakes Chemical Corporation. 2001. Initial submission: Letter from Great Lakes Chemical Corporation to U.S. EPA summarizing 90-day inhalation toxicity study of octabromodiphenyl oxide in albino rats, dated 05/25/01. Submitted to U.S. EPA under TSCA Section 8E, Fiche no. OTS0574171.

Great Lakes Water Quality Board. 1983. An inventory of chemical substances identified in the Great Lakes ecosystem: Vol 2: Windsor, Ontario, Canada, 19, 26, 28.

Great Lakes Water Quality Board. 1989. Report on the Great Lakes water quality: Appendix B-Great Lake surveillance, Vol 1, 2.3-9-2.3-11.

*Greaves J, Roboz J, Holland JF, et al. 1984. Determination of the binding of polybrominated biphenyls to serum proteins by negative chemical ionization mass spectrometry. Chemosphere 13(5/6):651-656.

*Griffin RS, Chou SFJ. 1981a. Attenuation of polybrominated biphenyls and hexachlorobenzene by earth materials. Cincinnati, OH: EPA-600/2-81-191, 25-27.

*Griffin RA, Chou FJ. 1981b. Movement of PCBs and other persistent compounds through soil. Water Sci Technol 13:1153-1163.

*Groce DF, Kimbrough RD. 1984. Stunted growth, increased mortality, and liver tumors of polybrominated biphenyl (PBB) dosed Sherman rats. J Toxicol Environ Health 14:695-706.

*Gupta BN, Moore JA. 1979. Toxicologic assessments of a commercial polybrominated biphenyl mixture in the rat. Am J Vet Res 40(10):1458-1468.

Gupta BN, McConnell EE, Goldstein JA, et al. 1983a. Effects of polybrominated biphenyl mixture in the rat and mouse. Toxicol Appl Pharmacol 68:1-18.

*Gupta BN, McConnell EE, Harris MW, et al. 1981. Polybrominated biphenyl toxicosis in the rat and mouse. Toxicol Appl Pharmacol 57:99-118.

Gupta BN, McConnell EE, Moore JA, et al. 1983b. Effects of a polybrominated biphenyl mixture in the rat and mouse. Toxicol Appl Pharmacol 68:19-35.

*Gustafsson K, Bjork M, Burreau S, et al. 1999. Bioaccumulation kinetic of brominated flame retardants (polybrominated diphenyl ethers) in blue mussels (*Mytilus edulis*). Environ Toxicol Chem 18(6):1218-1224.

*Guzelian PS. 1985. Clinical evaluation of liver structure and function in human exposed to halogenated hydrocarbons. Environ Health Perspect 60:159-164.

*Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

Haake JM, Merrill JC, Safe S. 1985. The in vitro metabolism of benzo[a]pyrene by polychlorinated and polybrominated biphenyl induced rat hepatic microsomal monooxygenases. Can J Physiol Pharmacol 63:1096-1100.

*Hagenmaier H, She J, Benz T, et al. 1992. Analysis of sewage sludge for polyhalogenated bibenzo-p-dioxins, dibenzofurans, and diphenylethers. Chemosphere 25(1-10):1457-1462.

*Haglund PS, Zook DR, Buser H-R, et al. 1997. Identification and quantification of polybrominated ethers and methoxy-polybrominated diphenyl ethers in Baltic biota. Environ Sci Technol 31:3281-3287.

*Hagmar L, Bergman A. 2001. Human exposure to BFRs in Europe. BFR:107-111.

Hagmar L, Bjork J, Sjodin A, et al. 2001. Plasma levels of persistent organohalogens and hormone levels in adult male humans. Arch Environ Health 56(2):138-143.

Hagmar L, Jakobsson K, Thuresson K, et al. 2000. Computer technicians are occupationally exposed to polybrominated diphenyl ethers and tetrabromobisphenol A. Organohalogen Compounds 47:202-205.

Hagmar L, Sjodin A, Hoglund P, et al. 2000. Biological half-lives of polybrominated diphenyl ethers and tetrabromobisphenol A in exposed workers. Organohalogen Compounds 47:198-201.

Hairstom DW. 1995. CRC alternatives: A cold war. Chem Eng (NY) 102:65-66.

*Hakk H, Larson G, Klasson-Wehler E, et al. 1999. Tissue disposition, excretion, and metabolism of 2,2', 4,4,'5-pentabromodiphenyl ether (BDE-99) in male Sprague-Dawley rats. Organohalogen Compounds 40:337-340.

*Hakk H, Larsen GL, Orn U, et al. 2000. Association of decabromodiphenyl ether with urinary and biliary carrier proteins. Organohalogen Compounds 49:108-111.

Halbert F, Halbert S. 1978. Bitter harvest. Grand Rapids, Michigan: William B. Erdmans Publishing company.

*Hale R, La Guardia M, Harvey E, et al. 2001. Brominated diphenyl ethers in land-spoiled sewage sludges in the US. BFR:149-152.

Hale RC, La Guardia MJ, Harvey EP, et al. 2000. Comparison of brominated diphenyl ether fire retardant and organochlorine burdens in fish from Virginia (USA). Organohalogen Compounds 47:65-68.

*Hale RC, La Guardia MJ, Harvey EP, et al. 2001. Polybrominated diphenyl ether flame retardants in Virginia freshwater fishes (USA). Environ Sci Technol 35(23):4585-4591.

*Hallgren S, Darnerud P. 1998. Effects of polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) on thyroid hormone levels and enzyme activities in rats. Organohalogen Compounds 35:391-394.

*Hallgren S, Sinjari T, Hakansson H, et al. 2001. Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice. Arch Toxicol 75(4):200-208.

Halvorson MR, Phillips TD, Safe SH, et al. 1985. Metabolism of aflatoxin B1 by rat hepatic microsomes induced by polyhalogenated biphenyl congeners. Appl Environ Microbiol 49(4):882-886.

Hanigan MH, Winkler ML, Drinkwater NR. 1993. Induction of three histochemically distinct populations of hepatic foci in C57BL/6J mice. Carcinogenesis 14(5):1035-1040.

*Hardell L, Lindstom G, van Bavel B, et al. 1998. Concentrations of the flame retardant 2,2',4,4'-tetrabrominated diphenyl ether in human adipose tissue in Swedish persons and the risk for non-Hodgkin's lymphoma. Oncol Res 10(8):429-432.

Hardy ML. 1999. Regulatory status and environmental properties of brominated flame retardants undergoing risk assessment in the EU: DBDPO, OBDPO, PEBDPO and HBCD. Polym Degrad Stab 64(3):545-556.

*Hardy ML. 2000a. Properties of the major commercial PBDPO flame retardant, DBDPO, in comparison to PBB and PCB. Organohalogen Compounds 47:233-236.

Hardy ML. 2000b. The toxicity of the commercial polybrominated diphenyl oxide flame retardants: DBDPO, OBDPO, PeBDPO. Organohalogen Compounds 47:41-44.

Hardy M. 2001. Assessment of reported decabromodiphenyl oxide blood and air levels in Swedish workers and their workplace. BFR:121-124.

*Hardy ML. 2002a. A comparison of the properties of the major commercial PBDPO/PBDE product to those of major PBB and PCB products. Chemosphere 45(5):717-728.

*Hardy ML. 2002b. The toxicology of the three commercial polybrominated diphenyl oxide (ether) flame retardants. Chemosphere 46(5):757-777.

Harju M, Andersson, PL, Haglund P, et al. 2002. Multivariate physiochemical characterization and quantitative structure-property relationship modelling of polybrominated diphenyl ethers. Chemosphere 47:375-384.

Harner T. 2001. Measurements on octanol-air partition coefficients (KOA) for polybrominated diphenyl ethers (PBDEs): Predicting partitioning in the environment. BFR:55-58.

Harner T, Shoeib M. 2002. Measurements of octanol-air partition coefficients (KOA) for polybrominated diphenyl ethers (PBDEs): Predicting partitioning in the environment. J Chem Eng Data 47(2):228-232.

Harris SJ, Cecil HC, Bitman J. 1978a. Effects of feeding a polybrominated biphenyl flame retardant (FireMasterBP-6) to male rats. Bull Environ Contam Toxicol 19:692-696.

*Harris SJ, Cecil HC, Bitman J. 1978b. Embryotoxic effects of polybrominated biphenyls (PBB) in rats. Environ Health 23:295-300.

Hartonen K, Bowadt S, Hawthorne SB, et al. 1997. Supercritical fluid extraction with solid-phase trapping of chlorinated and brominated pollutants from sediment samples. J Chromatogr A 774(1-2):229-242.

*Hass JR, McConnell EE, Harvan DJ. 1978. Chemical and toxicologic evaluation of Firemaster BP-6. J Agric Food Chem 26:94-99.

Haung Q, Rusling JF. 1995. Formula reduction potentials and redox chemistry of polyhalogenated biphenyls in a bicontinuous microemulsion. Environ Sci Technol 29(1):98-103.

*Haworth S, Lawlor T, Mortelmans K, et al. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 5:3-142.

*HazDat. 2002. PBBs and PBDEs. Hazardous substance release and health effects database. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/hazdat.html.

*Heinz GH, Erdman TC, Haseltine SD, et al. 1985. Contaminant levels in colonial waterbirds from Green Bay and Lake Michigan, 1975-80. Environ Monit Assess 5:223-236.

*Heinz GH, Haseltine SD, Reichel WL, et al. 1983. Relationships of environmental contaminants to reproductive success in red-breasted mergansers [Mergu serrator] from Lake Michigan. Environ Pollut Ser A 32:211-232.

*Helleday T, Tuominen KL, Bergman A, et al. 1999. Brominated flame retardants induce intragenic recombination in mammalian cells. Mutat Res 439(2):137-147.

*Henck JW, Rech RH. 1986. Effect of perinatal polybrominated biphenyl exposure on acquisition and performance of an autoshaping paradigm. Neurotoxicology 7(2):651-664.

*Henck JW, Mattson JL, Rezabek DH, et al. 1994. Development neurotoxicity of polybrominated biphenyls. Neurotoxicol Teratol 16(4):391-399.

*Henderson AK, Rosen D, Miller GL, et al. 1995. Breast cancer among women exposed to polybrominated biphenyls. Epidemiology 6(5):544-546.

Henry B, Grant SG, Klopman G, et al. 1998. Induction of forward mutations at the thymidine kinase locus of mouse lyphoma cells: evidence for electrophilic and non-electrophilic mechanisms. Mutat Res 397(2):313-335.

*Hesse JL, Powers RA. 1978. Polybrominated biphenyl (PBB) contamination of the Pine River, Gratiot, and Midland counties, Michigan. Environ Health Perspect 23:19-25.

*Hill RH. 1985. Effects of polyhalogeanted aromatic compounds on porphyrin metabolism. Environ Health Perspect 60:139-143.

*Hill RH, Patterson DG, Orti DL, et al. 1982. Evidence of degradation of polybrominated biphenyls in soil samples from Michigan. J Environ Sci Health B 17(1):19-33.

*Hillery BR, Basu I, Sweet CW, Hites RA. 1997. Temporal and spatial trends in a long-term study of gas-phase PCB concentrations near the great lakes. Environ Sci Technol 31:1811-1816.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

Hoel DG, Haseman JK, Hogan MD, et al. 1988. The impact of toxicity on carcinogenicity studies: implications for risk assessment. Carcinogenesis 9(11):2045-2052.

Holladay SD. 1999. Prenatal immunotoxicant exposure and postnatal autoimmune disease. Environ Health Perspect Suppl 107:687-691.

Holladay SD, Smialowicz RJ. 2000. Development of the murine and human immune system: differential effects of immunotoxicants depend on time of exposure. Environ Health Perspect Suppl 108:463-473.

*Hollowell G, Norman W, Staehling W, et al. 1998. Iodine nutrition in the United States. Trends and public health implications: Iodine excretion data from national health and nutrition examination surveys I and III (1971-1974 and 1988-1994). J Clin Endocrinol Metab 83(10):3401-3408.

*Hooper H, McDonald TA. 2000. The PBDEs: an emerging environmental challenge and another reason for breast-milk monitoring programs. Environ Health Perspect 108(5):387-392.

9. REFERENCES

*Hoque A, Sigurdson AJ, Burau KD, et al. 1998. Cancer among a Michigan cohort exposed to polybrominated biphenyls in 1973. Epidemiology 9(4):373-378.

*Hori S, Akutsu K, Kitagawa M, et al. 2000. Development of analysis for polybrominated diphenyl ether in seafood and actual contamination of seafood. Organohalogen Compounds 47:214-217.

*Howard SK, Werner PR, Sleight SD. 1980. Polybrominated biphenyl toxicosis in swine: Effects on some aspects of the immune system in lactating sows and their offspring. Toxicol Appl Pharmacol 55:146-153.

*Howie L, Dickerson R, Davis D, et al. 1990. Immunosuppressive and monooxygenase induction activities of polychlorinated diphenyl ether congerers in C57BL/6N mice: quantitive structure-activity relationships. Toxicol Appl Pharmacol 105:254-263.

*HSDB. 2002a. Hazardous Substances Data Bank. http://toxnet.nlm.nih.gov/cgi-bin/sis/search. April 18, 2002.

*HSDB. 2002b. Hazardous Substances Data Bank. http://toxnet.nlm.nih.gov/cgi-bin/sis/search. June 24, 2002.

HSDB. 2002c. Hazerdous Substances Data Bank. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

Huber S, Ballschmiter K. 2001. Characterization of five technical mixtures of brominated flame retardants. Fresenius J Anal Chem 371(6):882-890.

*Hughs MF, Edwards BC, Mitchell CT, et al. 2001. In vitro dermal absorption of flame retardant chemicals. Food Chem Toxicol 39(12):1263-1270.

*Humble CG, Speizer FE. 1984. Polybrominated biphenyls and fetal mortality in Michigan. Am J Public Health 74(10):1130-1132.

*Humphrey HE, Hayner NS. 1975. Polybrominated biphenyls: An agricultural incident and its consequences. II. An epideiological investigation of human exposure. In: Proceedings of the 9th Trace Substances in Environmental Health Annual Conference, Columbia, MO, April 12-23, 1975. University of Missouri, Columbia, MO, 57-63.

IARC. 1978. IARC monographs on the evaluation of carcinogenic risks humans. Vol. 18: Polychlorinated biphenyls and polybrominated biphenyls. World Health Organization, Lyon, France, 108-125.

*IARC. 1986. IARC monographs of the evaluation of carcinogenic risks humans. Vol. 41: Some halogenated hydrocarbons and pesticide exposures. World Health Organization, Lyon, France, 261-292.

*IARC. 1987. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 1-42: Polybrominated Biphenyls (Group 2B) Overall evaluations of carcinogenicity: An updating of IARC monographs. World Helath Organization, Lyon, France, 321-322.

IARC. 1990. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 48: Decabromodiphenyl oxide. World Health Organization, Lyon, France, 73-84.

*Ikonomou MG, Crewe N, He T, et al. 1999. Polybrominated-diphenyl-ether in biota samples from coastal British Columbia, Canada. Organohalogen Compounds 40:341-345.

*Ikonomou MG, Fisher M, He T, et al. 2000. Congener patterns, spatial and temporal trends of polybrominated diphenyl ethers in biota samples from the Canadian west coast and the northwest territories. Organohalogen Compounds 47:77-80.

*IRCD. 1974. Decabromodiphenyl ether. Acute toxicity studies in rats and rabbits. International Research and Development Corporation. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0523319.

*IRDC. 1975a. Octabromodiphenyl ether. Acute toxicity studies in rats and rabbits. International Research and Development Corporation. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS052222968.

*IRDC. 1975b Pentabromodiphenyl ether. Acute toxicity studies in rats and rabbits. International Research and Development Corporation. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0522286.

*IRDC. 1976. Decabromodiphenyl ether and octabromodiphenyl ether. A twenty-eight day toxicity study in rats. International Research and Development Corporation. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0523322.

*IRDC. 1977. Octabromodiphenyl ether. Thirteen week feeding study in rats. International Research and Development Corporation. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0522297.

*IRDC. 1978. Octabromodiphenyl ether. Subacute inhalation toxicity study in rats. International Research and Development Corporation. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0522293.

*IRIS. 2002. Integrated Risk Information System. http://www.epa.gov/iris. April 18, 2002.

Jackson TF, Halbert FL. 1974. A toxic syndrome associated with the feeding of polybrominated biphenyl-contaminated protein concentrate to dairy cattle. J Am Vet Med Assoc 165:437-439.

Jackson MA, Stack HF, Waters MD. 1993. The genetic toxicology of putative nongenotoxic carcinogens. Mutat Res 296(3):241-277.

*Jacobs LW, Chou SF, Tiedje JM. 1976. Fate of polybrominated biphenyls (PBBs) in soils: Persistence and plant uptake. J Agric Food Chem 24:1198-1201.

*Jacobs LW, Chou SF, Tiedje JM. 1978. Field concentrations and persistence of polybrominated biphenyls in soils and solubility of PBB in natural waters. Environ Health Perspect 23:1-8.

Jacobs MN, Lewis DFV. 1999. A QSAR study of organochlorine and isoflavenoid compounds ligand binding affinity to the human oestrgen receptor α. Organohalogen Compounds 41:517-520.

Jacobson JL, Fein GG, Jacobson SW, et al. 1984. The transfer of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) across the human placenta and into maternal milk. Am J Public Health 74(4):378-379.

Jacobson JL, Humphrey HEB, Jacobson SW, et al. 1989. Determinants of polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and dichlorodiphenyl trichloroethane (DDT) levels in the sera of young children. Am J Public Health 79:1401-1404.

*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(2):156-162.

Jakobsson K, Thuresson K, Rylander L, et al. 2002. Exposure to polybrominated diphenyl ethers and tetrabromobisphenol A among computer technicians. Chemosphere 46(5):709-716.

*Jansson B, Asplund L. 1987. Brominated flame retardants-ubiquitous environmental pollutants? Chemosphere 16(10-12):2343-2349.

*Jansson B, Andersson R, Asplund L, et al. 1991. Multiresidue method for the gas-chromatographic analysis of some polychlorinated and polybrominated polutants in biological samples. Fresenius Z Anal Chem 340:439-445.

*Jansson B, Andersson R, Asplund L, et al. 1993. Chlorinated and brominated persistant organic compounds in biological samples from the environment. Environ Toxicol Chem 12(7):1163-1174.

*Jaret P. 2000. Health concerns: Defense systems under fire. 38(6):36-41.

*Jensen RK, Sleight S. 1986. Sequential study on the synergistic effects of 2,2',4,4',5,5'-hexa-bromobiphenyl and 3,3',4,4',5,5'-hexabromobiphenyl on hepatic tumor promotion. Carcinogenesis 7:1771-1774.

Jensen RK, Zile MH. 1988. Effect of dietary retinoic acid on circulatory vitamin A homeostasis in polybrominated biphenyl-treated rats. J Nutr 118:416-419.

*Jensen RK, Sleight SD, Aust SD, et al. 1983. Hepatic tumor-promoting ability of 3,3',4,4',5,5'-hexabromobiphenyl: The interrelationships between toxicity, induction of hepatic microsomal drug metabolizing enzymes, and tumor-promoting ability. Toxicol Appl Pharmacol 71:163-176.

*Jensen RK, Sleight SD, Aust SD. 1984. Effect of varying the length of exposure to polybrominated biphenyls on the development of gamma-glutamyl transpetidase enzyme-alterd foci. Carcinogenesis 5:63-66.

*Jensen RK, Sleight SD, Goodman JI, et al. 1982. Polybrominated biphenyls as promoters in experimental hepatocarcinogenesis in rats. Carcinogenesis 3:1183-1186.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johansson M, Larsson C, Bergman A, et al. 1998. Structure-activity relationship for inhibition of CYP11B1-dependent glucocorticoid synthesis in Y1 cells by aryl methyl sulfones. Pharmacol Toxicol (Amsterdam) 83:225-230.

Johnson A, Olson N. 2001. Analysis and occurence of polybrominated diphenyl ethers in Washington state freshwater fish. Arch Environ Contam Toxicol 41(3):339-344.

Johnston CA, Demarest KT, McCormack KM, et al. 1980. Endocrinological, neurochemical, and anabolic effects of polybrominated biphenyls in male and female rats. Toxicol Appl Pharmacol 56:240-247.

Jones KC, Alcock RE, Kalatzi OI, et al. 2001. Environmental measurements and the global distribution of PBDE's. BFR:163-166.

Juchau MR. 1993. Chemical teratogenesis. Prog Drug Res 41:9-50.

Kaiser R, Marcus M, Michels Blanck H, et al. 2001. PBB exposure and benign breast disease in a cohort of U.S. women. Am J Epidemiol 153:S266.

*Kaiser TE, Reichel WL, Locke LN, et al. 1980. Organochloride pesticide, PCB, and PBB residues and necropsy data for bald eagles from 29 states-1975-77. Pestic Monit J 13(4):145-149.

Kang K-S, Wilson MR, Hayashi T, et al. 1996. Inhibition of gap junction intercellular communication in normal human breast epithelial cells after treatment with pesticides, PCBs, and PBBs, alone or in mixtures. Environ Health Perspect 104(2):192-200.

*Kasza L, Collins WT, Capen CC, et al. 1978a. Comparative toxicity of polychlorinated biphenyl and ploybrominated biphenyl in the rat thyroid gland: Light and electron microscope alterations after subacute dietary exposure. J Environ Pathol Toxicol 1:587-599.

Kasza L, Weinberger MA, Hinton DE, et al. 1978b. Comparative toxicity of polychlorinated biphenyl and polybrominated biphenyl in the rat liver: Light and electron microscopic alterations after subacute dietary exposure. J Environ Pathol Toxicol 1:241-257.

*Kateley JR, Insalaco R, Codere S, et al. 1982. Host defense systems in cattle exposed to polybrominated biphenyl. Am J Vet Res 43(7):1288-1295.

Kato Y, Yumoto S, Nagano Y, et al. 2000. 3-Methylsulfonyl-2,2',4',5-tetrabromobiphenyl, a metabolite of 2,2',4',5-tetrabromodiphenyl induces CYP2B1/2 in rats. Organohalogen Compounds 49:209-212.

*Kavanagh TJ, Rubinstein C, Liu PL, et al. 1985. Failure to induce mutations in Chinese hamster V79 cells and WB rat liver cells by polybrominated biphenyls, Firemaster BP-6, 2,2',4,4',5,5'-hexa-bromobiphenyl ,3,3',4,4',5,5'-hexabromobiphenyl, and 3,3',4,4'-tetrabromobiphenyl. Toxicol Appl Pharmacol 79:91-98.

Kawakami I, Sase E, Yagi Y, et al. 2000. Dioxin-like compounds from an incineration plant of normal municipal solid waste. Organohalogen Compounds 46:197-200.

*Kawasaki M. 1980. Experiences with the test scheme under the chemical control law of Japan: An approach to structure-activity correlations. Ecotoxicol Environ Saf 4:444-454.

*Kay K. 1977. Polybrominated biphenyls (PBB) environmental contamination in Michigan, 1973-1976. Environ Res 13:74-93.

Kholkute SD, Rodriguez J, Dukelow WR. 1994. The effects of polybrominated biphenyls and perchlorinated terphenyls on in vitro fertilization in the mouse. Arch Environ Contam Toxicol 26(2):208-211.

*Kierkegaard A, Balk L, Tiarnlund U, et al. 1999. Dietary uptake and biological effects on decabromodiphenyl ether in rainbow trout (*Oncorhynchus mykiss*). Environ Sci Technol 33:1612-1617.

*Kimbrough R, Buckley J, Fishbein L, et al. 1978a. Animal toxicology. Environ Health Perspect 24:173-184.

*Kimbrough RD. 1987. Human health effects of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). Annu Rev Pharmacol Toxicol 27:87-111.

*Kimbrough RD, Burse VW, Liddle JA. 1978b. Persistent liver lesions in rats after a single oral dose of polybromiated biphenyls (FireMaster FF-1) and contaminant PBB tissue levels. Environ Health Perspect 23:265-273.

*Kimbrough RD, Groce DF, Korver MP, et al. 1981. Induction of liver tumors in female Sherman strain rats by polybrominated biphenyls. J Natl Cancer Inst 66(3):535-542.

*Kimbrough RD, Korver MP, Burse VW, et al. 1980. The effect of different diets or mineral oil on liver pathology and polybrominated biphenyl concentration in tissues. Toxicol Appl Pharmacol 52:442-453.

Kitchin KT, Brown JL. 1994. Dose-response relationship for rat liver DNA damage caused by 49 rodent carcinogens. Toxicology 88:31-49.

Kitchin KT, Brown JL, Kulkarni AP, et al. 1993. Predicting rodent carcinogenicity of halogenated hydrocarbons by in vivo biochemical parameters. Teratog Carcinog Mutagen 13(4):167-184.

*Klasson-Wehler EK, Hovander L, Bergman A. 1997. New organohalogen in human plasma-Identification and quantification. Organohalogen Compounds 33:420-425.

*Kluwe WM, Hook JB. 1978. Polybrominated biphenyl-induced potentiation of chloroform toxicity. Toxicol Appl Pharmacol 45:861-869.

*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.

*Kluwe WM, Hook JB, Berstein J. 1982. Synergistic toxicity of carbon tetrachloride and several aromatic organohalide compounds. Toxicology 23:321-336.

*Kluwe WM, McCormack KM, Hook JB. 1978. Potentiating of hepatic and renal toxicity of various compounds by prior exposure to polybrominated biphenyls. Environ Health Perspect 23:241-246.

Kluwe WM, McNish R, Smithson K, et al. 1981. Depletion by 1,2-dibromoethane, 1,2-dibromo-3-chloropropane, tris(2,3-dibromopropyl)phosphate, and hexachloro-1,3-butadiene of reduced nonprotein sulfhydryl groups in target and nontarget organs. Biochem Pharmacol 30:2265-2271.

*Kociba RJ, Frauson LO, Humiston CG, et al. 1975. Results of a two-year dietary feeding study with decabromodiphenyl oxide (DBDPO) in rats. J Combust Toxicol 2(4):267-285.

Kodavanti PRS, Ward TR, Derr-Yellin EC, et al. 1998. Congener-specific distribution of polychlorinated biphenyls in brain regions, blood, liver, and fat of adult rats following repeated exposure to Aroclor 1254. Toxicol Appl Pharmacol 153:199-210.

*Kohli J, Safe S. 1976. The metabolism of brominated aromatic compounds. Chemosphere 6(6):433-437.

*Kohli J, Wyndham C, Smylie M, et al. 1978. Metabolism of bromobiphenyls. Biochem Pharmacol 27:1245-1249.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29:4430-4433.

*Kong HL, Sayler GS. 1983. Degradation and total mineralization of monohalogenated biphenyls in natural sediment and mixed bacterial culture. Appl Environ Microbiol 46(3):666-672.

*Kong HL, Sayler GS. 1984. Microbial degradation and mineralization of brominated biphenyls and brominated benzoates. In: Proceedings of the 84th American Society for Microbiology Annual Meeting, St. Louis, MO, March 4-9 [Abstract Q76]. American Society for Microbiology, Washington, DC, 217.

Koss G, Weider T, Seubert S, et al. 1994. 2,2' 4,4', 5,5'-Hexabromobiphenyl: Its toxicokinetics, biotransformation and porphyrinogenic action in rats. Food Chem Toxicol 32(7):605-610.

Koster P, Debets FMH, Strik JJTWA. 1980. Porphyrinogenic action of fire retardants. Bull Environ Contam Toxicol 25(2):313-315.

*Kotake AN, Schoeller DA, Lambert GH, et al. 1982. The caffeine CO_2 breath test: Dose response and route of N-demethylation in smokers and nonsmokers. Clin Pharmacol Ther 32:261-269.

*Kraus AL, Bernstein IA. 1986. Influence of adipocyte triglyceride on the partition of 2,2',4,4',5,5'-hexabromobiphenyl between 3T2L1 adipocytes and surrounding pseudoblood. J Toxicol Environ Health 19:541-554.

*Kreiss K, Roberts C, Humphrey HEB. 1982. Serial PBB levels, PCB levels, and clinical chemistries in Michigan's PBB cohort. Arch Environ Health 37(3):141-146.

Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. 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 RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Kristofferson A, Voie AOA, Funnum F. 2002. Ortho-substituted polybrominated biphenyls activate resiratory burst in granulocytes from humans. Toxicol Lett 24(1-2):161-166.

*Ku PK, Hogberg MG, Trapp AL, et al. 1978. Polybrominated biphenyl (PBB) in the growing pig diet. Environ Health Perspect 23:13-18.

*Kubiczak GA, Oesch F, Borlakoglu JT, et al. 1989. A unique approach to the synthesis of 2,3,4,5-substituted polybrominated biphenyls: Quantitation in FireMaster FF-1 and FireMaster BP-6. J Agric Food Chem 37:1160-1164.

*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. Arch Environ Contam Toxicol 28(4):494-499.

*Kuehl DW, Haebler R, Potter C. 1991. Chemical residues in dolphins from the U.S. Atlantic coast including Atlantic bottlenose obtained during the 1987/88 mass mortality. Chemosphere 22(11):1071-1984.

*Kuo C-H, Hook JB. 1982. Effects of drug-metabolizing enzyme inducers on cephaloridine toxicity in Fischer 344 rats. Toxicology 24:293-303.

*Kuosmanen K, Hyotylainen T, Hartonen K, et al. 2002. Pressurized hot water extraction coupled on-line with liquid chromatography-gas chromatography for the determination of brominated flame retardants in sediment samples. J Chromatogr A 943(1):113-122.

La Guardia MJ, Hale RC, Harvey E, et al. 2000. Endocrine disruptors (octylphenol, nonylphenol, nonyl phenol ethoxylates and polybrominated diphenyl ethers) in land applied sewage sludge biosolids. In: Preprints of extended abstracts. American Chemical Society, Division of Envrionmental Chemistry. 220th ACS National Meeting, Washington, DC. Vol 40(2):97-99.

*LaKind JS, Berlin CM. 2000. PBDEs in breast milk: where do we go from here? Organohalogen Compounds 47:241-244.

Lambert GH, Hsu CC, Humphrey H. 1992a. Cytochrome P450IA2 in vivo induction: a potential biomaker of polyhalogenated biphenyls and their related chemical's effects on the human. Chemosphere 25(1-2):197-200.

*Lambert GH, Schoeller DA, Hsu CC, et al. 1992b. Cytochrome P4501A2 activity in humans exposed to PCBs and dioxins. Organohalogen Compounds 10:32-35.

*Lambert GH, Schoeller DA, Humphrey HEB, et al. 1990. The caffeine breath test and caffeine urinary metabolite ratios in the Michigan cohort exposed to polybrominated biphenyls: A preliminary study. Environ Health Perspect 89:175-181.

*Lambrecht LK, Barsotti DA, Allen JR. 1978. Response of nonhuman primates to a polybrominated biphenyl mixture. Environ Health Perspect 23:139-145.

Lamesh RA. 1992. Polychlorinated biphenyls: An overview of metabolic toxicologic and health consequences. Vet Hum Toxicol 34:256-260.

*Landrigan PJ, Wilcox KR, Silva J. 1979. Cohort study of Michigan residents exposed to polybrominated biphenyls: Epidemiologic and immunologic findings. Ann NY Acad Sci 320:284-294.

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.

Law RJ, Allchin CR. 2001. Brominated flame retardants in the UK environment. BFR:139-141.

*Law RJ, Allchin CR, Bennett ME, et al. 2000. Polybrominated diphenyl ethers in the blubber of harbour porpoises (*Phocoena phocoena L.*) stranded on the coasts of England and Wales. Organohalogen Compounds 47:249-252.

LeBoeuf RA, Kerchaert GA, Aardema MJ, et al. 1996. The pH 6.7 Syrian hamster embryo cell transformation assay for assessing the carcinogenic potential of chemicals. Mutat Res 356:85-127.

*Lee KP, Hebert RR, Sherman H, et al. 1975a. Bromine tissue residue and hepatotoxic effects of octabromobiphenyl in rats. Toxicol Appl Pharmacol 34:115-127.

*Lee KP, Hebert RR, Sherman H, et al. 1975b. Octabromobiphenyl-induced ultrastructural changes in rat liver. Arch Environ Health 30:465-471.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

*Lemesh KA. 1992. Polychlorinated biphenyls: An overview of metabolic toxicologic and health consequences. Vet Hum Toxicol 34:256-268.

*Lenior D, Zier B, Bieniek D, et al. 1994. The influenece of water and metals on PBDD/F concentration in incineration of decabromobiphenyl ether in polymeric matrices. Chemosphere 28(11):1921-1928.

Leonards PEG, Santillp D, Bridgen K, et al. 2001. Brominated flame retardants in office dust samples. BFR:299-302.

Leung H-W. 1991. Development and utilization of physiologically based pharmacokinetic models for toxicological applications. J Toxicol Environ Health 32:247-267.

*Leung H-W. 1993. Physiologically-based pharmacokinetic modeling. In: Ballentine B, Marro T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164

*Lewis RG, Sovocool GW. 1982. Identification of polybrominated biphenyls in the adipose tissues of the general population of the United States. J Anal Toxicol 6:196-198.

*Life Sciences Research Israel LTD. 1987. FR-1208: Teratology study in the rat. Submitted to U.S. EPA under TSCA Section 4/8, Fiche no. OTS0513908.

Lind Y, Atuma S, Aune M, et al. 2001. Polybrominated diphenyl ethers (PBDEs) in breast milk from Uppsala woman- extension and up-dating of data. BFR:117-120.

*Lindstroem G, Hardell L, Van Bavel B, et al. 1998. Current level of 2,2'4,4'-tetrabrominated diphenyl ether in human adipose tissue in Sweden. A risk factor for non-Hodgkin's lymphoma? Organohalogen Compounds 35:431-434.

*Lindstom GUM. 1999. Aspects of polybrominated diphenyl ethers as indoor, occupational, and environmental pollutants. Organohalogen Compounds 43:445-446.

Lindstrom G, Van Bavel B, Hardell L, et al. 1997. Identification of the flame retardants polybrominated diphenyl ethers in adipose tissue from patients with non-Hodgkin's lymphoma in Sweden. Oncol Rep 4:999-1000.

*Lindstrom G, Wingfors H, Dam M, et al. 1999. Identification of 19 polybrominated diphenyl ethers (PBDEs) in long-finned pilot whale (*Globicephala melas*) from the Atlantic. Arch Environ Contam Toxicol 36(3):355-363.

*Livingston AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

*Loganathan BG, Kannn K, Watanabe, et al. 1995. Isomer-specific determination and toxic evaluation of polychlrinated 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.

*Loose LD, Mudzinski SP, Silkworth JB. 1981. Influence of dietary polybrominated biphenyl on antibody and host defense responses in mice. Toxicol Appl Pharmacol 59:25-39.

Lopes TJ, Furlong T, Edward T. 2001. Occurrence and potential adverse effects of semivolatile organic compounds in streambed sediment, United States, 1992-1995. Environ Toxicol Chem 20(4):727-737.

*Luckey F, Fowler B, Litten S. 2001. Establishing baseline levels of polybrominated diphenyl ethers in Lake Ontario surface waters. BFR:337-339.

*Luijk R, Govers HAJ. 1992. The formation of polybrominated dibenzo-p-dioxins (PBDDs) and dibenzofurans (PBDFs) during pyrolysis of polymer blends containing brominated flame retardants. Chemosphere 25(3):361-374.

Luross JM, Alaee M, Cannon CM, et al. 2001. Spatial and temporal distribution of poybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Great Lakes. BFR:401-404.

*Luross JM, Aalee M, Sergeant DB, et al. 2000. Spatial and temporal distribution of polybrominated diphenyl ethers in lake trout from the great lakes. Organohalogen Compounds 47:73-76.

*Luster MI, Boorman GA, Harris MW, et al. 1980. Laboratory studies on polybrominated biphenyl-induced immune alterations following low-level chronic or pre/postnatal exposure. Int J Immunopharmacol 2:69-80.

*Luster MI, Faith RE, Moore JA. 1978. Effects of polybrominated biphenyls (PBB) on immune response in rodents. Environ Health Perspect 23:227-232.

Lutes CC, Charles MJ, Odum JR, et al. 1992. Chamber aging studies on the atmospheric stability of polybrominated dibenzo-p-dioxins and dibenzofurans. Environ Sci Technol 26(5):991-998.

*Lyman WJ, Reehl WF, Rosenblatt, DH. 1990. Handbook of chemical properties estimation methods. American Chemical Society: Washington, DC, 4-9, 15-1 to 15-29.

Mackay D. 1982. Correlation of bioconcentration factors. Environ Sci Technol 16:274-278.

Madra S, Smith AG. 1992. Induction of cytochrome F450 activities by polychlorinated biphenyls in isolated mouse hepatocytes. Influence of Ah-phenotype and iron. Biochem Pharmacol 44(3):455-464.

Mamantov A. 1985. The photolysis of polychlorinated diphenyl ethers and chloroanisoles may proceed via carbenes. Chemosphere 14(6/7):905-908.

Manchester-Neesvig JB, Valters K, Sonzogni WC. 2001. Comparison of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBS) in Lake Michigan salmonids. Environ Sci Technol 35(6):1072-1077.

*Marsh G, Bergman A, Bladh L-G, et al. 1998. Synthesis of p-hydroxybromodiphenyl ethers and binding to the thyroid receptor. Organohalogen Compounds 37:305-308.

Marsh G, Hu J, Jakobsson E, et al. 1999. Synthesis and characterization of 21-polybrominated diphenyl ethers. Environ Sci Technol 33(17):3033-3037.

MARSSIM. 1997. Multi-agency radiation survey and site investigation manual. Nuclear Regulatory Commission, Energy Department, Environmental Protection Agency, and Defense Department. 660p. NUREG 1575, EPA 402 R 97 016.

*Martino LJ, Wilson-Martino NA, Benitz KF. 1981. The presence of intranuclear lipid inclusions in hepatocytes of mice after chronic ingestion of polybrominated biphenyl. Arch Toxicol 47:155-158.

Matthews EJ, Spalding JW, Tennant RW. 1993. Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in salmonella and carcinogenciity in rodent bioassays. Environ Health Perspect Suppl 101:347-482.

*Matthews HB, Kato S, Morales NM, et al. 1977a. Distribution and excretion of 2,4,5,2',4',5'-hexabromobiphenyl, the major component of Firemaster BP-6. J Toxicol Environ Health 3:599-605.

Mathews HB, Tuey DB, Anderson MW. 1977b. Pharmacokinetic models for lipiphilic compounds. Environ Health Perspect 20:257-262.

*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.

*McConnell EE, Harris MW, Moore JA. 1980. Studies on the use of activated charcoal and cholestyramine for reducing the body burden of polybrominated biphenyls. Drug Chem Toxicol 3:277-292.

*McCormack KM, Hook JB. 1982. Effects of lactation and nursing on tissue concentrations of polybrominated biphenyls and on microsomal enzyme activity in mammary gland and liver in maternal rats. Environ Res 27:110-117.

McCormack KM, Arneric SP, Hook JB. 1979. Action of exogenously administered steroid hormones following perinatal exposure to polybrominated biphenyls. J Toxicol Environ Health 5:1085-1094.

*McCormack KM, Kluwe WM, Rickert DE, et al. 1978. Renal and hepatic microsomal enzyme stimulation and renal function following three months of dietary exposure to polybrominated biphenyls. Toxicol Appl Pharmacol 44:539-553.

*McCormack KM, Lepper LF, Wilson DM, et al. 1981. Biochemical and physiological sequelea to perinatal exposure to polybrominated biphenyls: A multigeneration study in rats. Toxicol Appl Pharmacol 59:300-313.

McCormack KM, Roth RA, Wallace KB, et al. 1982a. Nonrespiratory metabolic function and morphology of lung following exposure to polybrominated biphenyls in rats. J Toxicol Environ Health 9:27-39.

*McCormack KM, Stickney JL, Bonhaus DW, et al. 1982b. Cardiac and hepatic effects of pre-and postnatal exposure to polybrominated biphenyls in rats. J Toxicol Environ Health 9:13-26.

*McDonald TA. 2002. A perspective on the potential health risks of PBDEs. Chemosphere 46(5):745-755.

McGregor DB, Brown A, Cattanach P, et al. 1988. Responses of the L5178Y tk+/tk$^-$ mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagen 12(1):85-154.

*MDCH. 2002. http://www.michigan.gov.mdch. May 30, 2002.

Meerts I, Lujiks E, Marsh G, et al. 1988. Polybrominated diphenylethers (PBDEs) as Ah-receptor agonists and antagonists. Organohalogen Compounds 37:147-150.

*Meerts I, Marsh G, van Leeuwen-Bol I, et al. 1998. Interaction of polybrominated diphenyl ether metabolites (PBDE-OH) with human transthyretin *in vitro*. Organohalogen Compounds 37:309-312.

*Meerts IA, Letcher RJ, Hoving S, et al. 2001. In vitro estogenicity of polybrominated diphenyl ethers, hydroxlated PDBEs and polybrominated bisphenol A compounds. Environ Health Perspect 109(4):399-407.

Meerts IA, van Zanden JJ, Luijks EA, et al. 2000. Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin in vitro. Toxicol Sci 56(1):95-104.

Meironyte Guvenius DM, Bergman A, Noren K. 1998. Analysis of polybrominated diphenyl ethers in human milk. Organohalogen Compounds 35:387-390.

*Meironyte Guvenius DM, Bergman A, Noren K. 2001. Polybrominated diphenyl ethers in Swedish human liver and adipose tissue. Arch Environ Contam Toxicol 40:564-570.

*Meironyte Guvenius DM, Noren K, Bergman A. 1999a. Analysis of polybrominated diphenyl ethers in Swedish human milk. A time related trend study, 1972-1997. J Toxicol Environ Health A 58(6):329-341.

*Meironyte Guvenius DM, Noren K, Bergman A. 1999b. Analysis of polybrominated diphenyl ethers in Swedish human milk. A time-released trend study, 1972-1997. J Toxicol Environ Health A 58(6):1528-7394.

*Meironyte-Guvenius DM, Noren K. 1999c. Polybrominated diphenyl ethers in human liver and adipose tissues. A pilot study. Organohalogen Compounds 40:372-382.

*Meneses M, Wingfors H, Schuhmacher M, et al. 1999. Polybrominated diphenyl ethers detected in human adipose tissue from Spain. Chemosphere 39(13):2271-2278.

Mennear JH, Lee C-C. 1994. Polybrominated dibenzo-p-dioxins and dibenzofurans: literature review and health assessment. Environ Health Perspect Suppl 102:265-274.

*Mercer HD, Teske RJ, Condon A, et al. 1976. Herd health status of animals exposed to polybrominated biphenyls (PBB). J Toxicol Environ Health 2:335-349.

Merrill JC, Beck DJ, Kaminski DA, et al. 1995. Polybrominated biphenyl of cytochrome P450 mixed function oxidase activity in primary rat and human heptocytes. Toxicology 33:147-153.

*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):712-720.

*Meylan WM, Howard PH. 1991. Bond contribution methods for estimating Henry's Law Constants. Environ Toxicol Chem 10:1283-1293.

*Miceli JN, Marks BH. 1981. Tissue distribution and elimination kinetics of polybrominated biphenyls (PBB) from rat tissue. Toxicol Lett 9:315-320.

*Miceli JN, Nolan DC, Marks B, et al. 1985. Persistence of polybrominated biphenyls (PBB) in human post-mortem tissue. Environ Health Perspect 60:399-403.

*Michels Blanck HM, Marcus M, Hertzberg V, et al. 2000a. Determinants of polybromated biphenyl serum decay among women in the Michigan PBB cohort. Environ Health Perspect 108(2):147-152.

*Michels Blanck H, Marcus M, Rubin C, et al. 2000b. Growth in girls exposed perinatally to polybrominated biphenyls and polychlorinated biphenyls. Am J Epidemiol 151(11):S23.

Michels Blanck H, Marcus M, Tolbert PE, et al. 1999. Age at menarche in girls exposed perinatally to polybrominated biphenyl. Am J Epidemiol 149:S21.

*Microbiological Associates Inc. 1996. Pentabromodiphenyloxide and octabromodiphenyl oxide. Maximization test in Guinea Pigs. Submitted to U.S. EPA under TSCA Section FYI, Fiche no. OTS0001281.

*Millis CD, Mills RA, Sleight SD, et al. 1985. Toxicity of 3,4,5,3',4', 5'-hexabrominated biphenyl and 3,4,3',4'-tetrabrominated biphenyl. Toxicol Appl Pharmacol 78:88-95.

*Millischer R, Girault F, Heywood R, et al. 1980. Decabromobiphenyl: Toxicologic study. Toxicol Eur Res 2:155-161.

Mills RA, Millis CD, Dannan GA, et al. 1985. Studies on the structure-activity relationships for the metabolism of polybrominated biphenyls by rat liver microsomes. Toxicol Appl Pharmacol 78:96-104.

*Mirsalis JC, Tyson CK, Loh EN, et al. 1985. Induction of hepatic cell proliferation and unscheduled DNA synthesis in mouse hepatocytes following in vivo treatment. Carcinogenesis 6:1521-1524.

*Mirsalis JC, Tyson CK, Steinmetz KL, et al. 1989. Measurement of unscheduled DNA synthesis and s-phase sythesis in rodent hepatocytes following in vivo treatment: Testing of 24 compounds. Environ Mol Mutagen 14:155-164.

Moisey J, Simon M, Wakeford B, et al. 2001. Spatial and temporal trends of polybrominated diphenyl ethers detected in Great Lakes Herring Gulls, 1981 to 2000. BFR:153-157.

*Moore RW, Dannan GA, Aust SD. 1978. Induction of drug metabolizing enzymes in polybrominated biphenyl-fed lactating rats and their pups. Environ Health Perspect 23:159-165.

*Moore RW, Sleight SD, Aust SD. 1979. Effects of 2,2'-dibromobiphenyl and 2,2',3,4,4',5,5'-heptabromobiphenyl on liver microsomal drug metabolizing enzymes. Toxicol Appl Pharmacol 48:73-86.

*Moorhead PD, Willett LB, Brumm CJ, et al. 1977. Pathology of experimentally induced polybrominated biphenyl toxicosis in pregnant heifers. J Am Vet Med Assoc 170:307-313.

Morck A, Klasson Wehler E. 2001. Metabolism of decabromodiphenyl ether (BDE-209) in the rat. Organohalogen Compounds 52:9-12.

*Morreale de Escobar G, Obregon MJ, Escobar del Rey F. 2000. Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? J Clin Endocrinol Metab 85(11):3975-3987.

*Morris PJ, Quensen JF, Tiedje JM, et al. 1992. Reprodctive debromination of the commercial polybrominated biphenyl mixture Firemaster BP6 by anaerobic microorganisms from sediments. Appl Environ Microbiol 58(10):3249-3256.

*Morris PJ, Quensen JF III, Tiedje JM, et al. 1993. An assessment of the reduction debromination of polybrominated biphenyls in the Pine River Reservoir. Environ Sci Technol 27(8):1580-1586.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:485-527.

*Mulligan KJ, Caruso JA. 1980. Determination of polybrominated biphenyl and related compounds by gas - liquid chromatography with a plasma emission detector. Analyst 105:1060-1067.

*Murata T, Zabik ME, Zabik MY. 1977. Polybrominated biphenyls in raw milk and processed dairy products. J Dairy Sci 60(4):516-520.

Myhr B, McGregor D, Bowers L, et al. 1990. L5178Y Mouse lymphoma cell mutation assay results with 41 compounds. Environ Mol Mutagen 16:138-167.

*Myhr BC, Caspary WJ. 1991. Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: Results for 31 coded compounds in the National Toxicology Program. Environ Mol Mutagen 18:51-83.

Nagayama J, Takasuga T, Tsuji H. 2001. Contamination levels of brominated flame retardants, dioxins and organochlorine compounds in the blood of Japanese adults. BFR:113-116.

*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.

NATICH. 1988. NATICH data base report on state, local and EPA air toxics activities. Research Triangle Park, NC: National Air Toxics Information Clearinghouse, U.S. Environmental Protection Agency.

*National Safety Council. 1999. Baseline report: Recycling of selected electronic products in the United States. Washington, DC: National Safety Council 1-47.

*Needham LL, Hill RH, Orti DL, et al. 1982. Investigation of hyperkeratotic activity of polybrominated biphenyls in Firemaster FF-1. J Toxicol Environ Health 9:877-887.

Nemec M, Holsen J, Naas D, et al. 1992. The developmental toxicity of FM-100 in the rat and rabbit following repeated exposure by inhalation. Teratology 45(5):475-476.

*Neufeld ML, Sittenfield M, Wolk KF. 1977. Market input/output studies: Task IV. Polybrominated biphenyls. Washington, DC. EPA-560/6-77-017.

*Noren K, Meironyte D. 1998. Contaminants in Swedish human milk. Decreasing levels of organochlorine and increasing levels of organochlorine compounds. Organohalogen Compounds 38:1-4.

*Noren K, Meironyte D. 2000. Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20-30 years. Chemosphere 40:1111-1123.

NIES/EPA. 2002. Superfund Basic Research Program. Current research programs. http://benson.niehs.nih/sbrp/Program2000/program00.cfm.

*Norris JM, Ehrmantraut JW, Gibbons CL, et al. 1973. Toxicological and environmental factors involved in the selection of decabromodiphenyl oxide as a fire retardant chemical. Appl Polym Symp 22:195-219.

*Norris JM, Ehrmantraut JW, Kociba RJ, et al. 1975a. Evaluation of decabromodiphenyl oxide as a flame-retardant chemical. Chem Hum Health Environ 1:100-116.

*Norris JM, Kociba RJ, Humiston CG, et al. 1975b. The toxicity of decambromo diphenyl and octabromo biphenyl as determined by subacute and chronic dietary feeding studies in rats. Toxicol Appl Pharmacol 33:170.

*Norris JM, Kociba RJ, Schwetz BA, et al. 1975c. Toxicology of octabromobiphenyl and decabromodiphenyl oxide. Environ Health Perspect 11:153-161.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

NRC. 2000. Decabromodiphenyl oxide. In: Toxicological risks of selected flame-retardant chemicals. National Research Council (US): Subcommittee on Flame-Retardant Chemicals. Washington, DC: National Academy Press, 72-98.

*NTP. 1983. NTP technical report on the toxicology and carcinogenesis studies of a polybrominated biphenyl mixture (Firemaster FF-1) (CAS NO. 67774-32-7) in F344/N rats and B6C3F1 mice (gavage studies): Research Triangle Park, NC: National Toxicology Program.

*NTP. 1986. NTP technical report on the toxicology and carcinogenesis studies of decabromodiphenyl oxide (CAS NO. 1163-19-5) in F344/N rats and B6C3F1 mice (feed studies): Research Triangle Park, NC: National Toxicology Program.

*NTP. 1992. NTP technical report on the perinatal toxicology and carciogenesis studies of polybrominated biphenyls (Firemaster FF-1) (CAS NO. 67774-32-7) in F344/N rats and B6C3F1 mice (feed studies): Research Triangle Park, NC: National Toxicology Program.

*NTP. 2002. Names and synonyms of carcinogens. National Toxicology Program. http://ntp-server.niehs.nih.gov/htdocs/8_RoC/RAHC_list.html. April 18, 2002.

*Nylund K, Asplund L, Jansson B, et al. 1992. Analysis of some polyhalogenated organic pollutants in sediment and sewage sludge. Chemosphere 24(12):1721-1730.

*Oberg T, Warman K, Bergstrom J. 1987. Brominated aromatics from combustion. Chemosphere 16(10-12):2451-2465.

O'Connor JC, Frame SR, Davis LG, et al. 1999. Detection of thyroid toxicants in a tier 1 screening battery and alterations in thyroid endpoints over 28 days of exposure. Toxicol Sci 51:54-70.

*Ohta S, Ishizuka D, Nishimura H, et al. 2000. Real situation of contamination by polybrominated diphenyl ethers as flame retardants in market fish and mother milk of Japan. Organohalogen Compounds 47:218-221.

*Ohta S, Ishizuke D, Nishimura H, et al. 2002. Comparison of polybrominted diphenyl ethers in fish, vergetables, and meats and levels in human milk of nursing women in Japan. Chemosphere 46(5):689-696.

*O'Keefe PW. 1978. Formation of brominated dibenzofurans from pyrolysis of the polybrominated biphenyl fire retardant, Firemaster FF-1. Environ Health Perspect 23:347-350.

*Okey AB, Vella LM, Harper PA. 1989. Detection and characterization of a low affinity form of cytosolic Ah receptor in livers of mice nonresponsive to induction of cytochrome P1-450 by 3-methylcholanthrene. Mol Pharmacol 35:823-830.

*Olsson A, Vitnish M, Plikshs M, et al. 1999. Halogenated environmental contaminants in perch (Perca fluviatilis from Lativian coastal areas. Sci Total Environ 239(1-3):19-30.

Olsson M, Karlsson B, Ahnland E. 1994. Diseases and environmental contaminants in seals from the Baltic and the Swedish west coast. Sci Total Environ 154:217-227.

*Opperhuizen A, Velde EW, Gobas FAPC, et al. 1985. Relationship between bioconcentration in fish and steric factors of hydrophobic chemicals. Chemosphere 14(11/12):1871-1896.

*Orn U, Klasson-Wehler E. 1998. Metabolism of 2,2',4,4'-tetrabromodiphenyl ether in rat and mouse. Xenobiotica 1998:199-211.

*Orti DL, Hill RH, Patterson DG, et al. 1983. Structure elucidation of some minor components of the polybromobiphenyl mixture, Firemaster. Arch Environ Contam Toxicol 12:603-614.

Ott MG, Zober A. 1996. Morbidity study of extruder personnel with potential exposure to brominated dioxins and furans. II. Results of clinical laboratory studies. Occup Environ Med 53(12):844-846.

*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.

*Pardini AT, Jones CS, Noble, et al. 2001. Persistent pollutants in land-sludges. Nature 412:140-141.

*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(9):5967-5976.

*Patterson DG, Sjodin A, Bergman A. 2000. Brominated flame retardants in serum from US blood donors. Organohalogen Compounds 47:45-48.

Pazdernik TL, Rozman KK. 1985. Effect of thyroidectomy and thyroxine on 2,3,7,8-tetra-chlorodibenzo-*p*-dioxin-induced immunotoxicity. Life Sci 36:695-703.

Pelota J, Yla-Mononen L. 2001. The commercial pentabromodiphenyl ether as a global POP. BFR:33-36.

*Peters AJ, Coleman P, Jones KC. 1999. Organochlorine pesticides in UK air. Organohalogen Compounds 41:447-450.

*Pettigrew A. 1993. Flame retardants (halogenated). 10:960-976.

*Pharmakon Associates Inc. 1984. Initial submission: Acute oral toxicity in rats (14 days) of Saytex 115 (Pentabromodiphenyloxide). Submitted to the U.S. EPA under TSCA Section FYI, Fiche no. OTS0000972.

Pijenburg AM, Everts JW, de Boer J, et al. 1995. Polybrominated biphenyl and diphenylether flame retardants: analysis, toxicity, and environmental occurrence. Rev Environ Contam Toxicol 141:1-26.

*Poland A, Glover E, Kende AS. 1976. Stereospecific, high affinity binding of 2,3,7,8-tetra-chlorodibenzo-p-dioxin by hepatic cytosol. Evidence that the binding species is receptor for induction of aryl hydrocarbon hydrolase. J Biol Chem 251:4936-4946.

*Poland A, Palen D, Glover E. 1982. Tumour promotion by TCDD in skin of HRS/J hairless mice. Nature 300:85-87.

*Polin D, Leavitt RA. 1984. Colestipol and energy restriction as an approach to hasten removal of PBBs from chickens. J Toxicol Environ Health 13:659-671.

*Polin D, Bursian SJ, Underwood MS, et al. 1991. Elimination of PBBs in rats, effect of mineral oil and/or feed restriction. J Toxicol Environ Health 33:197-212.

*Polin D, Lehning E, Pullen D, et al. 1985. Procedures to enhance withdrawal of xenobiotics from chickens. J Toxicol Environ Health 16:243-254.

*Pomerantz I, Burke J, Firestone D, et al. 1978. Chemistry of PCBs and PBBs. Environ Health Perspect 24:133-146.

Porterfield SP. 1994. Vulnerability of the developing brain to thyroid abnormalities: environmental insults to the thyroid system. Environ Health Perspect Suppl 102:125-230.

Priest B. 2001. Brominated flame retardants: Commercially available analytical standards. BFR:193-194.

Pullen S. 2001. Immunotoxic effects of polybrominated flame retardants. Naunyn-Schmiedebergs Arch Pharmacol 363(4):R141.

*Purdy R, Safe S. 1980. The in vitro metabolism of 2,2',4,4',5,5'-hexabromobiphenyl. J Environ Pathol Toxicol 4:277-284.

*Quensen JP III, Morris PJ, Boyd SA. 1990. Dehalogenation of PCBs and PBBs by anaerobic microorganisms from sediments. In: Proceedings of the 90th American Society for Microbiology Annual Meeting, Anaheim, CA [Abstract Q-44]. American Society for Microbiology, Washington, DC. 90:295.

*Raber BT, Carter JW. 1986. Localization of ultrastructural alterations induced in rat liver by dietary polybromobiphenyls (Firemaster BP-6). Arch Environ Contam Toxicol 15:725-732.

Rahman F, Lanford KH, Scrimshaw MD, et al. 2001. Polybrominated diphenyl ether (PBDE) flame retardants. Sci Total Environ 275(1-3):1-17.

Rangga-Tabbu C, Sleight SD. 1992. Development of preneoplastic lesions in the liver and nasal epithelium of rats initiated with N-nitrosodimethylamine or N-nitrosopyrrolidine and promoted with polybrominated biphenyls. Food Chem Toxicol 30(11):921-926.

*Rappe C, Buser HR. 1980. Chemical properties and analytical methods. In: Kimbrough RD ed. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier/North-Holland Biomedical Press, 41-76.

*Render JA, Aust SD, Sleight SD. 1982. Acute pathologic effects of 3,3',4,4',5,5'-hexabromobiphenyl in rats: Comparison of its effects with Firemaster BP-6 and 2,2',4,4',5,5'-hexabromobiphenyl. Toxicol Appl Pharmacol 62:428-444.

Renner R. 2000a. Increasing levels of flame retardants found in North American environment. Environ Sci Technol 34(21):452A-453A.

Renner R. 2000b. What fate for brominated fire retardants? Environ Sci Technol 34(9):222A-226A.

Renner R. 2001. Firesafe but not failsafe. Flame retardants cause neurotoxic effects. Environ Health Perspect 109(9):A434-435.

*Rezabek MS, Sleight SD, Jensen RK. 1987. Short-term oral administration of polybrominated biphenyls enhances the development of hepatic enzyme-altered foci in initiated rats. J Toxicol Environ Health 20:347-356.

*Rezabek MS, Sleight SD, Jensen RK, et al. 1989. Effects of dietary retinyl acetate on the promotion of hepatic enzyme-altered foci by polybrominated biphenyls in initiated rats. Food Chem Toxicol 27(8):539-544.

*Rickert DE, Dent JG, Cagen SZ, et al. 1978. Distribution of polybrominated biphenyls after dietary exposure in pregnant and lactating rats and their offspring. Environ Health Perspect 23:63-66.

Riess M, Ernst T, Popp R, et al. 2000. Analysis of flame retarded polymers and recycling materials. Chemosphere 40(9-11):937-941.

*Ringer RK, Aurelich RJ, Bleavins MR. 1981. Biological effects of PCBs and PBBs on mink and ferrets- a review. In: Khan MAQ, Stanton RD, eds. Toxicology of halogenated hydrocarbons: Health and ecological effects. New York: Pergamon Press, 329-343.

Robertson LW, Andres JL, Safe SH, et al. 1983a. Toxicity of 3,3',4,4'- and 2,2',5,5'-tetrabromobiphenyl: correlation of activity with aryl hydrocarbon hydroxylase induction and lack of protection by antioxidants. J Toxicol Environ Health 11:81-91.

*Robertson LW, Chittim B, Safe SH, et al. 1983b. Photodecomposition of a commercial polybrominated biphenyl fire retardant: High-resolution gas chromatographic analysis. J Agric Food Chem 31:454-457.

Robertson LW, Parkinson A, Bandiera S, et al. 1981. Potent induction of rat liver microsomal, drug-metabolizing enzymes by 2,3,3',4,4',5-hexabromobiphenyl, a component of Firemaster. Chem Biol Interact 35:13-24.

*Robertson LW, Parkinson A, Bandiera S, et al. 1984a. PCBs and PBBs: Biological and toxic effects on C57BL/6J and DBA/2J inbred mice. Toxicology 31:191-206.

*Robertson LW, Parkinson A, Campbell MA, et al. 1982. Polybrominated biphenyls as aryl hydrocarbon hydroxylase inducers: Structure-activity correlations. Chem Biol Interact 42:53-66.

*Robertson LW, Safe SH, Parkinson A, et al. 1984b. Synthesis and identification of highly toxic polybrominated biphenyls in the fire retardant Firemaster BP-6. J Agric Food Chem 32:1107-1111.

*Robertson LW, Silberhorn EM, Glauert HP. 1991. Do structure-activity relationships for the acute toxicity of PCBs and PBBs also apply for induction of heptocellular carcinoma? Environ Toxicol Chem 10:715-728.

*Roboz J, Greaves J, Bekesi JG. 1985. Polybrominated biphenyls in model and environmentally contaminated human blood: Protein binding and immunotoxicological studies. Environ Health Perspect 60:107-113.

Roboz J, Suzuki RK, Bekesi JG, et al. 1980. Mass spectrometric identification and quantification of polybrominated biphenyls in blood compartments of exposed Michigan chemical workers. J Environ Pathol Toxicol 3:363-378.

Rodriguez H, Loechler EL. 1993. Mutational specificity of the (+) - anti-diol epoxide of benzo [a] pyrine in a supF gene of an Escherichia coli plasmid: DNA sequence context influences hotspots, mutagenic specificity and the extent of SOS enhancements of mutagenesis. Carcinogenesis 14(3):373-383.

*Roes U, Dent JG, Netter KJ, et al. 1977. Effect of polybrominated biphenyls on bromobenzene lethality in mice. J Toxicol Environ Health 3:663-671.

Rogan WJ. 1995. Environmental poisoning of children- lessons from the past. Environ Health Perspect 103:19-23.

Rogan WJ. 1996. Pollutants in breast milk. Arch Pediatr Adolesc Med 150:981-990.

Ronen Z, Abeliovich A. 2000. Anaerobic-aerobic process for microbial degradation of tetrabromobisphenol A. Appl Environ Microbiol 66(6):2372-2377.

*Rosen DH, Flanders WD, Friede A, et al. 1995. Half-life of a polybrominated biphenyl in human sera. Environ Health Perspect 103(3):272-274.

Rosenkranz HS, Klopman G. 1990. Structural basis of carcinogenicity in rodents of genotoxicants and non-genotoxicants. Mutat Res 228:105-124.

*Rosenman KD, Anderson HA, Selikoff IJ, et al. 1979. Spermatogenesis in men exposed to polybrominated biphenyl (PBB). Fertil Steril 32:209-213.

*Rossman TG, Molina M, Meyer L, et al. 1991. Performance of 133 compounds in the lambda prophage induction endpoint of the Microscreen assay and a comparison with *IS. typhimurium* mutagenicity and rodent carcinogenicity assays. Mutat Res 260:349-367.

Rozman K, Pfeifer B, Kerecsen L, et al. 1991. Is a serotonergic mechanism involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced appetite suppression in the Sprgue-Dawley rat? Arch Toxicol 65:124-128.

Rozman K, Rozman T, Scheufler E, et al. 1985. Thyroid hormones modulate the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J Toxicol Environ Health 16:481-491.

*Rozman KK, Rozman TA, Williams J, et al. 1982. Effect of mineral oil and/or cholestyramine in the diet on biliary and intestinal elimination of 2,4,5,2',4',5'-hexabromodiphenyl in the Rhesus monkey. J Toxicol Environ Health 9:611-618.

RTECS. 1987. Registry of toxic effects of chemical substances 3:1985-1986. Centers for Disease Control, National Institute for Occupational Safety and Health, 2401-2402.

*Ruzo LO, Zabik MJ. 1975. Polyhalogenated biphenyls: Photolysis of hexabromo and hexachlorobiphenyls in methanol solution. Bull Environ Contam Toxicol 13(2):181-182.

*Ruzo LO, Sundstrom G, Hutzinger O, et al. 1976. Photodegradation of polybrominated biphenyl (PBB). J Agric Food Chem 24:1062-1065.

*RTI. 1993. Research Triangle Institute. http://www.rti.org/. May 5, 2002.

*Ryan JJ, Patry B. 2000. Determination of brominated diphenyl ethers (BDE's) and levels in Canadian human milks. Organohalogen Compounds 47:57-60.

Ryan JJ, Patry B. 2001. Body burdens and exposure from food for poybrominated diphenyl ethers (BDEs) in Canada. BFR:103-106.

Safe S. 1993. Toxicology structure- function relationship and human and environmental health impacts of polychlorinated biphenyls progress and problems. Environ Health Perspect 100(0):259-268.

*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, Phil D. 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(1):51-88.

Safe S, Bandiera S, Sawyer T, et al. 1985. Effects of structure on binding to the 2,3,7,8-TCDD receptor protein and AHH induction-halogentated biphenyls. Environ Health Perspect 61:21-33.

*Safe S, Kohli J, Crawford A. 1978. FireMaster BP-6: Fractionation, metabolic and enzyme induction studies. Environ Health Perspect 23:147-152.

*Safe SH, Zacharewski T. 1997. Organochlorine exposure and risk for breast cancer. In: Aldaz CM, Gould MN, McLachlan J, et al, eds. Etiology of breast and gynecological cancers. New York, NY: Wiley-Liss Inc, 133-145.

Saki S, Watanabe J, Honda Y, et al. 2001. Combustion of brominated flame retardant and behavior of its byproducts. Chemosphere 42(5-7):519-531.

Sakai S, Wantanabe J, Takatsuki H, et al. 2001. Presence of PBDDs/DFs in flame retardant materials and their behavior in high-temperature melting processes. BFR:59-63.

Sanderson JT, Aarts JMMJG, Brouwer A, et al. 1996. Comparison of Ah receptor-mediated luciferase and ethoxyresorufin-O-deethylase induction in H4IIE cells: Implications for their use as bioanalytical tools for the detection of polyhalogenated aromatic hydrocarbons. Toxicol Appl Pharmacol 137:316-325.

*Sasaki S. 1978. The scientific aspects of the chemical substances control law in Japan. In: Hutzinger O, VonLetyveld LH, Zoetman BC eds. Aquatic Pollutants: Transformation and biological effects: Oxford: Pergamon Press: 283-298.

Schaefer A. 2001. Lake Michigan heavily contaminated with PBDEs. Environ Sci Technol 35(7):139A-140A.

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 soils. Arch Environ Health 49:452-458.

*Schmidt S, Fortnagel P, Wittich R-M. 1993. Biodegradation and transformation of 4,4'-dihalodiphenyl ethers by Sphingomonas sp. strain SS33. Appl Environ Microbiol 59(11):3931-3933.

Schnare DW, Ben M, Shields MG. 1984. Body burden reductions of PCBs, PBBs and chlorinated pesticides in human subjects. Ambio 13:378-380.

*Schramm H, Robertson LW, Oesch F. 1985. Differential regulation of hepatic glutathione transferase and glutathione peroxidase activities in the rat. Biochem Pharmacol 34(20):3735-3739.

*Schroter-Kermani C, Helm D, Hermann T, et al. 2000. The German environmental specimen bank-application in trend monitoring of polybrominated diphenyl ethers in human blood. Organohalogen Compounds 47:49-52.

Schussler GC. 2000. The thyroxine-binding proteins. Thyroid 10:141-149.

*Schwartz EM, Rae WA. 1983. Effect of polybrominated biphenyls (PBB) on developmental abilities in young children. Am J Public Health 73(3):277-281.

*Seagull EAW. 1983. Developmental abilities of children exposed to polybrominated biphenyls (PBB) Am J Public Health 73(3):281-285.

Selden JR, Dolbeare F, Miller JE, et al. 1994. Validation of a flow cytometric in vitro DNA repair (UDS) assay in rat heptocytes. Mutat Res 315(2):147-167.

*Sellstrom U, Jansson B. 1995. Analysis of tetrabromobisphenol A in a product and environmental samples. Chemosphere 31(4):3085-3092.

*Sellstrom U, Jansson B, Kierkegaard A, et al. 1993. Polybrominated diphenyl ethers (PBDE) in boilogical samples from the Swedish environment. Chemosphere 26(9):1703-1718.

*Sellstrom U, Kierkegaard M, Alsberg T, et al. 1999. Brominated flame retardants in sediments from European estuaries, the Baltic Sea and in sewage sludge. Organohalogen Compounds 40:383-386.

*Sellstrom U, Kierkkegaard A, De Wit C, et al. 1998a. Polybrominated diphenyl ethers and hexabromocyclododecane in sediment and fish from a Swedish river. Environ Toxicol Chem 17(6):1065-1072.

*Sellstrom U, Soderstrom G, de Wit C, et al. 1998b. Photolytic debromination of decabromodiphennyl ether (DeBDE). Organohalogen Compounds 35:447-450.

*Sepkovic DW, Byrne JJ. 1984. Kinetic parameters of L-[125I]triiodothyronine degradation in rats pretreated with polyhalogenated biphenyls. Food Chem Toxicol 22(9):743-747.

*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

*Shah BP. 1978. Environmental considerations for the disposal of PBB-contaminated animals and wastes. Environ Health Perspect 23:27-35.

*She J, Wrinkler J, Visita P, et al. 2000. Analysis of PBDEs in seal blubber and human breast adipose tissue samples. Organohalogen Compounds 47:53-56.

Shelby MD, Witt KL. 1995. Comparison of results from mouse bone marrow chromosome aberration and microbucleous tests. Environ Mol Mutagen 25(4):302-313.

Shelby MD, Erexson GL, Hook GJ, et al. 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. Environ Mol Mutagen 21(2):160-179.

*Shelton DR, Tiedje JM. 1981. Development of tests for determining anaerobic biodegradation potential. Washington, DC. EPA 568/5/-81-813. PB84-166495.

Shepard EC, Phillips TD, Irvin TR. 1984. Aflatoxin B1 metabolism in the rat: Polyhalogenated biphenyl enhanced conversion to aflatoxin M1. Xenobiotica 14(9):741-750.

Sherman JD. 1991. Polybrominated biphenyl exposure and human cancer: Report of a case and public health implications. Toxicol Ind Health 7(3):197-205.

*Silberhorn EM, Glauert HP, Robertson LW. 1990. Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. Crit Rev Toxicol 20(6):439-496.

*Silva J, Kauffman CA, Simon DG, et al. 1979. Lymphocyte function in humans exposed to polybrominated biphenyls. J Reticuloendothel Soc 26(4):341-347.

*Simmons MS, Kotz KT. 1982. Association studies of polybrominated biphenyls in aquatic systems. Bull Environ Contam Toxicol 29:58-63.

*Sinjari T, Damerud P, Hallgren S. 1998. Competitive inhibition of 1251-thyroxin (T4) binding to choroid plexus by hydroxylated PCE metabolites. Organohalogen Compounds 37:241-244.

*Sjodin A, Carlsson H, Thuresson K, et al. 2001a. Flame retardants in indoor air at an electronics recycling plant and at other work environments. Environ Sci Technol 35(3):448-454.

*Sjodin A, Hagmar L, Klasson-Wehler E, et al. 1999a. Flame retardant exposure: polybrominated diphenyl ethers in blood from Swedish workers. Environ Health Perspect 107(8):643-648.

*Sjodin A, Hagmar L, Klasson-Wehler E, et al. 2000. Influence of the consumption of fatty Baltic Sea fish on plasma levels of halogenated environmental contaminants in Latvian and Swedish men. Environ Health Perspect 108:1035-1041.

*Sjodin A, Jakobsson E, Kierkegaard A, et al. 1998. Gas chromatographic identification and quantification of polybrominated diphenyl ethers in a commercial product, Bromkal 70-5DE. J Chromatogr A 822(1):83-89.

Sjodin A, Patterson DG Jr, Bergman A. 2001b. Brominated flame retardants in serum from U.S. blood donors. Environ Sci Technol 35(19):3830-3833.

Sjodin A, Thuresson K, Hagmar L, et al. 1999b. Occupational exposure to polybrominated diphenyl ethers at dismantling of electrons. Ambient air and human serum analysis. Organohalogen Compounds 43:447-451.

*Sleight S. 1985. Effects of PCBs and related compounds on hepatocarcinogenesis in rats and mice. Environ Health Perspect 60:35-39.

*Sleight SD, Sanger VL. 1976. Pathologic features of polybrominated biphenyl toxicosis in the rat and guinea pig. J Am Vet Med Assoc 169:1231-1235.

*Sleight SD, Mangkoewidjojo S, Akoso BT, et al. 1978. Polybrominated biphenyl toxicosis in rats fed an iodine-deficient, iodine-adequate, or iodine-excess diet. Environ Health Perspect 23:341-346.

Sonzogni W, Manchester-Neesvig J. 2001. Polybrominated diphenyl ethers (PBDEs) in Lake Michigan Salmonids. Stockholm, Sweden. BFR:377-378.

*Sparling J, Fung D, Safe S. 1980. Bromo and chlorobiphenyl metabolism: Gas chromatographic mass spectrometric identification of urinary metabolites and the effects of structure on their rates of excretion. Biomed Mass Spectrom 7(1):13-19.

Spear PA, Higueret P, Garcin H. 1994. Effects of fasting and 3,3,4.4'-5,5'-hexabromobiphenyl on plasma transport of thyroxine and retinol: Fasting reverses elevation of retinol. J Toxicol Environ Health 42(2):173-183.

*SRI. 2001. 2001 Directory of Chemical Producers- United States of America. Menlo Park, CA: Stanford Research Institution International, 462.

*Stafford, CJ. 1983. Halogenated diphenyl ethers indentified in avian tissues and eggs by GC/MS. Chemosphere 12(11/12):1487-1495.

*Stanley JS, Cramer PH, Thornburg KR, et al. 1991. Mass spectral confirmation of chlorinated and brominated diphenyl ethers in human adipose tissues. Chemosphere 23(8-10):1185-1186.

*Stern GA, Ikonomou MG. 2000. Temporal trends of polybrominated diphenyl ethers in SE baffin beluga: Increasing evidence of long range atmospheric transport. Organohalogen Compounds 57:81-84.

*Strandberg B, Dodder NG, Basu I, et al. 2001. Concentrations and spatial variations of polybrominated diphenyl ethers and other organohalogen compounds in Great Lakes air. Environ Sci Technol 35(6):1078-1083.

Strandman T, Kiviranta H, Kumpulainen J, et al. 2001. Polybrominated diphenyl ethers (PBDEs) in Finnish food items. BFR:307-310.

*Strandman T, Koistinen J, Kiviranta H, et al. 1999. Levels of some polybrominated diphenyl ethers (PBDEs) in fish and human adipose tissue in Finland. Organohalogen Compounds 40(:):355-358.

*Strandman T, Koistinen J, Variainen T. 2000. Polybrominated diphenyl ethers (PBDEs) in placenta and human milk. Organohalogen Compounds 47:61-64.

Strassner HT, Arnolds CW. 1992. Environment and pregnancy. Princ Pract Med Ther Preg:89-105.

Striebich RC, Rubey WA, Tirey DA, et al. 1991. High-temperature degradation of polybrominated flame retardant materials. Chemosphere 23(8-10):1197-1204.

*Stross JK, Nixon RK, Anderson MD. 1979. Neuropsychiatric findings in patients exposed to polybrominated biphenyls. Ann N Y Acad Sci 320:368-372.

*Stross JK, Smokler IA, Isbister J, et al. 1981. The human health effects of exposure to polybrominated biphenyls. Toxicol Appl Pharmacol 58:145-150.

*Sugiura K. 1992. Microbial degradation of polychlorinated biphenyls in aquatic environments. Chemosphere 24:881-890.

*Sundstrom G, Hutzinger O. 1976. The synthesis and gas chromatographic properties of bromobiphenyls. Sci Total Environ 6:15-29.

*Sundstom G, Hutzinger O, Safe S, et al. 1976. Identification of 2,2'4,4'5,5'-hexabromobiphenyl as the major component of flame retardant Firemaster® PB-6. Chemosphere 5:11-14.

*Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air, and water solubility. Residue Rev 85:18-28.

Swanson MB, Davis GA, Kincaid LE, et al. 1997. A screening method for ranking and scoring chemicals by potential human health and environmental impacts. Environ Toxicol Chem 16(2):372-383.

Sweeney AM, Symanski E, Burau KD, et al. 2001. Changes in serum PBB and PCB levels over time among women of varying ages at exposure. Environ Res 86:128-139.

*Takase I, Omori T, Minoda Y. 1986. Microbial degradation products from biphenyl-related compounds. Agric Biol Chem 50(3):681-686.

*Takenaka S, Takahashi K. 1991. Enhancement of fecal excretion of polychlorinated biphenyls by the addition of rice bran fiber to the diet in rats. Chemosphere 22(3-4):375-381.

Taylor MJ, Lucier GW, Mahler JF, et al. 1992. Inhibition of acute TCDD toxicity by treatment with anti-tumor necrosis factor antibody or dexamethasone. Toxicol Appl Pharmacol 117:126-132.

Tennant RW. 1993. A perspective on nonmutagenic mechanisms in carcinogenesis. Environ Health Perspect Suppl 101:231-236.

ter Schure AFH, Larsson P. 2001. Atmospheric deposition of polybrominated diphenylethers (PBDEs) BFR:375-376.

Theiss JC, Stoner GD, Shimkin MB, et al. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res 37(8):2717-2720.

*Thoma H, Hutzinger O. 1987. Pyrolysis and GC/MS-analysis of brominated flame retardants in on-line operation. Chemosphere 16(6):1353-1360.

*Thoma H, Hauschulz G, Knorr E, et al. 1987. Polybrominated dibenzofurans (PBDF) and dibenzodioxins (PBDD) from the pyrolysis of neat brominated diohenylethers, biphenyls and plastic mixtures of these compounds. Chemosphere 16(1):277-285.

*Thomas AR, Marcus M, Zhang RH, et al. 2001. Breast-feeding among women exposed to polybrominated biphenyls in Michigan. Environ Health Perspect 109(11):1133-1137.

*Thomas RG. 1990. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods: Environmental behavior of organic compounds: Washington, DC: American Chemical Society.

Thomsen C, Leknes H, Lundanes E, et al. 2001a. Brominated flame retardants in laboratory air. J Chromatogr A 923(1-2):299-304.

*Thomsen C, Lundanes E, Becher G. 2001b. Brominated flame retardants in plasma samples from three different occupational groups in Norway. J Environ Monitor 3(4):366-370.

Thomsen C, Lundanes E, Becher G. 2002. Brominated flame retardants in archived serum samples from Norway: A study on temporal trends and the role of age. Environ Sci Technol 36:1414-1418.

*Tilson HA. 1992. Study design considerations in developmental neurotoxicology. Neurotoxicol Teratol 14:199-203.

*Tilson HA, Cabe PA. 1979. Studies on the neurobehavioral effects of polybrominated biphenyls in rats. Ann N Y Acad Sci :325-336.

Tittlemier SA, Tomy GT. 2000. Vapor pressure of six brominated diphenyl ether congeners. Organohalogen Compounds 47:206-209.

Tittlemier SA, Tomy GT. 2001. Vapor pressures of six brominated dipheyl ether congeners. Environ Toxicol Chem 20(1):146-148.

Tomy G, Tittlemier S, Braekevelt E, et al. 2001. The physio-chemical properties of some brominated flame retardants. BFR :229-232.

*TRI 99. 2002. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Trotter WJ. 1977. Confirming low levels of hexabromobiphenyl by gas-liquid chromatography of photolysis products. Bull Environ Contam Toxicol 18:726-733.

Tsongas TA. 1996. PBBs: potential effects in children. Environ Health Perspect 104(12):1267-1268.

*Tuey DB, Matthews HB. 1980. Distribution and excretion of 2,2',4,4',5,5'-hexabromobiphenyl in rats and man: Pharmacokinetic model predictions. Toxicol Appl Pharmacol 53:420-431.

Tysklind M, Sellstom U, Soderstrom G, et al. 2001. Abiotic transformation of polybrominated diphenylethers (PBDEs): Photolytic debromination of decambro diphenyl ether. BFR:51-54.

Uno Y, Takaswas H, Miyagawa M, et al. 1994. An in vivo-in vitro replications DNA synthesis (RDS) test using rat hepatocytes as an early prediction assay for nongenotoxic heptacarcinogens: Screening of 22 known positives and 25 noncarcinogens. Mutat Res 320(3):189-205.

*USDA. 1998. United States Department of Agriculture.
Web Access: http://www.usda.gov/OPHS/bluebook/histcom.htm

*Valciukas JA, Lilis R, Anderson HA, et al. 1979. The neurotoxicity of polybrominated biphenyls: Results of a medical field survey. Ann N Y Acad Sci :337-367.

*Valciukas JA, Lilis R, Wolff MS, et al. 1978. Comparative neurobehavioral study of a polybrominated biphenyl-exposed population in Michigan and a nonexposed group in Wisconsin. Environ Health Perspect 23:199-210.

*van Bavel B, Sundelin E, Lillback J, et al. 1999. Supercritical fluid extraction of polybrominated diphenyl ethers PBDEs from long-finned pilot whale (Globicephala melas) from the Atlantic. Organohalogen Compounds 40:359-362.

van Birgelen APJM. 1999. Uncertainties in the toxic equivalency factor concept: Future directions. Organohalogen Compounds 44:505-508.

Van-Den-Berg KJ, van Raaij JAGM, Bragt PC, et al. 1991. Interactions of halogenated industrial chemicals with transthyretin and effects on thryoid hormone levels in vivo. Arch Toxicol 65:15-19.

*Veith GD, DeFoe VD, Bergstedt BV. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. J Fish Res Board Can 36:1040-1048.

Vetter W, Muller JF, Gaus C, et al. 2001. Bioaccumulative natural brominated compounds in marine mammals. Stockholm, Sweden. BFR:385-389.

Viberg H, Fredriksson A, Eriksson P. 2002. Neonatal exposure to the brominated flame retardant 2,2',4,4',4-pentabromodiphenyl ether causes altered susceptibility if the cholinergic transmitter system in the adult mouse. Toxicol Sci 67:104-107.

*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.

*von Meyerinck L, Hufnagel B, Schmoldt A, et al. 1990. Inductions of rat liver microsomal cytocrome P-450 by the pentabromo diphenyl ether bromkal 70 and half-lives of its components in the adipose tissue. Toxicology 61(2):259-274.

*Vos JG, van Genderen H. 1973. Toxicological aspects of immunosuppression. Pest Environ Control:527-545.

*Waritz RJ, Aftosmis JG, Culik R, et al. 1977. Toxicological evaluations of some brominated biphenyls. Am Ind Hyg Assoc J 38:307-320.

*Wasito, Sleight SD. 1989. Promoting effect of polybrominated biphenyls on tracheal papillomas in syrian golden hamsters. J Toxicol Environ Health 27:173-187.

Watanabe I, Sakai S-I. 2001. Environmental release and behavior of brominated flame retardants- an overview. Organohalogen Compounds 52:1-4.

*Watanabe I, Tatsukawa R. 1987. Formation of brominated dibenzofurans from the photolysis of flame retardant decabromobiphenyl ether in hexane by UV and sun light. Bull Environ Contam Toxicol 39:953-959.

*Wantanabe I, Tatsukawa R. 1990. Anthropogenic aromatics in the Japanese environment. Workshop on brominated aromatic flame retardants, Skokloster, Sweden. KEMI, National Council Inspectorate, Solna, Sweden, 1990, 63-71.

*Watanabe I, Kashimoto T, Tatsukawa R. 1986. Confirmation of the presence of the flame retardant decabromiphenyl ether in river sediment from Osaka, Japan. Bull Environ Contam Toxicol 36(6):839-842.

*Watanabe I, Kashimoto T, Tatsukawa R. 1987. Polybrominated biphenyl ethers in marine fish, shellfish and river and marine sediments in Japan. Chemosphere 16(10-12):2389-2396.

*Watanabe I, Kawano M, Tatsukawa R. 1995. Polybrominated and mixed polybromo/chlorinated dibenzo-p-dioxins and -dibenxofurans in the Japanese environment. Organohalogen Compounds 24:337-240.

*Watanabe IAH, Kawano MC, Wang YD, et al. 1992. Polybrominated dibenzo-p-dioxins (PBDDs) and dibenzofurans (PBDFs) in atmospheric air in Taiwan and Japan. Organohalogen Compounds 9:309-312.

Weber LW, Greim H. 1997. The toxicity of brominated and mixed-halogenated dipenzo-p-dioxins and dibenzofurans: an overview. J Toxicol Environ Health 50(3):195-215.

Weber LWD, Lebofsky M, Greim H, et al. 1991a. Key enzymes of gluconeogenesis are dose-dependent reduced in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-treated rats. Arch Toxicol 65:119-123.

Weber LWD, Lebofsky M, Stahl BU. 1991b. Reduced activities of key enzymes of gluconeogenesis as possible cause of acute toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats. Toxicology 66:133-144.

*Weil WB, Spencer M, Benjamin D, et al. 1981. The effect of polybrominated biphenyl on infants and young children. J Pediatr 98:47-51.

Welch LW. 1998. Reproductive and developmental hazards - an overview for occupational and environmental health nurses. AAOHN J 46(2):57-65.

Welsch F, Morgan KT. 1985. Placental transfer and developmental toxicity of 2,2',4,4',5,5'-hexabromobiphenyl in B6C3F1 mice. Toxicol Appl Pharmacol 81:431-442.

Wenning R. 2001. Probabalisitic human health risk assessment of penta-, octa-, and deca- brominated dphenyl ethers. Organohalogen Compounds 52:39-42.

Wenning RJ. 2002. Uncertainties and data needs in risk assessment of three commercial polybrominated diphenyl ethers: probabilistic exposure analysis and comparison with European commission results. Chemosphere 46(5):779-796.

*Werner PR, Sleight SD. 1981. Toxicosis in sows and their pigs caused by feeding rations containing polybrominated biphenyls to sows during pregnancy and lactation. Am J Vet Res 42:183-189.

*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, Maibach HI, Bucks DA, 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.

*WHO. 1994a. Brominated diphenyl ethers. International programme on chemical safety. Environmental Health Criteria. World Health Organization. http://www.inchem.org/documents/ehc/ehc/.

*WHO. 1994b. Brominated diphenyl ethers. International programme on chemical safety. Environmental Health Criteria 162. World Health Organization. http://www.inchem.org/documents/ehc/ehc/.

*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: Academic Press.

*WIL Research Laboratories. 1984. 90-day dietary study in rats with pentabromodiphenyl oxide (DE-71) (Final Report). Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0524336.

*WIL Research Laboratories. 1986. A range-finding teratology study in rats with DE-79. Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0522298.

*Willett LB, Durst KI. 1978. Effects of PBBs on cattle. IV. Distribution and clearance of components of FireMaster BP-6. Environ Health Perspect 23:67-74.

Willett LB, Irving HA. 1976. Distribution and clearance of polybrominated biphenyls in cows and calves. J Dairy Sci 59(8):1429-1439.

*Willett LB, Brumm CJ, Williams CL. 1978. Method for extraction, isolation, and detection of free polybrominated biphenyls (PBBs) from plasma, feces, milk, and bile using disposable glassware. J Agric Food Chem 26(1):122-126.

Willett LB, Durst HI, Liu T-TY, et al. 1982. Performance and health of offspring of cows experimentally exposed to polybrominated biphenyls. J Dairy Sci 65:81-91.

*Willett LB, Schanbacher FL, Durst HI, et al. 1988. Relationships between concentrations of polybrominated biphenyls detected in milk, blood and body fat of contaminated dairy cattle. In: Proceedings of the 75th American Dairy Science Association Annual Meeting, Blacksburg, VA, June 15-18, 1980. [Abstract P134]. J Dairy Sci 63 (Suppl. 1):144.

*Williams DT, LeBel GL, Junkins E. 1988. Organohalogen residues in human adipose autopsy samples from six Ontario municipalities. J Assoc Off Anal Chem 71(2):410-414.

*Williams GM, Tong C, Telang S. 1984. Polybrominated biphenyls are nongenotoxic and produce an epigenetic membrane effect in cultured liver cells. Environ Res 34:310-320.

*Wilson-Martino NA, Martino LJ, Millman-Feder NG, et al. 1980. The presence of hepatic intramitochondrial crystalline inclusions in polybrominated biphenyl-treated mice. Arch Toxicol 45:233-239.

*Wolff MS, Aubrey B. 1978. PBB homologs in sera of Michigan dairy farmers and Michigan chemical workers. Environ Health Perspect 23:211-215.

*Wolff MS, Selikoff IJ. 1979. Variation of polybrominated biphenyl homolog peaks in blood of rats following treatment with Firemaster FF-1. Bull Environ Contam Toxicol 21:771-774.

*Wolff MS, Toniolo, PG. 1995. Environmental organochlorine exposure as a potential etiologic factor in breast cancer. Environ Health Perspec 103(7):141-145.

*Wolff MS, Anderson HA, Camper F, et al. 1979a. Analysis of adipose tissue and serum from PBB (polybrominated biphenyl)-exposed workers. J Environ Pathol Toxicol 2:1397-1411.

Wolff MS, Anderson HA, Rosenman KD, et al. 1979b. Equilibrium of polybrominated biphenyl (PBB) residues in serum and fat of Michigan residents. Bull Environ Contam Toxicol 21:775-781.

*Wolff MS, Anderson HA, Selikoff IJ. 1982. Human tissue burdens of halogenated aromatic chemicals in Michigan. JAMA 247(15):2112-2116.

Wong A, Duan Lei Y, Alaee M, et al. 2001. Vapor pressure of the polybrominated diphenylethers. BFR:195-198.

*Yagi O, Sudo R. 1980. Degradation of polychlorinated biphenyls by microorganisms. J Water Pollut Control Fed 52:1035-1043.

*Yamamoto H, Okumura T, Nishkawa Y, et al. 1997. Determination of decabromodiphenyl ether in water and sediment samples by gas chromatograpy with electron capture detection. J AOAC Int

80(1):102-106.

*Zabik ME, Johnson TM, Smith S. 1978. Effects of processing and cooking on PBB residues. Environ Health Perspect 23:37-41.

*Zacharewski T, Harris M, Safe S, et al. 1988. Applications of the in vitro aryl hydrocarbon hydroxylates induction assay for determining "2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents": Pyrolyzed brominated flame retardants. Toxicology 51:177-189.

*Zegers BN, Lewis WE, Boon JP. 2000. Levels of some polybrominated diphenyl ether (PBDE) flame retardants in dated sediment cores. Organohalogen Compounds 47:229-232.

Zeiger E. 1987. Carcinogenicity of mutagens predictive capability of the Salmonella mutagenesis assay for rodent carcinogenicity. Cancer Res 47:1287-1296.

Zeiger E. 1990. Mutagenicity of 42 chemicals in Salmonella. Environ Mol Mutagen 16:32-54.

Zeiger E, Anderson B, Haqorth S, et al. 1987. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ Mutagen 9:1-110.

Zelinski V, Lorenz W, Bahadir M. 1993. Brominated flame retardants and resulting PBDD in accidental fire residues from private residences. Chemosphere 27(8):1519-1528.

Zhou T, Taylor MM, De Vito MJ, et al. 2000. Thyroid hormone disruptive effects of brominated diphenyl ethers following developmental exposure. Toxicologist 54(1):260-261.

*Zhou T, Ross DG, De Vito MJ, et al. 2001. Effects of short-term *in vivo* exposure to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weaning rats. Toxicol Sci 61:76-82.

*Zhou T, Taylor MM, DeVito MJ, et al. 2002. Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption. Toxicol Sci 66:105-116.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

*Zier B, Lenoir D, Lahaniatis ES, et al. 1991. Surface catalyzed halogenation-dehalogenation reactions of aromatic bromine compounds adsorbed on fly ash. Chemosphere. 22(12):1121-1129.

Zitko V. 1977. The accumulation of polybrominated biphenyls in fish. Bull Environ Contam Toxicol 17(3):285-292.

*Zitko V. 1979. The fate of highly brominated aromatic hydrocarbons in fish. ACS Symp Ser 99:177-182.

Zitko V. 1999. Qualitative determination of 10,10'-oxybisphenoxarsine and decabromodiphenyl ether in plastics. Chemosphere 38(3):629-632.

*Zitko V, Hutzinger O. 1976. Uptake of chloro- and bromobiphenyls, hexachloro- and hexabromobenzene by fish. Bull Environ Contam Toxicol 16(6):665-673.

Zober A, Ott MG. 1997. Digestive tract neoplasma among employees with past exposure to brominated dioxins. Occup Environ Med 54(1):66.

Zober MA, Ott MG, Paepke O, et al. 1992. Morbitity study of extruder personnel with potential exposure to brominated dioxins and furans: I: Results of blood monitoring and immunological tests. Br J Ind Med 49(8):532-544.

*Zoeller RT, Crofton RM. 2000. Thyroid hormone action in fetal brain development and potential for distribution by environmental chemicals. Neurotoxicology 21(6):935-946.

*Zweidinger R, Cooper SD, Erickson MD, et al. 1979. Sampling and analysis for semivolatile brominated organics in ambient air. Am Chem Soc Abstr Pap 94:217-231.

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.

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.

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.

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.

Less Serious Effects—Health effects that are not expected to cause significant dysfunction or death, or those whose significance to the organism are not entirely clear.

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.

Serious Effects—Health effects that evoke failure in a biological system and can lead to morbidity or mortality.

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 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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.

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.

MINIMAL RISK LEVEL WORKSHEET

Chemical name: Polybrominated Biphenyls (PBBs)
CAS number(s): 36355-01-8 (unspecified hexabromo mixture)
Date: September 2002
Profile status: Draft for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 3
Species: Rat

MRL: 0.01 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Allen-Rowlands CF, Castracane VD, Hamilton MG, et al. 1981. Effect of polybroninated biphenyls (PBB) on the pituitary - thyroid axis of the rat. Proc Soc Exp Biol Med 166:506-514.

Experimental design: Groups of 8–11 male rats were treated with 0, 1, 3, or 6 mg/kg/day doses of an unspecified mixture of PBBs in lecithin liposomes by gavage for 10 days. Plasma T_4 was assayed on treatment days 10 and 20. Other end points were evaluated on treatment day 20; these included plasma TSH levels, 5-hour thyroid uptake of ^{131}I, incorporation of ^{131}I into monoiodotyrosine, diiodotyrosine, T_3 or T_4, amount of intrathyroidal iodide, thyroid and liver weights, and body weights. Differences between mean values for the measured parameters in the control and PBB-treated groups were analyzed with the Student's *t*-test, with a *P* value of 0.05 considered as statistically significant.

Effects noted in study and corresponding doses: Plasma (T_4) was significantly ($p<0.05$) decreased at $3 mg/kg/day after 10 and 20 days; this reduction was both dose and time-dependent. Plasma TSH levels were significantly elevated ($p<0.01$) at 6 mg/kg/day. The 6 mg/kg dose also produced a significant increase ($p<0.01$) in the 5-hour thyroid uptake of ^{131}I and a significant depression ($p<0.01$) in the incorporation of ^{131}I into monoiodotyrosine, without any apparent effect on the incorporation of ^{131}I into diiodotyrosine, T_3 or T_4. There was a significant increase ($p<0.01$) of intrathyroidal iodide (nine rats/dose evaluated). At $3 mg/kg, the absolute thyroid weights were significantly increased ($p<0.01$) (not evaluated at 1 mg/kg). Relative liver weight was significantly increased at $1 mg/kg/day, but no treatment related effects on body weight were observed. The 1 mg/kg/day dose is considered a NOAEL.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[X] 10 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? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL: It is well documented in intermediate-duration studies that the thyroid is a target of PBBs showing a spectrum of effects, including decreases in serum T_3 and T_4 hormone, thyroid enlargement, effects in the follicular cells (e.g., reduced size, hyperplasia with columnar appearance, and papillary projections) and accumulation of colloid droplets (Akoso et al. 1982; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978; Norris et al. 1975; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978).

Agency Contact (Chemical Manager): Dr. Hana Pohl

MINIMAL RISK LEVEL WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
CAS number(s): 32534-81-9 (pentaBDE), 32536-52-0 (octaBDE), 1163-19-5 (decaBDE)
Date: September 2002
Profile status: Draft for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 34
Species: Rat

MRL: 0.03 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Zhou T, Taylor MM, DeVito MJ, et al. 2002. Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption. Toxicol Sci 66:105-116.

Experimental design: Groups of 47, 47, 55, and 55 primparous Long-Evans rats were administered a technical pentaBDE mixture (DE-71) in corn oil by gavage from gestation day (Gd) 6 through postnatal day (Pnd) 21, except for Pnd 0 (day of birth). DE-71 is a technical mixture consisting primarily of tetra and penta congeners. Dams were sacrificed on Gd 20 and Pnd 22 and offspring were sacrificed on Gd 20 and Pnds 4, 14, 36, and 90). Serum and liver samples were obtained from a minimum of eight litters at each age point and analyzed for thyroid hormone (total T_4 and T_3) concentrations, liver weight, and hepatic microsomal enzyme (EROD, PROD, UDPGT) activities. Serum T_3 was not assayed in Gd 20 fetuses due to insufficient serum sample volume. Other study end points included number of pups delivered on Gd 21, number and sex of pups on Pnds 4, 7, 14, and 21, body weight of pups on Pnds 4, 7, 14, 21, 36, and 90, eye opening status (pups with at least one eye open) on Pnds 11–18, and maternal body weight on Gd 6 through Pnd 21.

The litter was the statistical unit for all analyses. Analysis of variance (ANOVA) was used to analyze for effects of treatment and interactions. If there was more than one independent variable, significant interactions were followed by step-down ANOVA tests for each independent variable (e.g., treatment and age). A nested design was used when more than one reading for each litter was obtained (e.g., body weights for males and females from the same litter). Repeated-measure ANOVAs were applied to data on dam body weights, preweaning offspring body weights (Pnds 4–21), and eye opening. Postweaning offspring body weights (Pnds 36–91) were analyzed with a two-way ANOVA, with time and dose as independent variables and litter nested under treatment. For significant effects of treatment, Duncan's Multiple Comparison test was used for mean contrast comparisons. The fetal T_4 data were analyzed with the Kruskal-Wallis test followed by a Dunn Multiple Comparison tests (due to a lack of homogeneity of variance). A significance level of 0.05 was used for all statistical tests. Benchmark dose estimates were determined for alterations in thyroid hormones and hepatic enzyme activity using the U.S. EPA Benchmark Dose Software (BMDS, V 1.3).

Effects noted in study and corresponding doses: No treatment-related effects on gestation length, litter size, sex ratio, viability index (percent of pups surviving until day 4), maternal or offspring body weights, or offspring eye opening were observed. The perinatal maternal exposure to PentaPBE caused significant ($p<0.05$) decreases in serum total T_4 in dams at 30 mg/kg/day on Gd 20 and Pnd 22 (48 and 44%, respectively, relative to controls), and in fetuses and offspring at $10 mg/kg/day on Gd 20 (at least 15% reduced) and Pnds 4 and 14 (50 and 64% maximal in the 10 and 30 mg/kg/day groups, respectively). The effect on T_4 concentrations in offspring was age-dependent as values returned to control levels by Pnd 36. There were no exposure-related effects on serum total T_3 concentrations at any time in the dams or offspring. Relative liver weight was significantly ($p<0.05$) increased in dams from Gd 20 to Pnd 22

(approximately 8% above controls) at 30 mg/kg/day and offspring during the early preweaning period at $10 mg/kg/day. Liver weights in offspring were maximal at 30 mg/kg/day on Pnds 4 and 14 (35 and 39% above controls, respectively) and returned to control levels by Pnd 36. Microsomal enzyme activity was increased in both dams and offspring as shown by significantly elevated hepatic EROD and PROD at $10 mg/kg/day in dams on Gd 20 and Pnd 22 and offspring on Gd 20 and Pnds 4, 14, and 36, and signficantly elevated UDPGT at 30 mg/kg/day in dams on Gd 20 and Pnd 22 and offspring on Gd 20 and Pnds 4 and 14. Benchmark dose analysis of the data found that the BMD and BMDL (95% lower confidence bound confidence limit on the effective dose) resulting in a 20% reduction of serum T_4 (LED_{20}) were 2.36 and 0.94 mg/kg/day, respectively. The respective BMD and BMDL resulting in 50% increased enzyme activity were 0.43 and 0.31 mg/kg/day for EROD, 0.48 and 0.36 mg/kg/day for PROD, and 5.50 and 3.41 mg/kg/day for UDPGT.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

A NOAEL of 1 mg/kg/day and a LOAEL of 10 mg/kg/day were identified for reduced serum T_4 levels in fetal rats on Gd 20.

Uncertainty factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 3 for human variability

A component factor of 10 was not used for human variability because the MRL is based on effect levels identified in a sensitive subgroup (i.e., neonates exposed *in utero*).

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL: The NOAEL of 1 mg/kg/day and LOAEL of 10 mg/kg/day for reduced serum T_4 hormone levels in fetal rats that were exposed to pentaBDE in the acute MRL study (Zhou et al. 2002) are supported by a NOAEL of 3 mg/kg/day and LOAEL of 10 mg/kg/day for reduced serum T_4 levels in weanling rats that were exposed to octaBDE for 4 days (Zhou et al. 2001). Thyroid hormone levels were determined in groups of eight weanling (28-day-old) female Long-Evans that were treated by gavage for 4 days with commercial mixtures of decaBDE (DE-83R) or octaBDE (DE-79) in doses of 0.3, 1, 3, 10, 30, 60, or 100 mg/kg/day, or pentaBDE (DE-71) in doses of 0.3, 1, 3, 10, 30, 100, or 300 mg/kg/day. The animals were sacrificed on the day after the last exposure and evaluated for changes in serum total T_4, total T_3, and TSH, hepatic microsomal EROD, PROD, and UDPGT activities, and body and liver weight. No dose-related effects on any of the measured parameters were observed for decaBDE. OctaBDE and pentaBDE caused reduced thyroid hormone levels and increased microsomal enzyme activities.

Effects of octaBDE included dose-related reductions in serum total T_4 levels with statistically significant ($p<0.05$) decreases occurring at $10 mg/kg/day and a 70% maximum decrease compared to controls at 100 mg/kg/day (Zhou et al. 2001). Serum T_3 levels were reduced less than T_4 levels and were significant at $60 mg/kg/day with a maximum reduction of 25% at the highest dose of 100 mg/kg/day. There were no exposure-related changes in serum total TSH concentrations. Hepatic microsomal EROD and UDPGT

activities and relative liver weight were significantly ($p<0.05$) increased at $30 mg/kg/day and PROD activity was increased at $10 mg/kg/day in dose-related responses. No treatment-related effects on body weight or visible signs of toxicity were observed. Benchmark dose analysis of the octaBDE data found that the BMD and BMDL resulting in a 20% reduction in thyroid hormones (LED_{20}) were 9.25 and 5.29 mg/kg/day, respectively, for serum T_4 and 53.38 and 11.98 mg/kg/day, respectively, for serum T_3. The respective BMD and BMDL resulting in 50% increased enzyme activity were 3.66 and 2.45 mg/kg/day for EROD, 0.53 and 0.40 mg/kg/day for PROD, and 21.17 and 11.03 mg/kg/day for UDPGT.

Effects of pentaBDE included dose-related reductions in serum total T_4 levels with significant ($p<0.05$) decreases occurring at $30 mg/kg/day and an 80% maximum decrease compared to controls 300 mg/kg/day (Zhou et al. 2001). Serum total T_3 levels were reduced less than T_4 levels and were significant at $100 mg/kg/day with a maximum reduction of 30% at the highest dose of 300 mg/kg/day. There were no exposure-related changes in serum total TSH concentrations. Hepatic microsomal EROD and PROD activities and relative liver weight were significantly ($p<0.05$) increased at $10 mg/kg/day and UDPGT activity was increased at $30 mg/kg/day in dose-related responses. No treatment-related effects on body weight or visible signs of toxicity were observed. The BMD and BMDL resulting in a 20% reduction in thyroid hormones (LED_{20}) were 12.74 and 6.95 mg/kg/day, respectively, for serum T_4 and 32.94 and 8.56, respectively, mg/kg/day for serum T_3. The respective BMD and BMDL resulting in 50% increased enzyme activity were 2.88 and 1.82 mg/kg/day for EROD, 0.81 and 0.54 mg/kg/day for PROD, and 9.51 and 5.83 mg/kg/day for UDPGT.

Thyroid effects that mainly included reduced serum T_4 hormone levels and follicular cell hyperplasia have been observed in a number of other studies of PBDEs in orally-exposed animals. Other acute-duration studies showed decreases in serum T_4 in rats and mice exposed to $18 mg/kg/day pentaBDE for 14 days (Fowles et al. 1994; Hallgren et al. 2001). Effects observed in intermediate-duration studies include thyroid hyperplasia in rats exposed to $8 mg/kg/day octaBDE for 30 days (Norris et al. 1973, 1975) and reduced serum T_4 in rats exposed to $10 mg/kg/day pentaBDE for 90 days (WIL Research Laboratories 1984). Intermediate-duration exposure to a 77% decaBDE/22% nonaBDE commercial mixture caused thyroid hyperplasia in rats at doses $80 mg/kg/day for 30 days (Norris et al. 1973, 1975). Chronic (103-week) exposure to high-purity decaBDE ($97%) did not induce thyroid histopathological changes in rats at #2,550 mg/kg/day, although follicular cell hyperplasia developed in mice exposed to 2,240 mg/kg/day (NTP 1986).

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MINIMAL RISK LEVEL WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
CAS number(s): 32534-81-9 (pentaBDE), 32536-52-0 (octaBDE), 1163-19-5 (decaBDE)
Date: September 2002
Profile status: Draft for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 47
Species: Rat
MRL: 0.007 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: WIL Research Laboratories. 1984. 90-day dietary study in rats with pentabromodiphenyl oxide (DE-7) (Volume I-II). Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0524336.

Experimental design: PentaBDE (commercial mixture DE-71) was administered to Sprague-Dawley rats in the diet at dosage levels of 0, 2, 10, or 100 mg/kg/day for 90 days. Ten rats/sex/group were sacrificed after 4 weeks, 10 rats/sex/group were sacrificed at the end of the 90-day exposure period, and the remaining rats were sacrificed after a 6-week recovery period (5 rats/sex/group) or 24-week recovery period (5 rats/sex/group). Animals were observed daily for general appearance, behavior, signs of overt toxicity, and mortality during the dosing and recovery periods. Body weight and food consumption were measured during the dosing period and the first 4 weeks of the recovery period. Hematology, clinical chemistry (including serum T_3 and T_4), and urinalysis parameters, urine and liver porphyrin levels, and serum bromide levels were evaluated in 10 rats/sex/group at weeks 4 and 13. Bromine levels in liver, lung, kidney, thymus, and thyroid were evaluated at weeks 4, 13, 19, and 37. Gross necropsies and organ weight measurements (brain, gonads, heart, liver, kidneys, thymus, and thyroid) were performed on all rats. Histological examinations included liver, lung, kidney, thymus, thyroid, and gross lesions in all dose groups at the week 4, 13, 19, and 37 sacrifices and in all tissues (comprehensive evaluation) in the 0 and 100 mg/kg/day groups.

All statistical analyses were conducted using two-tailed tests for a minimum significance level of 5% comparing treatment groups to the controls. Analysis of weekly body weights, body weight changes, food consumption, clinical laboratory values, and absolute and relative organ weights were analyzed by a one-way analysis of variance and Dunnett's Test. The one-tailed Kolmogorov-Smirnov test was used for the 4- and 13-week histopathological diagnoses.

Effects noted in study and corresponding doses: Effects observed were observed at $2 mg/kg/day and included histological changes in the liver after 4 and 13 weeks of exposure as well as increased bromine levels in essentially all measured tissues. Hepatocytomegaly occurred in males at 2 mg/kg/day and both sexes were affected at the higher doses. Incidences of hepatomegaly in the control to high dose groups at 13 weeks were 0/10, 7/10, 10/10, and 10/10 in males and 0/10, 0/10, 8/10, and 10/10 (statistical tests not conducted) in females. Some hepatocytes in affected areas had vacuoles, which were empty in tissue sections and reportedly likely contained neutral lipid. Incidences of hepatocyte vacuolation at 13 weeks were 2/10, 4/10, 3/10, and 2/10 in males and 3/10, 5/10, 5/10, and 6/10 in females. The hepatocytomegaly was similar in incidence and severity after 4 and 13 weeks, appeared to be dose-related with respect to severity, and was not completely reversible as it was still observed in males at $10 mg/kg/day and in females at 100 mg/kg/day at 24 weeks postexposure in lessened severity and incidence. Females in the 2 and 100 mg/kg/day groups appeared to have an increased incidence of degeneration and necrosis of individual liver parenchymal cells at 24 weeks postexposure; the investigators concluded that this condition may represent the final loss of previously damaged cells and probably should be considered compound-related. Incidences of individual liver cell

degeneration/necrosis in the female control to high dose groups at 24 weeks postexposure were 2/5, 5/5, 2/5, and 5/5. Small increases in thyroid hyperplasia appeared to occur in lower dose groups; incidences in the control to high dose groups at 13 weeks were 0/10, 2/10, 2/10, and 5/10 in males and 0/10, 0/10, 1/10, and 4/10 in females. The thyroid hyperplasia was very slight in severity at 2 and 10 mg/kg/day, very slight to slight severity at 100 mg/kg/day, and reversible in that it was no longer observed at 24 weeks postexposure in any animals; the thyroid changes therefore were mild and transient. Serum T_4 levels were significantly reduced in both sexes at $10 mg/kg/day, indicating that 10 mg/kg/day is the LOAEL for thyroid effects. The slight thyroid hyperplasia and reductions in plasma T_4 levels are likely indirect consequences of hepatic enzyme induction. No compound-related changes were observed in any tissues other than the liver and thyroid at any dose level. Other effects observed at $10 mg/kg/day included increased serum bromide levels in both sexes at 4 weeks (only increased in both sexes at 100 mg/kg/day at 13 weeks), and increased urine porphyrins in both sexes and liver porphyrins in females (liver porphyrins increased in males at 100 mg/kg/day). Effects observed at 100 mg/kg/day included decreased body weight gain in both sexes, decreased food consumption in females, and increased serum cholesterol in both sexes at weeks 4 and 13, and increased absolute and relative liver weights in both sexes at 13 weeks (returned to normal ranges after 24 weeks of recovery).

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

The lowest tested dose, 2 mg/kg/day, is a minimal LOAEL for hepatic effects (hypertrophy, mild degeneration, and slight necrosis).

Uncertainty factors used in MRL derivation:

[X] 3 for extrapolation from a minimal LOAEL to a NOAEL
[X] 10 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 (reported doses)

Was a conversion used from intermittent to continuous exposure? NA.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA.

Other additional studies or pertinent information that lend support to this MRL: The hepatotoxic potential of PBDE mixtures is well-documented in animals by oral exposure. The spectrum of observed hepatic effects includes microsomal enzyme induction, liver enlargement, and degenerative histopathologic alterations that progress to tumors. Repeated dietary exposure to PBDEs typically caused liver enlargement with or without degenerative changes, and effects were generally dose-related in incidence and severity, more frequent and pronounced in males than females, and more severe with octaBDE and pentaBDE than decaBDE. Hepatic effects induced by chronic exposure to decaBDE included degeneration and thrombosis in rats exposed to 2,240 mg/kg/day and centrilobular hypertrophy and granulomas in mice exposed to $3,200 mg/kg/day (NTP 1986). Data from other intermediate-duration studies that support selection of the 2 mg/kg/day critical LOAEL include hepatic LOAELs of 5 mg/kg/day for cytomegaly (with vacuolation and necrosis at higher doses) in rats exposed to octaBDE for 13 weeks (IRDC 1977), 8 mg/kg/day for hepatocellular enlargement and vacuolation in rats exposed to octaBDE for 30 days (Norris et al. 1973, 1975), and 9 mg/kg/day for hepatocellular enlargement and increased liver weight in rats exposed to octaBDE or pentaBDE for 28 days (IRDC 1976).

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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

This chapter 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 end points 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 chapter covers end points 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 chapter. 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 Chapter 3 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 Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 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 end point 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 lowest-observed-adverse-effect level (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

Health Effects

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.

(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 1,1,2,2-tetrachloroethane 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 end point 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 9 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, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 6

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 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11	
Cancer						9	
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 6 [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).

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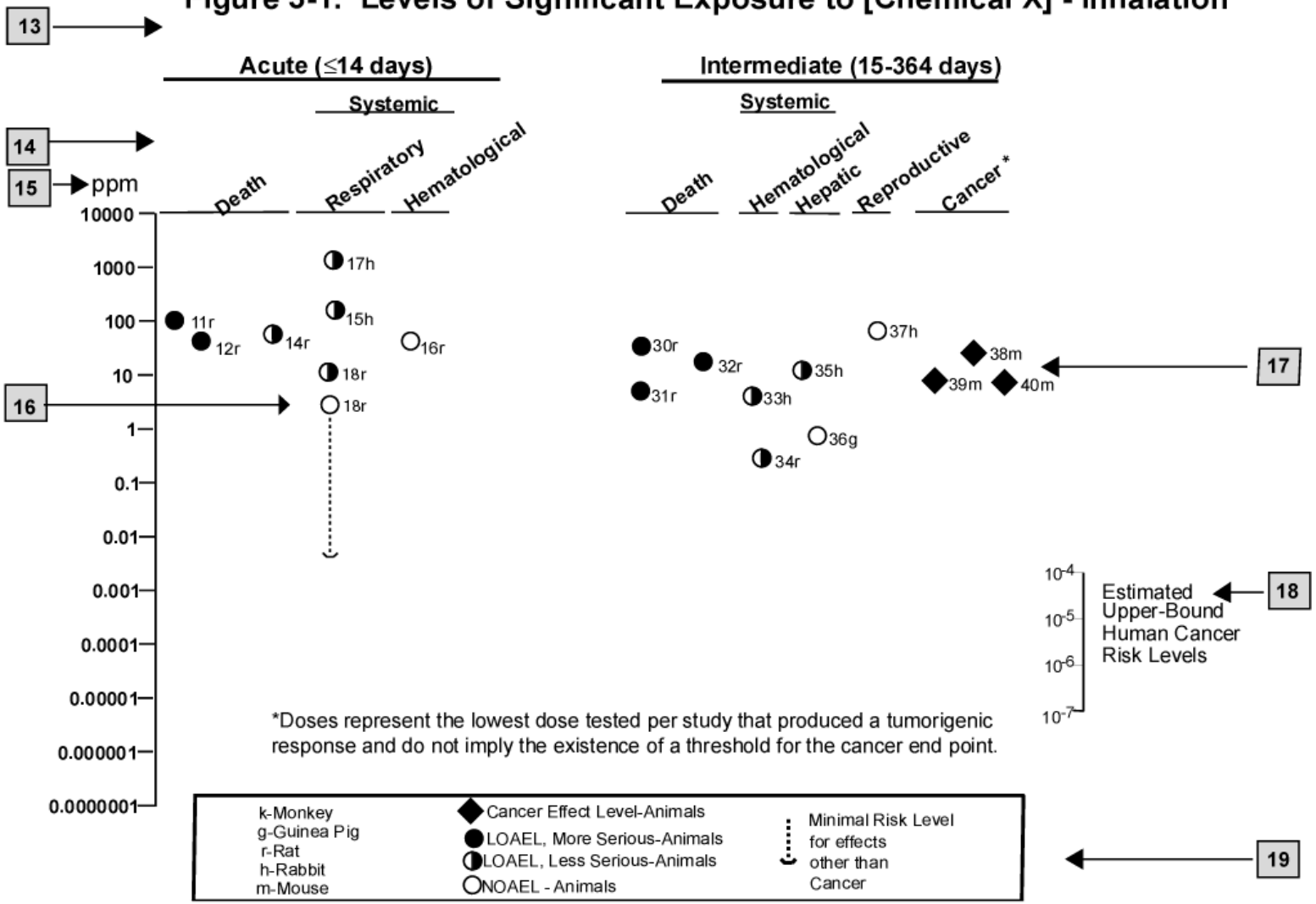
SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
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
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
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
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
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
LDH	lactic dehydrogenase
LH	luteinizing hormone
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

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
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
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
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
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
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
Pnd	postnatal day
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
RBC	red blood cell
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
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized 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 carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
$	greater than or equal to
=	equal to

APPENDIX C

<	less than
#	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

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