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

September 2004

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for PBBs and PBDEs, Draft for Public Comment, was released in 2002. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop F-32
Atlanta, Georgia 30333

FOREWORD

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

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

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

Each profile includes the following:

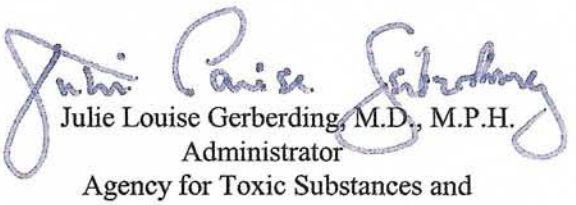
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

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

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

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



Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to 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 November 7, 2003 (68 FR 63098) . 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); October 21, 1999(64 FR 56792) and October 25, 2001 (66 FR 54014). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

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

Other Sections of Interest:

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

ATSDR Information Center

Phone:	1-888-42-ATSDR or (404) 498-0110	***Fax:***	(770) 488-4178
E-mail:	atsdric@cdc.gov	***Internet***:	http://www.atsdr.cdc.gov

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

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

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

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Hana R. Pohl, M.D., Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Stephen Bosch, B.S.
Syracuse Research Corporation, Syracuse, NY

Richard J. Amata, M.S.
Syracuse Research Corporation, Syracuse, NY

Carol J. Eisenmann, Ph.D.
Sciences International, Inc., Alexandria, VA

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

A peer review panel was assembled for polybrominated biphenyls and polybrominated diphenyl ethers. The panel consisted of the following members:

1. Martin Alexander, Ph.D., Professor, Department of Soil and Crop Sciences, Cornell University, Ithaca, New York;

2. Loren Koller, DVM, Ph.D., College of Veterinary Medicine, Oregon State University, 105 Magruder Hall, Corvallis, Oregon;

3. Christopher Metcalfe, Ph.D., Professor, Environmental and Resource Studies, Trent University, 1600 West Bank Drive, Peterborough, Ontario, Canada;

4. Larry W. Robertson, Ph.D., Professor, Graduate Center for Toxicology, University of Kentucky, Lexington, Kentucky; and

5. Lee R. Shull, Ph.D., Corporate Toxicology and Risk Assessment Practice Director, Montgomery, Watson, and Harza, Sacramento, California.

These experts collectively have knowledge of polybrominated biphenyls and polybrominated diphenyl ether's 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.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT—PBBs

This public health statement tells you about polybrominated biphenyls (PBBs) and the effects of exposure to PBBs.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. PBBs have been found in at least nine of the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that the number of sites at which PBBs are found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with PBBs. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE PBBs?

Polybrominated biphenyls (PBBs) are chemicals that were 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 PBBs were mixed into plastics rather than bound to them, they were able to leave the plastic and find their way into the environment. Commercial production of PBBs began in the 1970s. Manufacture of PBBs was discontinued in the United States in

1976. Concern regarding PBBs is mainly related to exposures resulting from an agriculture contamination episode that occurred in Michigan over a 10-month period during 1973–1974.

There are no known natural sources of PBBs in the environment. PBBs are solids and are colorless to off-white. PBBs enter the environment as mixtures containing a variety of individual brominated biphenyl (for PBBs) components, known as congeners. Some commercial PBB mixtures are known in the United States under the industrial trade name, FireMaster®. However, other flame retardant chemicals also may be identified by this name. PBBs are no longer used in North America because the agriculture contamination episode that occurred in Michigan in 1973–1974 led to the cessation of its production. More information on the physical properties and uses of PBBs can be found in Chapters 6 and 7.

1.2 WHAT HAPPENS TO PBBs WHEN THEY ENTER THE ENVIRONMENT?

In the past, PBBs entered the air, water, and soil during their manufacture and use. In addition, animal feed was accidentally mixed with 500–1,000 pounds of PBBs in lower Michigan in 1973. This contamination of the food chain affected millions of farm animals and humans living in Michigan at this time. PBBs entered the environment during the disposal of contaminated animal feed and animal products during the agriculture contamination episode. PBBs also entered the environment from PBB-containing wastes that manufacturers disposed of 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.

More information about what happens to PBBs in the environment can be found in Chapter 8.

1.3 HOW MIGHT I BE EXPOSED TO PBBs?

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 living 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 most people within the state of Michigan who were exposed to PBBs received very low levels of PBBs. The levels from exposure were slightly higher for people living in the lower peninsula of Michigan and highest among people 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, as well as the blood, urine, and body fat 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.

More information about exposure to PBBs can be found in Chapter 8.

1.4 HOW CAN PBBs ENTER AND LEAVE MY BODY?

If you breathe air that contains PBBs, or swallow food, water, or soil contaminated with PBBs, they can enter your body through your lungs and stomach and pass into the bloodstream. We don’t know how much of the PBBs will pass into the blood from the lungs; although most will probably pass into the blood from the stomach and intestines. If you touch soil containing PBBs,

it is highly unlikely that PBBs would pass through your skin into the bloodstream. It is not known how fast PBBs enter the blood from the lungs or stomach. There are no known current sources of PBBs because they are no longer produced and used in North America. They are rarely found in air and drinking water away from production plants and contaminated sites. Once PBBs are in your body, they can partially change into breakdown products called metabolites. Some metabolites and unchanged PBBs could leave your body, mainly in the feces and in very small amounts in the urine, within a few days. Other unchanged PBBs might stay in your body for many years. PBBs 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 also can enter the bodies of unborn babies through the placenta. More information on how PBBs can enter and leave your body can be found in Chapter 5.

1.5 HOW CAN PBBs AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. That sometimes involves animal testing. Animal testing may help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

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. Very little 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. Body weight loss and effects on the livers, kidneys, and thyroid glands were observed. A lifetime study of rats and mice fed PBBs at doses higher than those expected from environmental exposure. 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.

We do not know 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 babies of exposed rats 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. Because animals fed PBBs did develop cancer, 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.

We do not know whether the effects found in animals exposed to PBBs would also occur in people exposed in the same way. The amounts of PBBs that caused health effects in animals are much greater than levels of PBBs normally found in the environment. Long-term exposure to these chemicals has a greater potential to cause health effects than does short-term exposure to low levels because they tend to build up in your body over many years. More information on how PBBs can affect your health can be found in Chapter 5.

1.6 HOW CAN PBBs AFFECT CHILDREN?

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

Children are exposed to PBBs in generally the same way as are adults, mainly by eating contaminated food. Because of their smaller weight, children's intake of PBBs per kilogram (or pound) 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, although fetuses in the womb are also exposed. Children who live near hazardous waste sites might accidentally eat some PBBs by putting dirty hands or other soil/dirt-covered objects in their mouths, by eating without washing their hands, or similar behavior. Some children also eat dirt on purpose. It is not possible that children could be exposed to PBBs following transport of the chemical on clothing from the parent's workplace to the home because PBBs are no longer being produced or used.

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. Changes in nerve and brain function have been seen in animals that were exposed to PBBs in the womb and by

nursing. Animal studies also found that exposure to PBBs during pregnancy or lactation caused changes in thyroid hormone levels in the newborn animals and, at high doses, increases in prenatal death and structural birth defects.

As indicated above, children can be exposed to PBBs before birth and from breast milk. PBBs are stored in the mother's body and can be released during pregnancy, cross the placenta, and enter fetal tissues. Because PBBs dissolve readily in fat, they can accumulate in breast milk fat and be transferred to babies and young children. PBBs 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 and breast feeding. Because the nervous system and thyroid are still developing in the fetus and child, the effects of PBBs on these target systems might be more profound from exposure before and soon after birth. That could mean fetuses and children are more susceptible to PBBs than are adults.

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

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

Because PBBs are no longer produced or used, the risk of exposure to these compounds is limited. You and your children could be exposed to PBBs 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 still contain PBBs. Children should also be discouraged from eating the dirt, and careful handwashing practices should be followed.

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

Special tests can determine whether PBBs are in the blood, body fat, and breast milk. These are not regular or routine clinical tests, but could be ordered by a doctor to detect PBBs in people

exposed to them in the environment and at work. If your PBB 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 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 to a greater extent than the general population, they do not predict whether you will be harmed. Blood tests are the easiest, safest, and probably the best method for detecting recent or past exposures to large amounts of PBBs. Results of such tests should be reviewed and carefully interpreted by physicians with a background in environmental and occupational medicine. Exposures to PBBs have been of greatest concern in Michigan as explained in Sections 1.3 and 1.5. More information on tests used to determine whether you have been exposed to PBBs can be found in Chapter 5 (Section 5.11) and Chapter 9 (Section 9.1).

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

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically 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:

At present, there are no federal guidelines or recommendations for protecting human health from exposure to PBBs.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns about PBBs, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov/toxpro2.html and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. PUBLIC HEALTH STATEMENT—PBDEs

This public health statement tells you about polybrominated diphenyl ethers (PBDEs) and the effects of exposure to PBDEs.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. PBDEs have not been found in the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that PBDEs may be found in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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 PBDEs, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with PBDEs. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

2.1 WHAT ARE PBDEs?

PBDEs are flame-retardant chemicals that are added to a variety of consumer products to make them difficult to burn. Because PBDEs are added rather than reacted to the product, they could leave the product under ideal conditions and enter the environment, but this rarely happens. The first commercial productions of PBDEs began in the 1970s in Germany. Production of PBDEs has continued until the present. There are three commercial PBDE products (i.e., penta-, octa-,

and decabromodiphenyl ethers). Deca- and octa-brominated types of PBDEs are also produced outside of the United States (in China and Israel). Decabromodiphenyl ether (decaBDE) makes up 82% of these products manufactured globally. Its main use is for electronic enclosures, such as television cabinets. Octabromodiphenyl ether (octaBDE) product is used in plastics for business equipment. Pentabromodiphenyl ether (pentaBDE) product is used in foam for cushioning in upholstery. PBDEs have not been associated with actual health-related effects. Concerns have increased, however, because some of these chemicals (particularly PBDEs in the pentaBDEs) have been found in the environment at varying concentrations. Environmental concentrations of lower brominated PBDEs, which may be leveling off in Europe, appear to be increasing in certain areas of Canada and the United States.

PBDEs are a group of synthetic organic chemicals with no known natural sources in the environment, except for a few marine organisms that produce forms of PBDEs that contain higher levels of oxygen. Commercial decaBDE and octaBDE products are colorless to off-white solids, whereas commercial pentaBDE product is a thick liquid. PBDEs are not expected to evaporate into the air. PBDEs in the air are mostly found with dust rather than as a vapor. PBDEs enter the environment as mixtures containing a variety of individual brominated diphenyl ether (for PBDEs) components, known as congeners. Congeners are distinct members of a class of chemical substances. Some commercial mixtures of PBDEs may be known by their industrial trade names, (i.e., DE-60F Special, DE-61, DE-62, DE-71, DE-79, DE-83R, Saytex® 102E). PBDEs are still produced and widely used in the United States, although the sole manufacturer of penta- and octaPBDE commercial products in the United States is expected to quit making these chemicals by the end of 2004. More information on the physical properties and uses of PBDEs can be found in Chapters 6 and 7.

2.2 WHAT HAPPENS TO PBDEs WHEN THEY ENTER THE ENVIRONMENT?

PBDEs enter air, water, and soil during their manufacture and use in consumer products. When PBDEs are suspended in air, they can be present as particles. They eventually return to land or water as the dust settles and are washed out by snow and rainwater. 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 very small amounts of PBDEs that do occur in water stick to particles and eventually settle to the bottom. Sediments at the bottom of bodies of water, such as lakes and rivers, generally act as reservoirs for decaBDEs, which can remain there for years. Some lower brominated PBDEs (e.g., tetra- and penta-congeners of PBDE) in water may build up in fish to low concentrations (about 10 billionths of a gram to 1 millionth of a gram of PDBE per gram of fresh fish [or $10x10^{-9}$–$1x10^{-6}$ grams of PBDE per gram of fresh fish]). However, higher brominated PBDEs, such as decaBDE, are not found in fish at measurable concentrations. 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 particles. Rainwater is not expected to spread them much below the soil surface; thus, it is unlikely that PBDEs will enter groundwater.

More information about what happens to PBDEs in the environment can be found in Chapter 8.

2.3 HOW MIGHT I BE EXPOSED TO PBDEs?

Certain PBDE mixtures, especially decaBDE, are produced in many places in the world. Currently, the United States is the only producer of the pentaBDE mixture for commerce. However, production pentaBDE and octaBDE for commerce soon will begin to be phased out in the United States and elsewhere. Lower brominated PBDEs, such as tetraBDE and pentaBDE congeners, are found throughout the environment and are found at low levels in air, sediments, animals, and food. The concentrations of lower brominated PBDEs in blood, breast milk, and body fat indicate that most people are exposed to low levels of these PBDEs. Concentrations of lower brominated PBDEs have been increasing in tissues and body fluids of individuals living in the United States. Currently, levels of lower brominated PBDE congeners in individuals living in the United States are greater than levels reported in other regions of the world. Highly brominated congeners, such as decaBDE, are not commonly found throughout the environment. They may be found at low levels close to places where they are produced or used. In 2001, PBDEs were detected in dust and smoke samples taken near the World Trade Center disaster site. Although no definitive studies in the United States have been conducted to identify the sources of exposure, people appear to be exposed to the lower brominated congeners of PBDEs by eating food that contains these PBDEs. In the United States, the concentration of PBDEs

(primarily the tetra- and penta-brominated congeners of PBDEs) in outdoor air ranges from 2 to 77 trillionths of a gram per cubic meter (or $2–77x10^{-12}$ grams/m^3), which indicates low levels of exposure of the general population to these PBDEs. Indoor air concentrations of PBDEs in lecture halls, indoor environments with computers, and rooms with computers or other electronic devices, such as television sets, also have low levels of PBDEs in suspended dust. Workers involved in the manufacture and production of PBDE-containing resins are exposed to higher concentrations of PBDEs. Occupational exposure can also occur in confined workplaces where plastic and foam products containing PBDEs are recycled, or where computer monitors containing PBDEs are repaired. People who live near hazardous waste sites may be exposed to PBDEs by breathing air containing PBDE-contaminated dust. However, PBDE eventually settles or washes out of the air, so this potential exposure route likely to be minimal.

More information about exposure to PBDEs can be found in Chapter 8.

2.4 HOW CAN PBDEs ENTER AND LEAVE MY BODY?

The main source of exposure to PBDEs may be through foods, particularly those with high fat content, such as fatty fish. Some lower brominated PBDEs have been detected in air samples, indicating that people can also be exposed by inhalation. The ways that PBDEs might enter and leave your body depend on the chemical structures of the congener components. The higher brominated PBDEs, particularly decaBDE (the major PBDE in use today), act much differently in the body than do lower brominated PBDEs. If you breathe air that contains PBDEs, or swallow food, water, or soil contaminated with PBDEs, the lower brominated congeners are much more likely than decaBDE to enter your body through your lungs and stomach and pass into the bloodstream. If you touch soil containing PBDEs, which could happen at a hazardous waste site, it is highly unlikely that either lower or higher brominated PBDEs would pass through your skin into the bloodstream. Once PBDEs are in your body, the congeners might partially change into breakdown products called metabolites. DecaBDE might leave your body unchanged or as metabolites, mainly in the feces and in very small amounts in the urine, within a few days. Lower brominated PBDEs, generally tetra-, penta-, and hexaBDE congeners, might stay in your body for many years, stored mainly in body fat. The lower brominated PBDEs also

tend to concentrate in breast milk fat, and can enter the bodies of children through breast feeding. PBDEs also can enter the bodies of unborn babies through the placenta. More information on how PBDEs can enter and leave your body can be found in Chapter 5.

2.5 HOW CAN PBDEs AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Nothing definite is known about the health effects of PBDEs in people. Practically all of the available information is from studies of laboratory animals. Animal studies indicate that commercial decaBDE mixtures are generally much less toxic than the products containing lower brominated PBDEs. Because of its very different toxicity, decaBDE is expected to have relatively little effect on the health of humans. Rats and mice that ate food containing moderate amounts of lower brominated PBDEs for short periods of time had mainly thyroid effects. Rats and mice that ate smaller amounts over several weeks or months developed effects in the liver and in the thyroid. It is speculated that many of the thyroid effects of PBDEs are specific to the species of test animals, suggesting that they are less likely to occur in humans. Subtle behavioral changes have been observed in animals exposed to PBDEs as infants. One possible explanation for the behavioral effects might be related to changes in the thyroid, because development of the nervous system is dependent on thyroid hormones. PBDEs have not caused other kinds of birth defects in animals, but more studies are needed to determine if PBDEs can impair reproduction. Preliminary findings from short-term animal studies suggest that some PBDEs might impair the

immune system. Animals exposed to PBDEs by skin contact showed signs of skin irritation only if they had been scratched.

We don't know if PBDEs can cause cancer in people, although liver tumors developed in rats and mice that ate extremely large amounts of decaBDE throughout their lifetime. On the basis of evidence for cancer in animals, decaBDE is classified as a possible human carcinogen by EPA. Lower brominated PBDEs have not yet been tested for cancer. Neither the U.S. Department of Health and Human Services (DHHS) nor the International Agency for Research on Cancer (IARC) have classified the carcinogenicity of any PBDEs.

We don't know whether the effects found in animals exposed to PBDEs would also occur in people exposed in the same way. The amounts of PBDEs that caused health effects in animals are much greater than levels of PBDEs normally found in the environment. Long-term exposure to PBDEs has a greater potential to cause health effects than does short-term exposure to low levels because of their tendency to build up in your body over many years. Additionally, the lower brominated commercial pentaBDE and octaBDE products are much more likely to cause health effects than is decaBDE. More information on how PBDEs can affect your health can be found in Chapter 5.

2.6 HOW CAN PBDEs AFFECT CHILDREN?

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

Children are exposed to PBDEs in generally the same way as are adults, probably mainly by eating contaminated food. Because of their smaller weight, children's intake of PBDEs per kilogram (or pound) of body weight may be greater than that of adults. The most likely way that infants might be exposed to PBDEs is from breast milk containing lower brominated congeners, although fetuses in the womb could also be exposed. DecaBDE is poorly absorbed in the body and, therefore, is unlikely to be found in breast milk or the fetus to any significant extent. Children who live near hazardous waste sites might accidentally eat some PBDEs by putting

dirty hands or other soil/dirt covered objects in their mouths, or through eating without washing their hands. Some children also eat dirt on purpose. 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.

As indicated above, children can be exposed to PBDEs—mainly the lower brominated congeners—both before birth and from breast milk. The lower brominated PBDEs are much more likely than decaBDE to be stored in the mother's body and released during pregnancy, cross the placenta, and entering fetal tissues. Because lower brominated PBDEs dissolve readily in fat, they can accumulate in breast milk fat and be transferred to babies and young children. Lower brominated PBDEs have been found in breast milk. In most cases, however, 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 PBDEs and breast feeding. The nervous system and thyroid are still developing in the fetus and child. That means the effects of lower brominated PBDEs on these systems might be more significant if exposure occurs during the periods before and soon after birth. That suggests that fetuses and children are more susceptible to PBDEs than adults.

More information regarding children's health and exposure to PBDEs can be found in Chapter 5 (Section 5.7).

2.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PBDEs?

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

PBDEs are currently in widespread production and use. However, production of commercial pentaBDE and octaBDE products will soon begin to be phased out in the United States and elsewhere. You and your children may by exposed to lower brominated PBDEs by eating fish or wildlife 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 PBDEs. Children should also be discouraged from eating dirt, and careful handwashing practices should be followed.

As mentioned in Section 2.3, workplace exposure to PBDEs can occur during the production of commercial PBDE mixtures and of PBDE-containing plastic products. Workers involved in recycling plastic products, or who repair computers in confined workplaces can also be exposed to PBDEs. If you are exposed to PBDEs while at work, you may 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 whether those are likely to be carried home. If this is the case, you should shower and change clothing before leaving work. Your work clothes should be kept separate from other clothes and laundered separately.

2.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PBDEs?

Special tests can determine whether PBDEs are in the blood, body fat, and breast milk. These are not regular or routine clinical tests, but could be ordered by a doctor to detect PBDEs in people exposed to them in the environment and at work. If your 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 PBDEs that you have been exposed to, or how long you have been exposed. Blood tests cannot distinguish between recent or past exposures to PBDEs because these chemicals remain in the body a long time. Although tests can indicate whether you have been exposed to PBDEs to a greater extent than the general population, they do not predict whether you will be harmed. Blood tests are the easiest, safest, and probably the best method for detecting recent exposures to large amounts of PBDEs. Results of such tests should be reviewed and carefully interpreted by physicians with a background in environmental and occupational medicine. Nearly everyone has been exposed to pentaBDE commercial mixtures because they are found throughout the environment. That means people are more likely to have detectable amounts of the lower brominated PBDEs in their blood, fat, and breast milk. Recent studies have shown that levels of lower brominated

PBDEs in the general population of the United States continue to rise. The U.S. levels are 10–100 times higher than levels in individuals living in Europe.

More information on tests used to determine whether you have been exposed to PBDEs can be found in Chapter 5 (Section 5.11) and Chapter 9 (Section 9.1).

2.9 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. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals. Those levels are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically 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 PBDEs include the following:

EPA requires that companies that transport, store, or dispose of *p*-bromodiphenyl ether (a particular PBDE compound not found in any commercial PBDE product) 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 PBDEs, see Chapter 10.

2.10 WHERE CAN I GET MORE INFORMATION?

If you have more questions or concerns about PBDEs, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov/toxpro2.html and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-888-42ATSDR (1-888-422-8737), by e-mail at atsdric@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

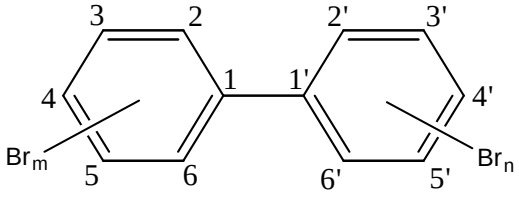
National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

3. RELEVANCE TO PUBLIC HEALTH—PBBs

3.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PBBs IN THE UNITED STATES

Polybrominated biphenyls (PBBs) 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 when conditions are ideal. 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.

PBBs are classes of structurally similar brominated hydrocarbons in which 2–10 bromine atoms are attached to the molecular structure (i.e., biphenyl). Monobrominated structures (i.e., one bromine atom attached to the molecule) are often included when describing PBBs. There are 209 different molecular combinations, or congeners, that are possible for PBBs. However, unlike polychlorinated biphenyls (PCBs), only a subset of these 209 congeners exists in commercial mixtures. Based on the number of bromine substituents, there are 10 homologous groups of PBB 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 are similar when viewed in one dimension, as shown below, where m+n = 1–10:



where m + n = 1–10

Due to the position and number of bromine atoms, there are important three-dimensional differences in the structures of PBBs that can influence the molecules' receptor interactions and toxicological properties (see Section 5.5, Mechanisms of Action).

People are environmentally exposed to PBBs 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 5.4, because PBBs are lipophilic and some congeners are not readily metabolized, they are likely to be retained in the body for long periods of time (years).

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 hexabromobiphenyl 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'-hepta-bromobiphenyl. 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 5.4.2.2, 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.

3.2 SUMMARY OF HEALTH EFFECTS

Most of the information on human health effects of PBBs comes from studies of Michigan populations where PBB-contaminated cattle feed accidentally led to entrance into the feed/food chain, and some information is available on health effects in PPB-exposed chemical workers. Although the human 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. A variety of symptoms (e.g., neurological and neuropsychiatric, gastrointestinal, hepatic, dermal, and musculoskeletal) have been reported, but the prevalence of these symptoms has not been definitively linked to the extent or types of exposure. Other reported effects in humans include neurodevelopmental effects in exposed children and immunological changes. Physical examinations and laboratory tests have shown few abnormalities that corresponded to the complaints, and prevalences of symptoms have 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 involved oral exposure, and numerous effects have been documented including hepatic, renal, dermal/ocular, immunological, neurological, and developmental. Other effects of oral exposure to PBBs include decreased thyroid function, body weight loss, and liver cancer. Adverse hepatic effects, as well as dermal and ocular effects, also 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, and the mixtures that were tested (octabromobiphenyl and decabromobiphenyl) are not the lower brominated products (i.e., Firemaster mixtures) expected to be the most toxic based on oral data. A number of PBB effects are dioxin-like and consistent with the Ah receptor-mediated mechanism of action, including altered vitamin A homeostasis, thymic atrophy, dermal and ocular effects (e.g., chloracne and inflammation of eyelids), and body weight changes (wasting syndrome). The main health effects of PBBs are discussed in detail below.

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, and in rats in intermediate-duration studies at doses as low as 0.05 mg/kg/day (increased number and decreased size of follicles). No information is available on possible changes in thyroid hormones following chronic exposure. Histological examinations in chronic-duration studies found no thyroid alterations in rats at doses as high as 1.5 mg/kg/day (highest tested dose), although follicular cell hyperplasia was induced in mice at ≥1.3 mg/kg/day. The no-observed-adverse-effect level (NOAEL) of 1 mg/kg/day was used 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 is 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 lympho-proliferative 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 is 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 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.

3.3 MINIMAL RISK LEVELS

A number of the toxic effects of PBBs, including immunotoxicity, inhibition of body weight gain, and hepatic changes, appear to be mediated by a common mechanism of toxic action that involves a specific cytosolic molecular receptor (Ah receptor) (see Chapter 5, Section 5.5.2, Mechanisms of Toxicity). Although numerous factors can influence the toxicity of PBBs; including differences in absorption, distribution, and retention among animal species, at the tissue level, the potency of some individual congeners is determined by the magnitude of the response that is initiated by its binding with the Ah receptor. The binding affinity, in turn, is determined by the substitution pattern of the congener, and

many of the most toxic congeners resemble the structural configuration of 2,3,7,8-TCDD, and therefore are dioxin-like in toxicity. However, congeners that exhibit Ah receptor-mediated responses constitute a fraction of the components in commercial PBB mixtures. Therefore, it is presumed that congeners that act by other mechanisms also contribute to the toxicity of PBB mixtures, and the toxicity of PBBs is commonly classified as either "dioxin-like" or "nondioxin-like." The mechanism(s) of toxicity for nondioxin-like PBB congeners is less clearly elucidated, but also may involve receptors (e.g., the estrogen receptor), or the involvement of reactive intermediates (e.g., arene oxides) that can form potentially toxic covalently bound substrate-macromolecular adducts.

People are environmentally exposed to PBB mixtures of different congeneric composition than the original commercial PBB products. Although the toxicity or potency of environmental PBB 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. 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, (2) different PBB congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PBBs 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 and other structurally similarly compounds (e.g., PCBs, CDDs, CDFs, and PBDEs) in the environment, data from commercial PBB mixtures are used to develop MRLs for assessing health risks from environmental exposures to PBBs.

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. Despite the fact that an appropriate statistical test (t-test rather than an ANOVA with multiple comparison tests) was used to analyze the data, ATSDR is confident with the designation of the NOAEL and LOAEL values. The data in the manuscript are presented graphically, with the animal numbers presented as a range (8–11 animals/group); thus, an ANOVA could not be performed from published report. However, using the graphical data, the change in plasma T_4 levels in the 3 mg/kg/day groups is clearly on the order of 20–30%, which represents a biologically significant change. As such, the identification of 3 mg/kg/day as a LOAEL, and 1 mg/kg/day as a NOAEL, is not contraindicated by the lack of appropriate statistical analysis.

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, 1975b; 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). As the most sensitive effect seen following intermediate-duration oral exposure was a serious LOAEL, without an accompanying NOAEL, 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 similarly precluded by the serious developmental effect (stillbirth) that occurred following exposures

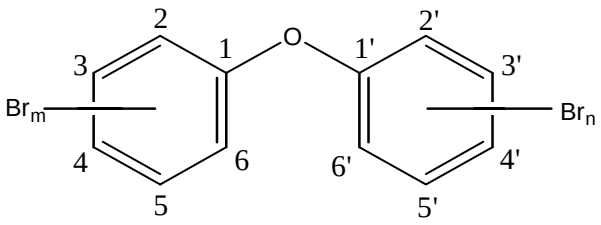
exceeding 1 year in duration. The serious LOAEL in monkeys is lower than the lowest chronic dosages tested in other species (0.5 and 1.3 mg/kg/day in rats and mice, respectively) that caused decreased survival (NTP 1992). ATSDR's classification of LOAELs into less serious and serious effects is discussed in the introduction to Section 5.2.

4. RELEVANCE TO PUBLIC HEALTH—PBDEs

4.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PBDEs IN THE UNITED STATES

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 when conditions are ideal. Production of PBDEs began in the 1970s and has continued to the present. Concern for the possible health effects of PBDEs has heightened recently due to evidence that components of pentabromodiphenyl ether (pentaBDE) commercial mixtures are ubiquitously distributed at very low levels in the environment, biota, human tissues, and breast milk. Body-burden data indicate that the general population is exposed to low levels of primarily lower brominated (e.g., tetra- and penta-) BDEs. For example, the median concentrations of BDE 47, BDE 153, BDE 183, BDE 209, and total PBDEs (sum of four congeners) were 0.63, 0.35, 0.17, <1, and 2.2 ng/g lipid weight, respectively. DecaBDE was found at levels above the limit of quantification (1 pmol/g lipid). Environmental concentrations of lower brominated PBDEs (i.e., tetraBDE and pentaBDE) appear to be leveling off in Europe, but appear to be increasing in certain areas in Canada and the United States, although data are too sparse to make broad statements regarding trends. The concentration of total PBDEs in air ranges from 5.5 pg/m^3 in rural environments to 52 pg/m^3 in urban air. Because PBDEs are hydrophobic in nature, this class of compounds has not been detected in water to any significant extent. Environmental concentrations of higher brominated commercial mixtures (e.g., decabromodiphenyl ether or decaBDE) are principally concentrated in soils and sediment near industrial point sources.

PBDEs are classes of structurally similar brominated hydrocarbons in which 2–10 bromine atoms are attached to the molecular structure (i.e., diphenyl ether). Monobrominated structures (i.e., one bromine atom attached to the molecule) are often included when describing PBDEs. There are 209 different molecular combinations, or congeners, that are possible for PBDEs, although only a limited number exist in commercial mixtures. Based on the number of bromine substituents, there are 10 homologous groups of 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 structure of PBDEs is shown below:



where m + n = 1–10

Due to the ether linkage and the position and number of bromine atoms, there are important three-dimensional differences in the structures of PBDEs that can influence the molecules' receptor interactions and toxicological properties as discussed in Section 5.5, Mechanisms of Action. In general, PBDEs are not expected to have the same array of three-dimensional conformations as either PBBs or polychlorinated biphenyls (PCBs).

People are environmentally exposed to PBDEs of different congeneric composition than the source commercial mixtures, which have specific congeneric compositions. People are also environmentally exposed to lower brominated PBDEs (e.g., tetra- and penta- brominated congeners) due to differential partitioning and transformation of the individual congeners in the environment, including transformation in food animals. Additionally, as discussed in Section 5.4, because 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).

Three commercial PBDE mixtures have been and continue to be produced: decaBDE, octaBDE, and pentaBDE. DecaBDE has accounted for more than 80% of world PBDE usage. The composition of commercial decaBDE is ≥97% decaBDE, with the remainder mainly nonabromodiphenyl ether (nonaBDE). Commercial octaBDE is a mixture of congeners ranging from hexabromodiphenyl ether (hexaBDE) to nonaBDE, and mixtures of pentaBDE are comprised of tetrabromodiphenyl ether (tetraBDE) to hexaBDE congeners. Congeners with less than four bromine atoms are generally not found in commercial PBDEs. The main isomers in the commercial pentaBDE product are 2,2',4,4',5-penta-bromodiphenyl ether (i.e., 2,2',4,4',5-pentaBDE or BDE 99; see Section 6-1) and 2,2',4,4'-tetrabromo-diphenyl ether (i.e., 2,2',4,4'-tetraBDE or BDE 47; see Section 6-1). DecaBDE seems to be largely resistant to environmental degradation. However, there is very little information on the environmental degradation of decaBDEs and the data that exist are controversial. Octa- and pentaBDE commercial mixture components, that have a total of four or less bromines, likely undergo differential partitioning

(e.g., bioconcentration in aquatic organisms) and possibly some type of transformation process (e.g., photodegradation) as well. The octa- and pentaBDE mixture components have more readily yielded the predominance of lower-brominated tetra- and penta-congeners, particularly BDE 47, BDE 99, and 2,2',4,4',6-pentaBDE (i.e., 2,2',4,4',6-pentaBDE or BDE 100; see Section 6.1), which have been detected in environmental and human tissue samples (including breast milk). Most studies indicate that levels of lower brominated BDEs in body fluids are a factor of 10–100 higher for individuals living in the United States compared to individuals living in other regions of the world (e.g., Europe). The main source of human exposure to lower brominated PBDE congeners may be from dietary intake, particularly from foods with high fat content (e.g., fatty fish). Lower-brominated tetra- and penta- congeners have been detected in air samples, including those taken from remote areas, indicating that inhalation may also be a potential exposure route for the general population.

4.2 SUMMARY OF HEALTH EFFECTS

Information is available on the potential health effects of all three classes of commercial PBDE products, i.e., decaBDE (also referred to as DBDPO), octaBDE, and pentaBDE. As subsequently discussed, the toxicity of decaBDE is generally much less pronounced than for octa- and pentaBDE commercial products following acute and repeated-dose exposures. This dissimilar toxicity is likely related to the preferential accumulation of lower brominated congeners in the body, due to their greater partitioning and retention in lipid-rich tissues and lower rates of metabolism and elimination relative to decaBDE. In particular, in comparison with the lower brominated mixtures, oral studies in rats found that 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 appear to be related to the number and location of bromines on the diphenyl oxide molecule, and correlate with environmental monitoring data indicating that decaBDE has low bioaccumulation potential. Three-dimensional differences in molecular structure might also contribute to the dissimilar toxicity between congeners (see discussions in Section 4.3 and Section 5.5.2).

The preponderance of health effects data on PBDEs is from studies of orally exposed laboratory animals. Based on the information summarized below and detailed in Chapter 5 (Health Effects), the animal data indicate that decaBDE is much less likely than lower brominated PBDEs to cause health effects in humans, and that main targets of concern for lower brominated PBDEs in humans are the liver, thyroid, and neurobehavioral development. Intermediate- and chronic-duration oral studies in rats and mice found that penta- and octaBDE commercial mixtures caused effects mainly in the liver and thyroid, particularly

enlargement and histological alterations in both organs and changes in serum levels of thyroid hormones. Little information is available on potential neurotoxic effects of PBDEs. PBDEs have not been tested for neurotoxicity using comprehensive test batteries, and most studies used a single dose level of a single congener. Mild impairments in spontaneous motor behavior and learning and memory were found in mice that were exposed to single low doses of 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',5,5'-hexaBDE (BDE 153), and/or 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209) during perinatal and/or early postnatal periods and tested later in life. Concern for neurodevelopmental toxicity of PBDEs is further raised by the documented effects of lower brominated commercial mixtures on thyroid hormone homeostasis, and critical involvement of thyroid hormones in central nervous system development.. Several acute-duration studies with commercial pentaBDE mixtures and the single congener, 2,2',4,4'-tetraBDE (BDE 47), suggest that immune suppression might be another important health end point for lower brominated BDEs, although comprehensive immunological evaluations have not been performed on any congener or commercial mixture. Information on the reproductive toxicity of PBDEs is limited to a one-generation study of a low-purity decaBDE product (77.4% decaBDE, 21.8% nonaBDE, 0.8% octaBDE) in rats that found no exposure-related functional effects. Developmental toxicity studies have shown no evidence of teratogenicity of penta- and octaBDEs in rats and rabbits, although fetotoxic effects, including skeletal ossification variations at maternally toxic doses, have occurred. No fetotoxic or teratogenic effects were induced in rats exposed to high, but not maternally toxic, doses of commercial decaBDE. Information on the carcinogenicity of PBDEs is limited to one chronic oral study of decaBDE and one chronic oral study of lower-brominated PBDEs. The decaBDE study found that lifetime exposure to a high-purity commercial product decaBDE caused neoplastic changes in the liver, including neoplastic nodules in rats and hepatocellular adenomas and carcinomas in mice. Equivocal increases in thyroid gland follicular cell tumors were also observed in mice. The study of lower brominated PBDEs used a former commercial product containing 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE. No neoplastic effects occurred in rats exposed to this mixture for approximately 2 years, but the power of this study to detect carcinogenic effects is limited by very low dose levels and testing of only one species. The weight of available genotoxicity evidence indicates that PBDEs are not genotoxic. Dermal application studies in rabbits showed that decaBDE, octaBDE, and pentaBDE were nonirritating 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 nonsensitizing 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 thyroid

stimulating hormone (TSH), low or borderline low serum T_4, and increased thyroid antimicrosomal antibody titers in workers exposed to decaBDE and/or unspecified PBBs. Due to the mixed nature of the exposure, the possible effects cannot be solely attributed to either chemical. There was no clear association between plasma levels of BDE 47 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 evidence in animals as summarized below, the thyroid is particularly sensitive to lower brominated PBDEs and a possible target of toxicity in exposed humans.

Thyroid effects, which mainly included reduced serum T_4 hormone levels and follicular cell hyperplasia, were consistently observed in rats and mice orally exposed to lower brominated commercial PBDE mixtures. Accompanying changes in serum TSH levels were not found, and the depression of serum T_4 seems to involve enhanced metabolic formation of hydroxylated metabolites of PBDEs, which bind with high affinity to thyroid transport proteins. 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 included 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 a high-purity (≥97%) commercial decaBDE mixture did not induce thyroid histopathological changes in rats at ≤2,550 mg/kg/day, although follicular cell hyperplasia was increased in mice exposed to 2,240 mg/kg/day of the same commercial product.

The extent that PBDEs affect circulating levels of T_4 or T_3 might vary with species and rats are often regarded as more sensitive than humans. The main basis for this opinion seems to be studies showing that PBDEs affect binding of thyroid hormones to transthyretin (TTR), the primary transport protein in rats. Because TTR is not the major transport protein in humans, the findings have been interpreted as evidence that humans will be less sensitive than rats to thryoid effects of PBDEs. As discussed in Section 5.5.3, the greater sensitivity of rats is thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid, and to a more rapid clearance of secreted hormone in the rat; the latter being, in part, related to the absence of thyroid binding globulin (TBG) in rats. Whereas TTR is the major thyroid hormone binding protein in rats, TBG is the main binding protein in humans and most other mammals.

However, although TTR is not the main transport protein in human serum, it is the principal protein involved in transport of T_4 to the brain in both rats and man. Therefore, without specific evidence that rats are more sensitive to PBDEs than humans, and considering the importance of TTR for the transport of thyroid hormones in the human brain, it is misleading to assume that PBDEs are unlikely to affect thyroid function in humans, or that humans are less sensitive to these effects than rats.

Neurological Effects. A limited amount of information is available on neurological effects of commercial PBDE mixtures. No clinical signs of neurotoxicity or neurohistopathology were observed in rats or mice exposed to commercial decaBDE in dietary doses as high as 16,000–19,000 mg/kg/day for 14 days, 8,000–9,000 mg/kg/day for 13 weeks, or 2,550–7,780 mg/kg/day for 103 weeks. Although the high doses and extended exposure durations provided opportunities for the induction and/or development of clinical signs, the study is limited by lack of testing for subtle behavioral changes and neuro-developmental effects. A commercial pentaBDE mixture was evaluated for several behavioral end points in offspring of rats that were perinatally exposed to 1–100 mg/kg/day by gavage on gestation day (GD) 6 through postnatal day (PND) 21. Evaluation of the offspring as adults showed no alterations in motor or sensory development as assessed by motor activity, habituation, and auditory startle response, although suggestive decreases in fear conditioning were observed.

Neurobehavioral effects of individual PBDE congeners were evaluated in mice that were exposed during perinatal and/or early postnatal periods to 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',5,5'-hexaBDE (BDE 153), or 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209). Most of these studies used similar single oral dose experimental designs and evaluated spontaneous motor behavior and swim maze performance at 2–6 months of age. The findings collectively indicate that the nervous system is a target of particular PBDE congeners during a defined critical phase of neonatal brain development, as shown by mild impairments in spontaneous motor behavior and learning and memory in older mice. One study used a different experimental design in which mice were exposed to BDE 99 from GD 6 to PND 21, and evaluated using a variety of somatic (body weight gain, hair growth, day of eyelid and ear opening, day of incisor eruption) and neurobehavioral (righting reflex, forelimb stick grasping reflex, forelimb placing reflexes, negative geotaxis, screen grasping and climbing, pole grasping, ultrasonic vocalizations, homing test) end points during PNDs 2–22, as well as spontaneous activity end points on PNDs 22–120. Findings were suggestive of delayed sensorimotor development and altered spontaneous behavior. Based on the limited available information (most of the studies were reported as abstracts), and considering the known effects of lower brominated PBDEs on thyroid hormone homeostasis and the

critical role that thyroid hormones play in development of the central nervous system, neurobehavioral development is a potential effect of concern for lower brominated PBDEs in humans.

Hepatic Effects. The hepatotoxic potential of lower brominated 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. For example, subchronic oral studies in rats showed that commercial pentaBDE mixtures were hepatotoxic at doses ≤10 mg/kg/day. Increased liver weight and hepatocellular enlargement with vacuolation occurred in rats exposed to commercial 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 to ≥2 mg/kg/day of commercial pentaBDE for 90 days in rats. In contrast, high purity commercial decaBDE caused no liver pathology in rats and mice at estimated doses as high as 2,000–8,000 and 2,375–9,500 mg/kg/day, respectively. High purity commercial decaBDE caused liver effects only following lifetime exposure to doses that were still very high. Exposure to 94–97% decaBDE for 103 weeks caused liver thrombosis and degeneration in rats at 2,240 mg/kg/day, and centrilobular hypertrophy and granulomas in mice at ≥3,200 mg/kg/day. No studies are available on hepatic effects of PBDEs in humans. Based on the evidence in animals, lower brominated 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 the same study, exposure to up to 72 mg/kg/day had no effect on natural killer cell (NKC) activity. *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 BDE 47 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, indicating that it is considerably less immunotoxic than pentaBDE. 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; however, it is of note that this preparation was only 77% decaBDE. A later study of decaBDE, using a >97% pure compound, reported no maternal or fetal toxicity at doses up to 1,000 mg/kg/day. 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 BDE 47 in a small group of Swedish men and women.

For most PBDEs, including pentaBDE and octaBDE, animal studies of carcinogenic effects are not available; cancer data on PBDEs in animals are limited to results of studies on commercial decaBDE products. In a bioassay conducted by the NTP, male and female rats were exposed to high purity commercial decaBDE (lots that were 96 or 94–97% 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, although the term neoplastic nodule is poorly defined and understood, and is no longer used by NTP to characterize hepatoproliferative lesions in rats. 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.

4.3 MINIMAL RISK LEVELS (MRLs)

PBDEs share some toxicological properties with other structurally similar polyhalogenated aromatic compounds, particularly PBBs, PCBs, chlorinated dibenzo-*p*-dioxins (CDDs), and chlorinated dibenzofurans (CDFs) (Agency for Toxic Substances and Disease Registry 1994, 1998, 2000). However, although these chemicals are structurally similar in two dimensions, PBDEs (and PCDEs) differ from the other classes on a three-dimensional basis. In particular, the oxygen bridge of the ether linkage in the diphenyl oxide molecule increases the distance between the biphenyl rings. This apparently reduces steric interactions between *ortho* substituents on the adjacent rings, such that the presence of *ortho* bromines is unlikely to present a barrier to rotation that would prevent the two aromatic rings from assuming a fully coplanar configuration (Chen et al. 2001; Hardy 2002b; Howie et al. 1990). In other words, the ether bridge makes PBDEs more noncoplanar in nature, and introducing *ortho* substitutions into PBDEs 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 PBBs or PCBs. Therefore, for PBDEs, the influences of the ether bridge and bromine position preclude clearly classifying the congeners as either dioxin-like (coplanar) or nondioxin-like (noncoplanar). This has implications not only for dioxin-type toxicities, which are mediated by the Ah (aryl hydrocarbon) receptor (AhR) pathway (and therefore might not be a significant issue for PBDEs), but also for nondioxin-type effects. The assumption that 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 compared to chlorine (Hardy 2000, 2002b). These differences contribute to dissimilar physical/chemical properties that can influence the relative toxicokinetics and toxicities of the chemicals. The geometrical differences in bromine and chlorine also have implications for understanding the mechanism(s) of effects for nondioxin-like PBB congeners, which are not as well characterized as for PCBs. In particular, it cannot necessarily be assumed, on the basis of two-dimensional structure, that the mechanisms and effects for nondioxin-like PBBs and PCBs are similar.

People are environmentally exposed to PBDE mixtures of different congeneric composition than the original commercial PBDE products. Although the toxicity or potency of environmental mixtures of congeners consequently might be greater or less than that of the original commercial PBDE product, there are insufficient mixture toxicity data on which to directly base MRLs for environmental 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 PBDEs, (2) different PBDE congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting 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 PBDEs, PBBs, PCBs, CDDs, and/or CDFs in the environment, data from commercial PBDE mixtures are used to develop MRLs for assessing health risks from environmental exposures to PBDEs.

There are important differences in the environmental chemistry and toxicity of decaBDE compared to lower brominated BDEs. DecaBDE seems to be largely resistant to environmental degradation, whereas octa- and pentaBDE commercial mixture components are likely to undergo differential partitioning and transformation, such that tetra- and pentaBDEs are the predominant congeneric forms that have been detected in the environment. Tetra- and pentaBDE congeners are also the main PBDEs in human tissues (blood, adipose, and breast milk), and BDE 47, BDE 99, and BDE 100 are particularly prevalent in both environmental and biological samples. The preferential accumulation of the lower brominated BDEs is likely due to their partitioning and retention in lipid-rich tissues; decaDBE does not appreciably partition into lipid-rich tissues and has higher rates of metabolism and elimination. These characteristics seem to be a function of both the number and location of bromines on the diphenyl oxide molecule. The tetra- and pentaBDEs appear to be relatively well absorbed, whereas the fully brominated decaBDE, a large poorly soluble molecule, is very poorly absorbed (≈1% or less of an oral dose) and rapidly eliminated (≈99% of the dose within 72 hours). Further, decaBDE is significantly less toxic than lower brominated BDE mixtures. For example, subchronic oral studies in rats showed that commercial octa- or pentaBDE

mixtures were hepatotoxic at doses as low as 2–10 mg/kg/day, while high purity commercial decaBDE caused no liver pathology at doses as high as 8,000–9,500 mg/kg/day (IRDC 1976, 1977; NTP 1986; WIL Research Laboratories 1984). Liver effects (thrombosis and degeneration) of commercial decaBDE in rats were only induced following lifetime exposure, and doses were still very high (2,240 mg/kg/day) (NTP 1986). A study in weanling rats showed that acute oral exposure to commercial decaBDE had no effect on thyroid hormones, while similar exposures to commercial octaBDE or pentaBDE mixtures caused decreases in serum T_4 and T_3 levels (Zhou et al. 2001). Similarly, acute postnatal oral exposure to pure decaBDE congener (BDE 99) was less potent than BDE 47, BDE 99, and 2,2',4,4',5,5'-hexaBDE (BDE 153) in inducing behavioral effects in adult mice (Eriksson et al. 1999, 2001a, 2002a; Viberg et al. 2001a, 2001b, 2002a, 2002b, 2003b). Due to the dissimilar toxicity and environmental chemistry of decaBDE as discussed above, separate MRLs were derived for decaBDE and lower brominated mixtures.

Inhalation MRLs

Decabromodiphenyl Ether

No MRLs were derived for acute-, intermediate-, or chronic-duration inhalation exposure to decaBDE due to a lack of inhalation studies on this BDE congener.

Lower Brominated BDEs

Derivation of an acute-duration MRL for lower brominated BDEs is not recommended at this time due to insufficient information. The inhalation database for acute-duration exposure to PBDEs is essentially limited to two 14-day unpublished industry-sponsored studies of octaBDE in rats (Great Lakes Chemical Corporation 1978, 2000). Liver and nasal effect levels were identified in these studies, but are inappropriate bases for MRL estimation. As discussed below, derivation of an acute MRL is precluded by inconsistencies between the studies and a lack of suitable information on thyroid hormone levels or another sufficiently sensitive end point.

In the Great Lakes Chemical Corporation (1978) study, groups of five male and five female Charles River CD rats were whole-body exposed to dust of an unspecified commercial octaBDE mixture in mean analytical concentrations of 0, 0.6, 3.7, 23.9, or 165.2 mg/m^3 for 8 hours/day for 14 consecutive days. The average mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particles were 3.5 µm and 2, respectively. Study end points included clinical signs (including observations for respiratory distress and nasal and ocular irritation), body weight and food consumption,

hematology (5 indices), blood chemistry (5 indices, thyroid hormones not assessed), urinalysis (10 indices), organ weights (5 organs including thyroid/parathyroid), gross pathology, and histology (21 tissues including nasal turbinates, trachea, lungs, and thyroid). The clinical laboratory tests were limited to rats in the control and two highest dose groups. The histological exams were limited to the control and highest dose groups, except for the liver, which was examined in all groups. Signs of increased respiration rate (rapid breathing) were observed by the end of each exposure period in rats exposed to ≥24 mg/m^3; this effect always disappeared by the following morning. Liver weight was significantly increased and hepatic lesions occurred in rats exposed to ≥3.7 mg/m^3. At 3.7 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 in the higher dose groups except that that the hepatocyte enlargement was multifocal to diffuse in distribution, and the presence of focal, small to large areas of hepatocellular necrosis of very slight to marked degree. There were no exposure-related histological changes in other tissues.

The Great Lakes Chemical Corporation (2000) study is currently only available as a secondary summary. This study was summarized in a recent European Union Risk Assessment Report (EU 2003a), but a report is not currently available in the Toxic Substances Control Act Test Submissions (TSCATS) database. The only pertinent information in the TSCATS database (as of March 2004) is a notice that the study was initiated (Great Lakes Chemical Corporation 2000), strongly suggesting that the completed study was never submitted.

In the Great Lakes Chemical Corporation (2000) study, a commercial octaBDE product (bromine content 78.7%, not otherwise identified) was administered to groups of five male and five female Crl:CD(SD)IGS BR rats, by nose-only inhalation as a dust aerosol, in measured concentrations of 0 (air only), 1.0, 10, 110, or 250 mg/m^3 for 6 hours/day, 5 days/week, for 2 weeks. MMADs in the low to high level groups were 2.9, 3.2, 2.9, and 2.9 µm; GSDs were not reported in the available study summary. Clinical signs, body weight, food consumption, and survival were evaluated throughout the study. Hematology, serum chemistry, urine indices, and thyroid hormones were not assessed. Necropsies, organ weight measurements, and histological examinations were performed following exposure termination. The histological examinations included nasal cavity, larynx, trachea, lungs, liver, kidneys, adrenals, brain, spleen, testes, and ovaries, but excluded thyroid and heart. Exposure-related effects occurred in the liver and nasal cavity. Hepatic effects included increased mean absolute and/or relative liver weights at ≥10 mg/m^3 in males and ≥110 mg/m^3 in females, with the greatest increases at 110 and 250 mg/m^3 (21–

44%). Centribobular hypertrophy similarly occurred in the liver at ≥10 mg/m^3 in both sexes (100% incidences in all groups except 4/5 females at 10 mg/m^3). Nasal effects included minimal to mild Goblet cell hyperplasia and/or hypertrophy at ≥1 mg/m^3 in males and ≥10 mg/m^3 in females. The nasal Goblet cell hyperplasia/hypertrophy occurred in nasal levels II and III in males at 1 mg/m^3, and generally in nasal levels II–VI in both sexes at ≥10 mg/m^3. No changes were found in the remaining squamous, respiratory, and olfactory nasal epithelia, or other parts of the respiratory tract.

As detailed above, hepatocellular hypertrophy was found at concentrations at ≥3.7 mg/m^3 in the Great Lakes Chemical Corporation (1978) study and ≥10 mg/m^3 in the Great Lakes Chemical Corporation (2000) study. This liver effect was accompanied by some degenerative hepatocellular changes in the 1978 study, but this was not confirmed by the later study. Additionally, slight histological changes in nasal Goblet cells occurred at ≥1 mg/m^3 in the Great Lakes Chemical Corporation (2000) study, but there were no nasal effects in the earlier study. Interpretation of the significance and adversity of the liver and nasal alterations is complicated by the inconsistency of findings between the studies and other factors, including the small numbers of animals per study (five/sex/level) and different methods of inhalation exposure (whole-body versus nose-only). Additionally, a well designed 13-week study (Great Lakes Chemical Corporation 2001a, 2001b) found (1) hepatocellular hypertrophy, but no degenerative liver changes, at higher a minimum effect level (16 mg/m^3) than in both 14-day studies, and (2) no clearly exposure-related changes in nasal Goblet cells at concentrations below 202 mg/m^3 (study summarized in intermediate MRL section). Further, the adversity of the slight nasal Goblet cell changes, which were predominantly minimal in severity and possibly suggestive of very slight nasal irritation in both the 14-day and 13-week studies, is unclear.

The available information indicates that there are insufficient bases for considering the hepatic and nasal changes as adverse acute effects. More importantly, exposure to ≥16 mg/m^3 caused changes in serum levels of thyroid hormones (decreased T_3, increased TSH) in the 13-week study. Thyroid hormone levels were not determined in either of the 14-day studies. Therefore, due to the lack thyroid hormone data in the 14-day studies, as well as the lack of any clear lowest-observed-adverse-effect levels (LOAELs) for the other end points in the 14-day studies, particularly at exposures levels below the LOAEL for thyroid effects in the 13-week study, there is no sufficiently sensitive basis for derivation of an MRL for acute-duration exposure.

- An MRL of 0.006 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to lower brominated BDEs.

The intermediate-duration inhalation MRL is based on a no-observed-adverse-effect level (NOAEL) of 1.1 mg/m^3 for changes in thyroid hormones in rats that were intermittently exposed to octaBDE for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b). Calculation of the MRL is detailed below.

The inhalation database for intermediate-duration exposure to PBDEs consists of one well-conducted 13-week study (Great Lakes Chemical Corporation 2001a, 2001b). This is an unpublished industry-sponsored study in which a commercial octaBDE product (bromine content 78.7%) was administered to groups of 10 male and 10 female Crl:CD(SD)IGS BR rats, via nose-only inhalation as a dust aerosol, in measured concentrations of 0 (air only), 1.1, 16, or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks. The mean MMADs in the low to high exposure groups were 2.0, 2.7, and 2.8 µm, and the corresponding mean GSDs were 3.37, 3.72, and 3.01. Clinical and physical signs, body weight, food consumption, and survival were evaluated throughout the study. Ophthalmic, hematology (11 indices), serum chemistry (18 indices), and serum thyroid hormone (TSH, total T_3, and total T_4) evaluations were performed near the end of the exposure period. Urinalyses were not conducted. Comprehensive necropies, organ weight measurements, and histological examinations (including respiratory tract and thyroid) were performed following exposure termination.

Hepatic, nasal, lung, thyroid, and ovarian effects were observed (Great Lakes Chemical Corporation 2001a, 2001b). The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at ≥16 mg/m^3 and liver weight (absolute and relative) at 202 mg/m^3. Total incidences of centrilobular hepatocellular hypertrophy in the 0, 1.1, 16, and 202 mg/m^3 groups were 1/10, 0/10, 3/10, and 10/10 in males, and 0/10, 0/10, 3/10, and 6/10 in females; severity was predominantly minimal in all groups and was not dose-related. Changes in nasal Goblet cells were increased at 202 mg/m^3, but showed no clear dose-related increasing trends for incidence or severity. Total incidences of nasal Goblet cell hypertrophy were slightly increased in nasal level II of both sexes at ≥1.1 mg/m^3; incidences in the 0, 1.1, 16, and 202 mg/m^3 exposure groups were 4/10 (all minimal), 9/10 (7 minimal, 2 mild), 6/10 (all minimal), and 10/10 (9 minimal, 1 mild) in males, and 2/10 (all minimal), 6/10 (all minimal), 4/10 (all minimal), and 8/10 (all minimal) in females. Nasal Goblet cell hypertrophy was also slightly increased in nasal level IV in males at 202 mg/m^3 (4/10, 0/10, 1/10, and 8/10, all minimal severity, not increased in females). Histological changes in the lungs included alveolar histiocytosis and chronic active inflammation that were only clearly increased in incidence at 202 mg/m^3. Total incidences of alveolar histiocytosis at 0, 1.1, 16, and 202 mg/m^3 were 3/10, 5/10, 5/10, and 10/10 in males, and 0/10, 5/10, 2/10, and 10/10 in females. Corresponding total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10, and 10/10 in males, and 0/10, 1/10, 1/10, and 10/10 in females. The severity of

both lesion types tended to increase from minimal to mild/moderate at 202 mg/m^3. Gross lung changes also occurred in both sexes at 202 mg/m^3; these included lung firmness and white discoloration and/or enlargement in the bronchial and/or mediastinal lymph nodes. The lymph node effects correlated with the histological finding of granulomatous inflammation. There were no exposure-related gross or histopathological changes in the spleen, bone marrow, thymus, or other tissues, including thyroid. Thyroid hormone assessments, however, showed exposure-related decreases in mean thyroxine (total T_4) at ≥16 mg/m^3 in both sexes, and increases in TSH at ≥16 mg/m^3 in males and 202 mg/m^3 in females. The changes were usually statistically significant ($p<0.05$ or $p<0.01$) compared to controls and were considered to be consistent with chemical-induced hypothyroidism. There were no serum T_3 changes. Qualitative histological evaluations of step sections of ovaries showed an absence of corpora lutea in 3/10 females at 202 mg/m^3, compared to 0/10 in the control and lower exposure groups. This 30% incidence was interpreted to be a treatment-related effect because an absence of corpora lutea was considered unusual in rats at 20 weeks of age.

Considering the questionable adversity of minimal severity nasal Goblet cell hypertrophy, lack of clear dose-related increasing trends for incidences and severity of this nasal effect, clear identification of both a NOAEL (1.1 mg/m^3) and LOAEL (16 mg/m^3) for changes in serum levels of thyroid hormones, and abundant evidence for thyroid effects of PBDEs in oral studies, the effects on thyroid hormones are the most appropriate basis for estimation of an intermediate-duration inhalation MRL. The MRL of 0.006 mg/m^3 was derived by dividing the $NOAEL_{HEC}$ of 0.53 mg/m^3 by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability) and a modifying factor of 3 (for an incomplete database reflecting a single study in one species). The $NOAEL_{HEC}$ was calculated using the following equations:

$$NOAEL_{ADJ} = 1.1 \text{ mg/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.196 \text{ mg/m}^3$$

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.196 \text{ mg/m}^3 \times 2.7 = 0.53 \text{ mg/m}^3$$

The RDDR for the extrathoracic (ET) region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculate the RDDR: MMAD of 2.0 µm with a mean GSD (sigma g) of 3.37, default human body weight of 70 kg, and a default female F344 rat body weight of 0.18 kg. Additional information on the derivation of the intermediate-duration inhalation MRL for lower brominated BDEs is provided in Appendix A.

No MRL was derived for chronic-duration inhalation exposure to lower brominated BDEs due to a lack of chronic studies.

Oral MRLs

Decabromodiphenyl Ether

No MRL was derived for acute-duration oral exposure to decaBDE due to insufficient data. Information is available on effects of acute exposure on body and liver weights, microsomal enzyme induction in the liver, and serum thyroid levels in weanling rats (Carlson 1980b; NTP 1986; Zhou et al. 2001), but the database is limited by lack of LOAELs and/or sufficiently sensitive end points.

- An MRL of 10 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to decabromodiphenyl ether.

The MRL was derived based on a NOAEL of 1,000 mg/kg/day for developmental toxicity in rats exposed to decaBDE for 19 days during gestation (Hardy et al. 2002). The MRL was estimated by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability)..

A commercial decaBDPE product (97.34% DBDPO, 2.66% nonaBDE and octaBDE) was administered to groups of 25 mated female Sprague-Dawley rats by gavage in corn oil in daily doses of 0, 100, 300, or 1,000 mg/kg/day on gestation days 0 through 19 (Hardy et al. 2002). Each female was sacrificed on gestation day 20 and necropsied. End points examined included maternal clinical observations, maternal body weight/weight gain and food consumption, maternal gravid uterine and liver weights, maternal gross lesions, total number of corpora lutea, uterine implantations, early and late resorptions, viable and nonviable fetuses, and fetal weight and sex. Fetuses were examined grossly (all fetuses), evaluated for skeletal/cartilaginous malformations and ossification variations (approximately half of each litter), and evaluated for visceral malformations (remaining fetuses). No treatment-related effects on any maternal or fetal end points were observed, indicating that 1,000 mg/kg/day was the NOAEL for maternal and developmental toxicity.

Only one intermediate-duration systemic toxicity study of high purity decaBDE has been conducted. In this study, a commercial decaBDE product (94–97% pure) was fed to F344 rats (10/sex/level) in estimated doses of 496–8,000 mg/kg/day, or B6C3F1 mice (10/sex/level) in estimated dietary doses of

589–9,500 mg/kg/day, for 13 weeks (NTP 1986). All animals were observed daily, weighed weekly, and necropsied at the end of the exposure period. Comprehensive histological examinations were performed, but limited to the control and high-dose groups. No hematology, clinical chemistry, or urine indices, or thyroid hormone levels, were evaluated. There were no compound-related clinical signs, deaths, body weight or food consumption changes, gross pathology, or histopathology, indicating that 8,000 and 9,500 mg/kg/day are intermediate-duration NOAELs for systemic toxicity in rats and mice, respectively. As discussed above, the NOAEL for developmental toxicity is 1,000 mg/kg/day (Hardy et al. 2002). Because doses of decaBDE higher than 1,000 mg/kg/day have not been tested for developmental toxicity, and the NTP (1986) study indicates that this dose is also a NOAEL for systemic toxicity, the 1,000 mg/kg/day developmental toxicity NOAEL is used as the basis for the MRL. Additional information on the derivation of the intermediate-duration oral MRL for decaBDE is provided in Appendix A.

No MRL was derived for chronic-duration oral exposure to decaBDE. Only one chronic study of high purity decaBDE has been conducted. In this study, a commercial decaBDE product (94–97% pure) was fed to F344 rats (50/sex/dose level) in dietary 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). Animals were examined daily for clinical signs. Body weights and food consumption were measured throughout the study, and comprehensive gross and histological examinations were performed on all animals in all dose groups, including those that were moribund or died during the study. No hematology, clinical chemistry, or urine indices, or thyroid hormone levels, were evaluated. Liver degeneration and thrombosis were significantly ($p<0.05$) increased in male rats at 2,240 mg/kg/day; respective incidences in the control, low, and high dose groups were 13/50, 19/50, and 22/50 for degeneration, and 1/50, 0/50, and 9/50 for thrombosis. The thrombosis was characterized by a near total occlusion of a major hepatic blood vessel by a dense fibrin coagulum. Neoplastic nodules in the liver were increased in males at ≥1,120 mg/kg/day and in females at 2,550 mg/kg/day in incidences that were dose-related and statistically significant, although no treatment-related increases in hepatocellular carcinomas were observed. Other effects in exposed rats included fibrosis of the spleen, lymphoid hyperplasia of the mandibular lymph nodes, and acanthosis of the forestomach at 2,240 mg/kg/day. In mice, histopathological changes occurred in 3,200 mg/kg/day in males in the liver (centrilobular hypertrophy and granulomas) and thyroid (follicular cell hyperplasia). An MRL was not derived because the lowest tested dose, 1,120 mg/kg/day in male rats, is a LOAEL for a liver lesion (neoplastic nodules) that is precancerous and associated with thrombosis in the same tissue.

Lower Brominated Diphenyl Ethers

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

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 pentaBDE 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 GD 6 through 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 PNDs 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 lower brominated BDEs is provided in Appendix A.

The human relevance of thyroid effects in rats is debatable. As discussed in the thyroid effects part of Section 4.2, mechanistic data indicate that humans are generally less sensitive than rodents because

(1) PBDEs likely affect thyroid function by displacing T_4 from serum-binding proteins in blood and by increasing liver metabolism of thyroid hormones, (2) the major plasma thyroid hormone transporter protein in rats, transthyretin (TTR), is only a minor binding protein in humans, and (3) a thyroid hormone binding globulin, not TTR, is the major transporter protein in humans (Blay et al. 1993; Capen 1997; Sinjari et al. 1998). The importance of the role of TTR in human thyroid homeostasis is unclear because, although it is not is the main transport protein in humans, TTR is necessary for thyroid hormone transport to the developing human fetus. Consequently, it is appropriate to use reduced serum T_4 in fetal rats as the critical effect for the MRL. Support for the relevance of this effect is provided by the lack of changes in thyroid hormones in the maternal animals at the dose that caused the effect on T_4 in the offspring.

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

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 the 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 in 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 decreases 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), 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 a thyroid LOAEL of 10 mg/kg/day for reduced serum T_4 levels in fetuses and neonatal offspring of rats that were exposed to pentaBDE from GD 6 through PND 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 lower brominated BDEs due to insufficient data. Only one chronic study of PBDEs other than high purity decaBDE has been conducted (Kociba et al. 1975; Norris et al. 1975b). In this study, Sprague-Dawley rats (25/sex/dose level) were fed a 77.4% pure commercial decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for approximately 2 years. Evaluations that included clinical signs, body weight, food consumption, hematology, clinical chemistry, urine indices, and comprehensive histological examinations showed no exposure-related effects. The highest NOAEL is 1 mg/kg/day (highest tested dose), but this NOAEL is not appropriate for MRL estimation due to insufficient sensitivity of the study. In particular, using the NOAEL of 1 mg/kg/day and an uncertainty factor of 100, a chronic oral MRL based on this study would be 5 times higher than the 0.002 mg/kg/day intermediate MRL. 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 be used as a value for chronic exposure.

5. HEALTH EFFECTS

5.1 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.

PBBs and 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 (mono-brominated 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 deca-bromobiphenyl. 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'-hexa-bromobiphenyl (BB 153) 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).

5. 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 the toxicity in livestock from Michigan farms that used large amounts of contaminated feed is generally attributed to PBBs, data on effects in animals from farms with low PBB contamination have generated some controversy, because the signs of toxicosis in these animals have not been reproduced in cattle experimentally exposed to PBBs at levels that caused tissue residue concentrations ≈100 times greater than those in the farm 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 5.4.2.2, 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 some PBDE congeners 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 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). Penta- and octa-BDEs are apparently being phased out of production and use. Great Lakes Chemical Corporation will cease production of penta- and octaBDE by the end of 2004 (Tullo 2003) and the European Union has banned the sale of all products containing more than 0.1% (by mass) penta- or octaBDE (EU 2003b).

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 may be different from the original PBB and PBDE source because of possible changes in congener composition resulting from differential partitioning and transformation in the environment and/or differential biological metabolism and retention.

5.2 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.

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.

5.2.1 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 5.2.3. The highest NOAEL and all LOAEL values from each reliable inhalation study of health effects end points in each species and duration category for PBDEs are recorded in Table 5-1 and plotted in Figure 5-1; due to the general lack of data regarding inhalation exposure to PBBs, no equivalent table is presented for PBBs.

5.2.1.1 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 dusts of commercial octaBDE products at levels of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), ≤250 mg/m^3 for 6 hours/day, 5 days/week for 14 days (Great Lakes Chemical Corporation 2000), or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b).

Table 5-1 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
	ACUTE EXPOSURE						
	Systemic						
1	Rat (CD)	14 d 8 h/d	Resp	3.7	24 (reversible rapid breathing)		Great Lakes Chemical Corporation 1978 OctaBDE
			Cardio	165			
			Gastro	165			
			Hemato	165			
			Hepatic	0.6	3.7 (hepatocytomegaly and focal hepatocellular degeneration)		
			Renal	165			
			Endocr	165			
			Ocular	165			
			Bd Wt	165			

Table 5-1 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
2	Rat (CD)	14d 5 d/wk 6 h/d	Resp	1			Great Lakes Chemical Corporation 2000 OctaBDE
			Hepatic	1	10		
			Renal	250			
			Bd Wt	250			

Table 5-1 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Systemic						
3	Rat (CD)	13 wk 5 d/wk 6 h/d	Resp	16	202 (alveolar histiocytosis, chronic active lung inflammation)		Great Lakes Chemical Corporation 2001 OctaBDE
			Cardio	202			
			Gastro	202			
			Hemato	202			
			Musc/skel	202			
			Hepatic	1.1	16 (centrilobular hepatocellular hypertrophy)		
			Renal	202			
			Endocr	1.1[b]	16 (decreased serum T4, increased serum TSH)		
			Dermal	202			
			Ocular	202			
			Bd Wt	202			
	Immuno/ Lymphoret						
4	Rat (CD)	13 wk 5 d/wk 6 h/d		16	202 (grossly discolored and enlarged bronchial and mediastinal lymph nodes associated with chronic active lung inflammation and alveolar histiocytosis)		Great Lakes Chemical Corporation 2001 OctaBDE

Table 5-1 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
	Reproductive						
5	Rat (CD)	13 wk 5 d/wk 6 h/d		16 F	202 F (absence of corpora lutea in ovaries)		Great Lakes Chemical Corporation 2001 OctaBDE

a The number corresponds to entries in Figure 5 1.

b Used to derive an intermediate-duration (15-364 days) inhalation minimal risk level (MRL) of 0.006 mg/m3 for lower brominated diphenyl ethers. The MRL was derived by converting the animal NOAEL of 1.1 mg/m3 to a duration-adjusted human equivalent concentration (NOAELHEC) of 0.53 mg/m3, and dividing by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability) and a modifying factor of 3 (for an incomplete data base).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; gastro = gastrointestinal; hemato = hematological; hr = hour(s); LOAEL = lowest observed adverse effect level; M = male; metab = metabolic; min = minute; mo = month(s); Musc/skel = muscular/skeletal; NOAEL = no observed adverse effect level; Resp = respiratory; T4 = thyroxine ; TSH = thyroid stimulating hormone; wk = week(s)

Figure 5-1. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers- Inhalation

Acute (≤14 days)

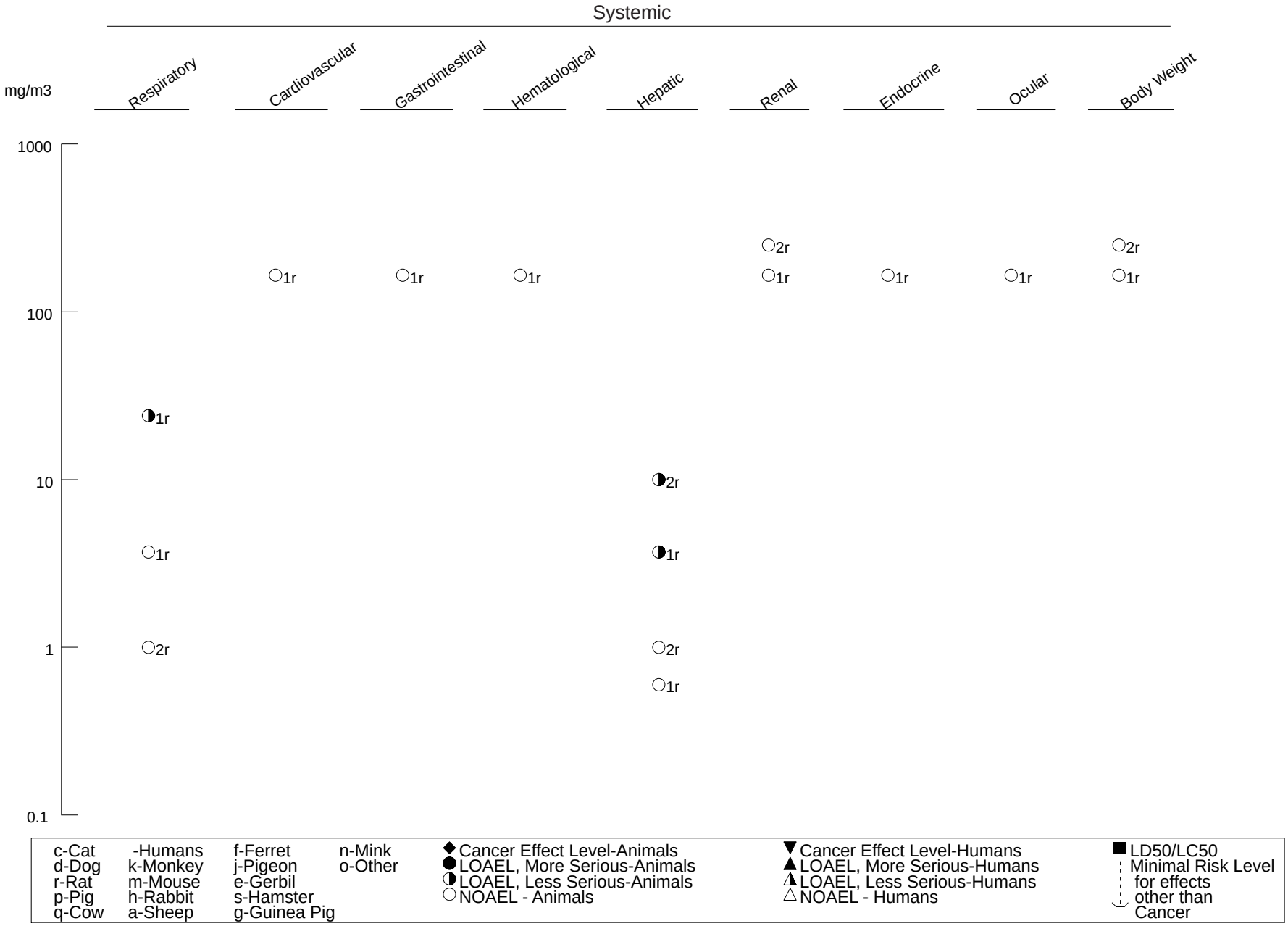
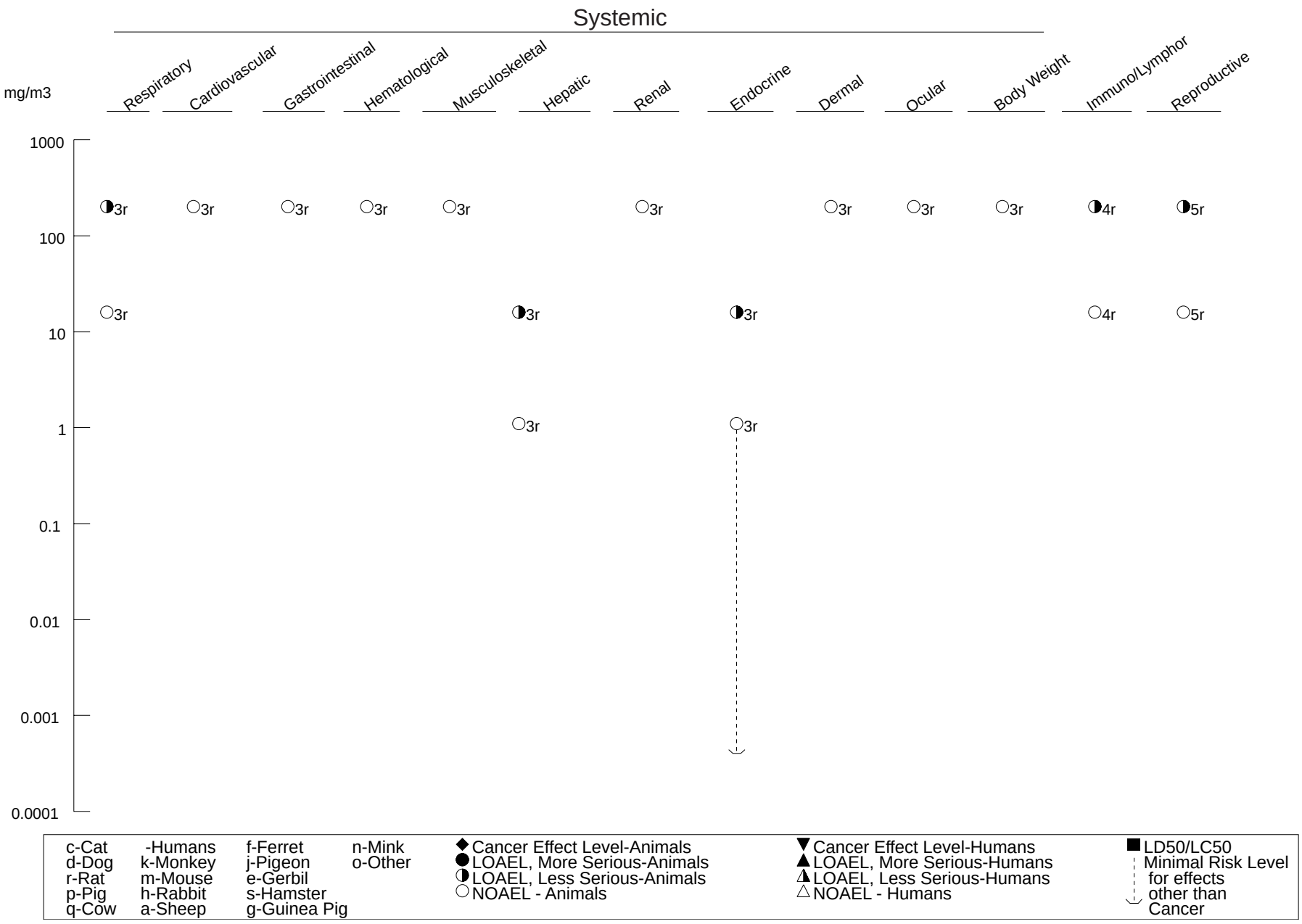


Figure 5-1. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers- Inhalation (*Continued*)

Intermediate (15-364 days)



5.2.1.2 Systemic Effects

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.

Two 14-day inhalation studies of commercial octaBDE have been conducted. In one study, rats were chamber-exposed to concentrations of 0, 0.6, 3.7, 23.9, or 165.2 mg/m^3 as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Increased respiration rate occurred at ≥23.9 mg/m^3. The rapid breathing pattern developed by the end of each exposure period, always disappeared by the following morning, and was not observed at lower exposure levels. Histological examinations of the control and 165.2 mg/m^3 rats (other groups not examined) showed no changes in

tissues that included nasal turbinates, trachea, lungs, and mediastinal lymph nodes). In the other study, rats were nose-only exposed to 0, 1.0, 10, 110, or 250 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 2 weeks (Great Lakes Chemical Corporation 2001a, 2001b). Histological examinations showed nasal alterations, consisting of minimal to mild goblet cell hyperplasia and/or hypertrophy at ≥1 mg/m^3 in males and ≥10 mg/m^3 in females. The nasal goblet cell changes occurred in nasal levels II and III at 1 mg/m^3 and generally in levels II-VI at ≥10 mg/m^3, and were considered indicative of very slight nasal irritation. No histopathology in the lungs or toxicolgically significant clinical signs were observed.

Histological changes in the lungs, but not clearly in the nasal cavity, were found in a study of rats that were nose-only exposed to 0, 1.1, 16, or 202 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b). The pulmonary effects included alveolar histiocytosis and chronic active inflammation, occurred in both sexes, and were only clearly induced at 202 mg/m^3. Total incidences of alveolar histiocytosis in the 0, 1.1, 16, and 202 mg/m^3 exposure groups were 3/10, 5/10, 5/10, and 10/10 in males, respectively, and 0/10, 5/10, 2/10, and 10/10 in females, respectively. Respective total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10, and 10/10 in males, and 0/10, 1/10, 1/10, and 10/10 in females. Both lesions were predominantly minimal or mild in severity, with moderate severity occurring in a few high-dose animals. Additional effects included gross pulmonary changes in both sexes at 202 mg/m^3; these included lung firmness and white discoloration and/or enlargement in the bronchial and/or mediastinal lymph nodes. The gross lymph node changes correlated with the histological granulomatous inflammation. Effects in nasal tissues were equivocal. Incidences of nasal goblet cell hypertrophy were slightly increased in nasal level II of both sexes at ≥1.1 mg/m^3, but incidences were not clearly dose-related and there was essentially no increase in severity from minimal with increasing dose. Total incidences of goblet cell hypertrophy in nasal level II in the 0, 1.1, 16, and 202 mg/m^3 exposure groups were 4/10, 9/10, 6/10, and 10/10 respectively, in males, and 2/10, 6/10, 4/10, and 8/10, respectively, in females. Minimal severity goblet cell hypertrophy was also slightly increased in nasal level IV in males at 202 mg/m^3 (4/10, 0/10, 1/10, and 8/10), but not in females.

Cardiovascular Effects.

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

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

No histopathological changes were observed in the heart of rats that were exposed to dusts of commercial octaBDE products at levels of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b).

Gastrointestinal Effects.

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

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 and lower gastrointestinal tract tissues of rats that were exposed to dusts of commercial octaBDE products at levels of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b).

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 occurred in rats that were exposed to 24.4 or 174 mg/m^3 of commercial octaBDE dust aerosol for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Evaluation of a limited number of indices (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. Comprehensive hematological assessments showed no unusual changes in rats exposed to commercial octaBDE as dust aerosol at concentrations of ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b).

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 °C. 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 decabromo-biphenyl 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 5.2.2.2 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.

Hepatic effects were observed in 14-day inhalation studies of dusts of commercial octaBDE mixtures. In one study, rats were chamber-exposed to concentrations of 0, 0.6, 3.7, 23.9, or 165.2 mg/m^3 as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Increased liver weight and hepatic histological changes occurred at 3.7 mg/m^3 and higher levels of exposure. At

3.7 mg/m^3, the liver lesions consisted of very slight to slight severity 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 ≥24.4 mg/m^3), except that the hepatocyte enlargement was multifocal to diffuse in distribution and accompanied by focal, small to large areas of hepatocellular necrosis of very slight to marked degree. In another study, rats were nose-only exposed to 0, 1.0, 10, 110, or 250 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 2 weeks (Great Lakes Chemical Corporation 2001a, 2001b). Hepatic effects included increased mean absolute and/or relative liver weights at ≥10 mg/m^3 in males and ≥110 mg/m^3 in females, with the greatest increases at 110 and 250 mg/m^3 (21–44%). Centribobular hypertrophy similarly occurred in the liver at ≥10 mg/m^3 in both sexes (100% incidences except for 4/5 females at 10 mg/m^3).

Similar hepatic changes were found in a study of rats that were nose-only exposed to 0, 1.1, 16, or 202 mg/m^3 commercial octaBDE as dust aerosol for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b). The liver was affected in both sexes as shown by dose-related increased centrilobular hepatocellular hypertrophy at ≥16 mg/m^3 and increased liver weight (absolute and relative) at 202 mg/m^3. Respective total incidences of centrilobular hepatocellular hypertrophy (predominantly minimal to mild) in the 0, 1.1, 16, and 202 mg/m^3 groups were 1/10, 0/10, 3/10, and 10/10 in males, and 0/10, 0/10, 3/10, and 6/10 in females. Serum chemistry evaluations showed no clear effects of exposure. Serum cholesterol was significantly increased (39.8% less than controls, $p<0.01$) in 202 mg/m^3 females, but the magnitude of the elevation was not considered toxicologically significant. Some other statistically significant serum chemistry alterations (increased mean globulin and total protein, decreased albumin/globulin ratio) also occurred in the 202 mg/m^3 females, but were not considered exposure-related due to small magnitudes of changes and lack of similar changes in the males.

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 dusts of commercial octaBDE products at levels of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), ≤250 mg/m^3 for 6 hours/day, 5 days/week for 14 days (Great Lakes Chemical Corporation 2000), or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b). Urinalyses were not performed in any of these studies.

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 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. In another study, plasma levels of thyroid hormones (T_3 and free T_4) and eight PBDE congeners (tetra- to heptaBDEs) were monitored for 198–221 days in three electronic dismantling workers (Pettersson et al. 2002). The hormones remained within normal ranges and there were no correlations between levels of hormones and congeners.

Inhalation studies of commercial octaBDE dust in rats showed no histopathological changes in the thyroids, parathyroids, adrenals, or pituitary following chamber exposure to 174 mg/m^3 as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), or in the adrenals (only endocrine tissue examined) following nose-only exposure to ≤250 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 14 days (Great Lakes Chemical Corporation 2000). Rats that were nose-only exposed to commercial octaBDE at levels of 1.1, 16, or 202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks similarly showed no histological changes in the adrenals, pancreas, parathyroids, pituitary, or thyroids (Great Lakes Chemical Corporation 2001a, 2001b). Measurements of serum levels of thyroid hormones in the 13-week rat study, however, showed exposure-related decreases in mean thyroxine (total T_4) at ≥16 mg/m^3 in both sexes, and increases in thyroid stimulating hormone (TSH) at ≥16 mg/m^3 in males and 202 mg/m^3 in females. The changes were usually statistically significant ($p<0.05$ or $p<0.01$) compared to controls and were considered by the investigators to be consistent with chemical-induced hypothyroidism. There were no serum T_3 changes, thyroid-attributable clinical signs or body weight

effects, or gross or histopathological changes in the thyroid. The 1.1 mg/m^3 LOAEL for thyroid effects was used as the basis for the intermediate-duration MRL for inhalation exposure to octaBDE, as indicated in the footnote to Table 5-1 and discussed in Chapter 4 and Appendix A.

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.

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

No gross or histological changes in the skin were observed in rats that were nose-only exposed to commercial octaBDE as dust aerosol at levels of ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b).

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 chamber-exposed to ≤174 mg/m^3 of commercial octaBDE as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Opthalmoscopic and histological examinations showed no ocular effects in rats following nose-only exposure to ≤202 mg/m^3 of commercial octaBDE dust aerosol for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b).

5.2.1.3 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 (Great Lakes Chemical Corporation 1978).

Inhalation studies of commercial octaBDE dusts in rats showed no histopathological changes in the spleen, mesenteric or mediastinal lymph nodes, bone marrow, or spleen following chamber exposure to 174 mg/m^3 as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), or in the spleens (only lymphoreticular tissue reported) following nose-only exposure to ≤250 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 14 days (Great Lakes Chemical Corporation 2000). Rats that were nose-only exposed to commercial octaBDE at levels of 1.1, 16, or 202 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 13 weeks similarly showed no effects in bone marrow, spleen, or thymus, although gross changes in pulmonary lymph nodes were observed at 202 mg/m^3. The effects included discolored and/or enlarged bronchial and mediastinal lymph nodes, and appeared to be associated with concurrent granulomatous inflammation of the lungs.

5.2.1.4 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 after inhalation exposure to PBDEs.

No clinical signs of neurotoxicity were observed in rats that were exposed to dusts of commercial octaBDE products at levels of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical

Corporation 1978), or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b). Histological examinations of nervous system tissues, performed only in the 13-week study, showed no effects in the brain (forebrain, midbrain, hindbrain), optic nerve, or a peripheral nerve (sciatic).

5.2.1.5 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 testes or ovaries from rats that were exposed to commercial octaBDE at concentrations of ≤174 mg/m^3 as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), or ≤250 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 2 weeks (Great Lakes Chemical Corporation 2001a, 2001b). A histological effect in the ovaries was found in a study of rats that were nose-only exposed to 0, 1.1, 16, or 202 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b). Absence of corpora lutea, based on qualitative evaluation of step sections of the ovary, was found in 3/10 females at 202 mg/m^3, compared to 0/10 incidences in the control and both lower exposure groups. The investigators interpreted this 30% increase in incidence be treatment-related because an absence of corpora lutea was considered unusual in rats at 20 weeks of age. No gross or histopathological changes were observed in the oviduct, uterus, or vagina, or in male reproductive tissues (testes with epididymides and vas deferens).

5.2.1.6 Developmental Effects

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

5.2.1.7 Cancer

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

5.2.2 Oral Exposure

The highest NOAEL and all LOAEL values from each reliable study of health effects end points in each species and duration category for PBDEs are recorded in Tables 5-2 (PBBs), 5-3 (lower PDBEs), or 5-4 (decaBDE) and plotted in Figures 5-2 (PBBs), 5-3 (lower PDBEs), or 5-4 (decaBDE).

5.2.2.1 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

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

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
	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)	once (GO)	Endocr	286 M			Allen-Rowlands et al. 1981 (NS)
4	Rat (Sprague-Dawley)	10 d 1x/d (GO)	Endocr	1[b]	3 M (decreased thyroid plasma T4 hormone)		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 observ (GO)	Hepatic		500 M (increased hepatic phospholipids and serum cholesterol)		Bernert et al. 1983 (FF-1)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)	

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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			
			Dermal	30			
			Ocular	30			
			Bd Wt	30			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
9	Rat (Sherman)	once 2-14 mo observ (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 observ (GO)	Hepatic		500 M (vacuolation of hepatocytes)		Kimbrough et al. 1980 (FF-1)
			Bd Wt	500 M			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
11	Rat (Sherman)	once 18-22mo observ (GO)	Resp	200 F			Kimbrough et al. 1981 (FF-1)
			Cardio	200 F			
			Hepatic		200 F (porphyrin accumulation)		
			Renal	200 F			
			Endocr	200 F			
			Dermal	200 F			
			Bd Wt	200 F			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
12	Rat (Sherman)	once 23mo observ (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)		

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
13	Rat (Sprague-Dawley)	once 28d observ (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. 1975b (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 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
	Immuno/ Lymphoret								
23	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)
24	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)
	Reproductive								
25	Rat (Sherman)	once 23mo observ (GO)			1000 F	(9% increased incidence of uterine polyps)			Kimbrough et al. 1981 (FF-1)
26	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								
27	Rat (Wistar)	once Gd 6-14 (GO)		40			200	(9.1-31.4% resorptions)	Beaudoin 1977 (BP-6)
28	Rat (Sprague-Dawley)	14 d Gd 7-20 (F)		5	50	(12% decrease in fetal body weight)			Corbett et al. 1975 (BP-6)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
29	Rat (Sherman)	Gd 7-14 1x/d (GO)					200	(increased mortality and liver neoplasms in offspring)	Groce and Kimbrough 1984 (FF-1)
30	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)
31	Rat (Sprague-Dawley, Iffa credo)	10 d Gd 6-15 1x/d (GO)		1000					Millischer et al. 1980 (DBB)
32	Rat (ChR-CD)	10 d Gd 6-15 ad lib (F)		9.1	86	(increased incidence of extra ribs)			Waritz et al. 1977 (OBB)
33	Mouse (Swiss/ IRC)	12 d Gd 7-18 (F)		5			50	(cleft palate)	Corbett et al. 1975 (BP-6)
	Cancer								
34	Rat (Sherman)	Gd 7-14 1x/d (GO)					200	(CEL: hepatocellular carcinoma in offspring)	Groce and Kimbrough 1984 (FF-1)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
35	Rat (Sherman)	once (GO)				1000 F (CEL: hepatocellular carcinoma)	Kimbrough et al. 1981 (FF-1)
	INTERMEDIATE EXPOSURE						
	Death						
36	Rat (Fischer 344/N)	4.5 wk 5 d/wk 22 d (GO)				149 M (90-day LD50) 65[c] F (90-day LD50)	Gupta and Moore 1979 (FF-1)
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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
40	Gn Pig (NS)	45 d ad lib (F)				2 F (7/8 died)	Vos and van Genderen 1973 (BP-6)
41	Mink (NS)	313 d ad lib (F)				0.47[c] M (LD50) 0.61 F (LD50)	Aulerich and Ringer 1979 (FF-1)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
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)	
			Dermal		18 F (edema, atrophy, and squamous metaplasia of sebaceous glands)		
			Bd Wt			18 F (27% body weight loss)	

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)		
			Dermal			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 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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			
			Dermal	10 M			
			Ocular	10 M			
			Bd Wt	10 M			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)
49	Rat (Sprague-Dawley)	20 d 1x/d (GO)	Endocr	6 M			Castracane et al. 1982 (NS)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)		
			Dermal	2 M			
			Bd Wt	2 M			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)	

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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 (increased liver weight, hepatocyte swelling, and necrosis)		
			Renal	30			
			Bd Wt	3	30 (significant decrease in body weight)		
54	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. 1978a (BP-6)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
55	Rat (Holtz- man)	5 wk ad lib (F)	Hepatic	0.25 M	2.5 M (hepatocyte hypertrophy and degeneration)		Kasza et al. 1978a (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 F	3 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)		

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
59	Rat (Sprague-Dawley)	30 d ad lib (F)	Cardio	800 M			Norris et al. 1975b (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			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
60	Rat (Sprague-Dawley)	8 mo ad lib (F)	Cardio	1			Norris et al. 1975b (OBB)
			Hemato	1			
			Hepatic	1			
			Renal	1			
			Endocr	1			
			Bd Wt	1			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
62	Rat (Sprague-Dawley)	7 mo ad lib (F)	Hepatic	2.5 F			Sepkovic and Byrne 1984 (OBB)
			Endocr	2.5 F			
63	Rat (Sprague-Dawley)	7 mo ad lib (F)	Endocr	2.5 F			Sepkovic and Byrne 1984 (HBB)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)		

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)		

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)	

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
72	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 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)		
			Dermal	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)		

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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)	
	Immuno/ Lymphoret						
76	Rat (Fischer 344)	5 wk 5 d/wk (GO)		0.03 M	3 M (decreased lymphocytic response to mitogen stimulation; decrease in absolute and relative thymus weight)		Luster et al. 1978 (FF-1)
77	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 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
78	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)
79	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)
80	Mouse (B6C3F1)	6 mo 5 d/wk 1x/d (GO)		3		10 (increased lethality due to infection with L monocytogenes; decreased response to mitogen stimulation)	Luster et al. 1980 (FF-1)
81	Gn Pig (NS)	45 d ad lib (F)			0.4 F (reduced antitoxin titers following toxoid challenge)	4 F (thymic atrophy and follicular depletion in spleen)	Vos and van Genderen 1973 (BP-6)
82	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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
	Neurological						
83	Rat (NS)	6 mo 5 d/wk 1x/d (GO)			10 (decreased limb strength)		Cabe and Tilson 1978 (FF-1)
84	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)
85	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)
86	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)
87	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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
	Reproductive						
88	Monkey (Rhesus)	25-50 wk ad lib (F)			0.73 M (hypoactive seminiferous tubules)		Allen et al. 1978; Lambrecht et al. 1978 (FF-1)
89	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)
90	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)
91	Rat (Fischer 344/N)	4-5 wk 5 d/wk 22 d (GO)		30[c] M 1000 F	100 M (squamous metaplasia, hyperplasia, and necrosis in epithelium of ductus deferens)		Gupta and Moore 1979 (FF-1)
92	Rat (Sprague-Dawley)	42 d Gd 8-ppd 28 ad lib (F)		5 F			McCormack et al. 1981 (BP-6)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
93	Mouse (B6C3F1)	4-5 wk 5 d/wk 1x/d (GO)		30				Gupta et al. 1981 (FF-1)
94	Mink (NS)	313 d ad lib (F)		0.24	0.39 F (10% reduction in body weight)			Aulerich and Ringer 1979 (FF-1)
	Developmental							
95	Rat (Wistar)	15 d Gd 0-14 8x (GO)		2.9		14.3	(increased resorptions)	Beaudoin 1979 (BP-6)
96	Rat (Holtz- man Sprague-Dawley)	4 wk 5 d/wk (G)		5				Geller et al. 1985 (FF-1)
97	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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
98	Rat (Sprague-Dawley)	40d Gd 6-Ppd 24 (F)			0.2 M (reduced crown-rump length)		Henck et al. 1994 (BP-6)
99	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)
100	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)
101	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)
102	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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
103	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)
104	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)
105	Mouse (C57B1/6)	Gd 0-ppd 21 1x/2d (GO)			3	(performance deficits in offspring in a learned task)			Tilson 1992 (FF-1)
106	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)
107	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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
	Cancer							
108	Rat (Sherman)	4 mo 12 x (GO)				100	(CEL: hepatocellular carcinoma)	Kimbrough et al. 1981 (FF-1)
109	Rat (Fischer 344/N)	25 wk 5 d/wk 1x/d (GO)				3	(CEL: hepatocellular carcinoma)	NTP 1983 (FF-1)
110	Mouse (B6C3F1)	25 wk 5 d/wk 1x/d (GO)				10	(CEL: hepatocellular carcinomas)	NTP 1983 (FF-1)
111	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)
	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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
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			
			Dermal	1.5			
			Bd Wt		0.5 (11-18% decreased final body weight)		

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
116	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)		
			Dermal	3.9			
			Bd Wt	3.9			

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
	Immuno/ Lymphoret						
117	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)
118	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)
	Reproductive						
119	Rat (Fischer 344/N)	115 wks Gd 0-ppd-56 (weaning) 104 wks post-weaning ad lib (F)		1.5 M 0.5[c] F	1.5 F (cystic endometrial hyperplasia)		NTP 1992, Chhabra et al. 1993 (FF-1)
120	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)

Table 5-2 Levels of Significant Exposure to Polybrominated Biphenyls - 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
	Developmental							
121	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							
122	Rat (Fischer 344/N)	115 wks Gd 0- ppd 56 104 wks post-weaning (F)				1.5	(CEL: leukemia)	NTP 1992, Chhabra et al. 1993 (FF-1)
						0.5	(CEL: hepatocellular adenoma and carcinoma)	
123	Mouse (B6C3F1)	116 wks Gd 0- ppd 56 105wks post-weaning (F)				3.9	(thyroid follicular cell adenoma)	NTP 1992, Chhabra et al. 1993 (FF-1)
						1.3	(CEL: hepatocellular adenoma and carcinoma)	

a The number corresponds to entries in Figure 5-2.

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 health effects and cancer effects between male and females are not indicated in Figure 5-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Ad lib - ad libitum; Bd Wt = body weight; BP-6 = FireMaster BP-6; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); DBB = deca=brominated biphenyl; DW = drinking water; endocr = endocrine; (F)= feed; F = female; FF-1 = FireMaster FF-1; (G) = gavage; gastro = gastrointestinal; Gd = gestation day; Gn Pig - Guinea Pig; (GO) = gavage in oil; Gwk = gestation week; HBB = hexa-brominated biphenyl; hemato = hematological; hr = hour(s); LD50 = lethal dose; 50% kill; 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; OBB octa-brominated biphenyl; observ = observation; ppd = post partum day; ppwk = post partum week; Resp = respiratory; T4 = thyroxine; wk = week(s); x = time(s)

Figure 5-2. Levels of Significant Exposure to Polybrominated Biphenyls- Oral

Acute (≤14 days)

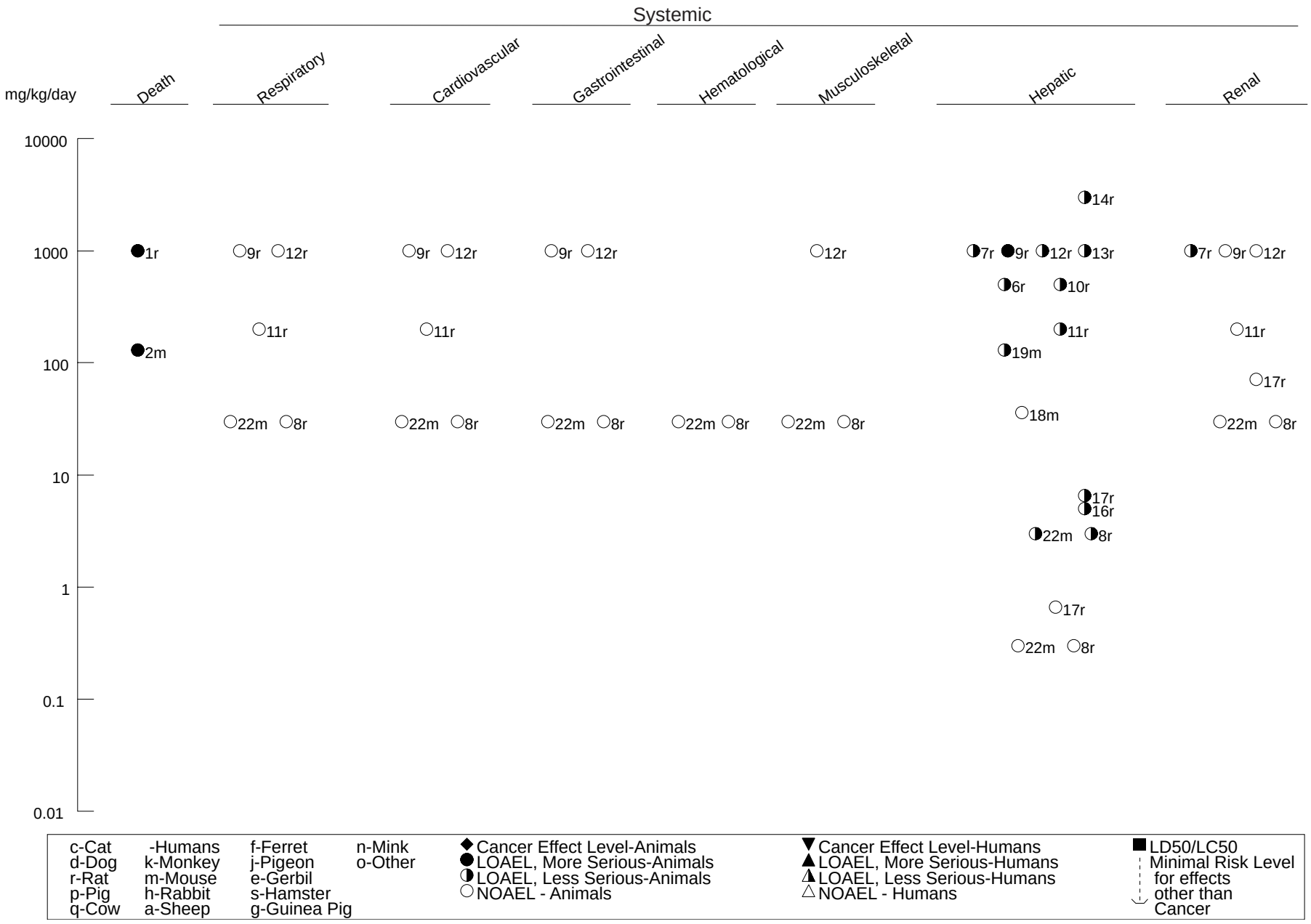


Figure 5-2. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

Acute (≤14 days)

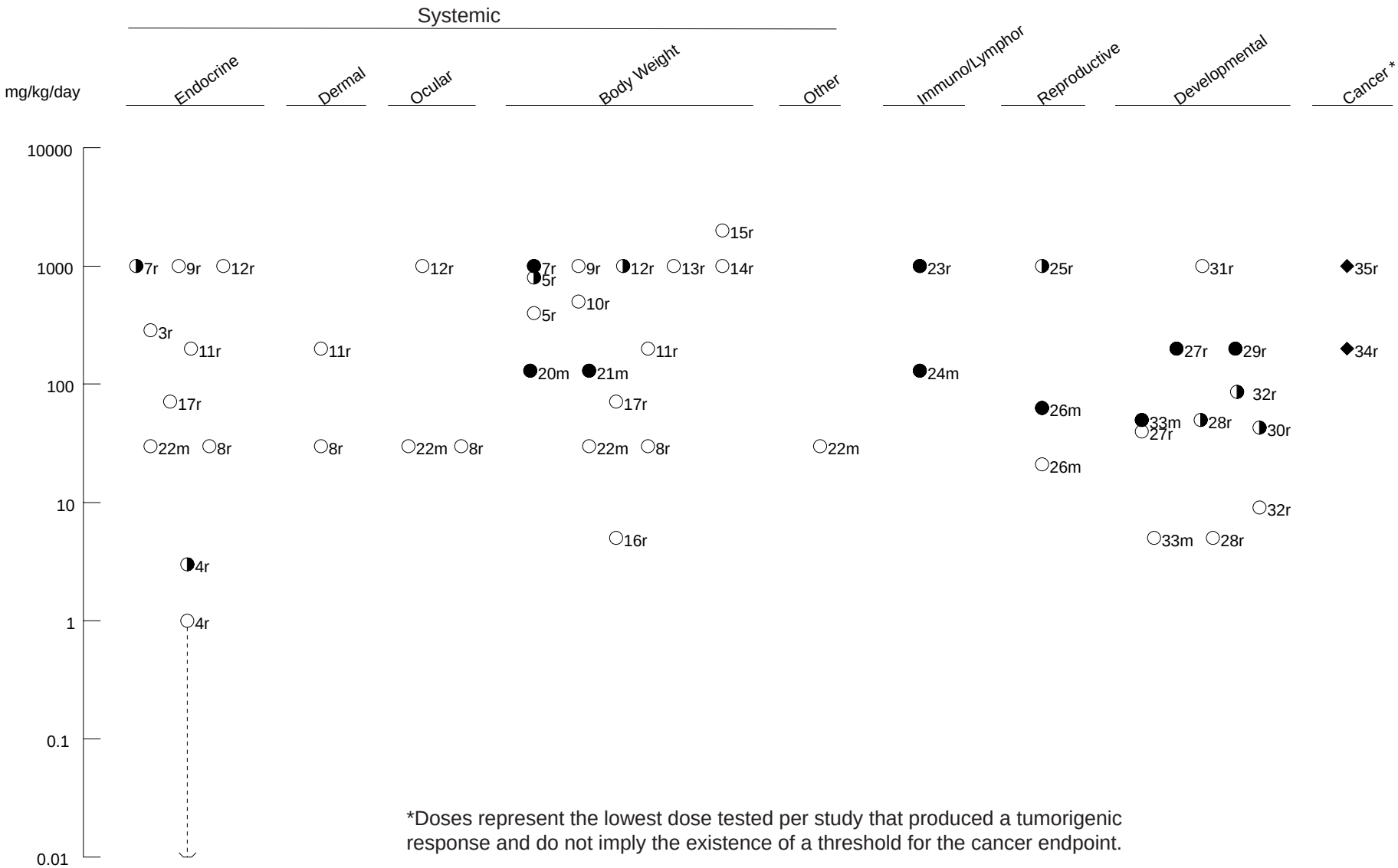


Figure 5-2. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

Intermediate (15-364 days)

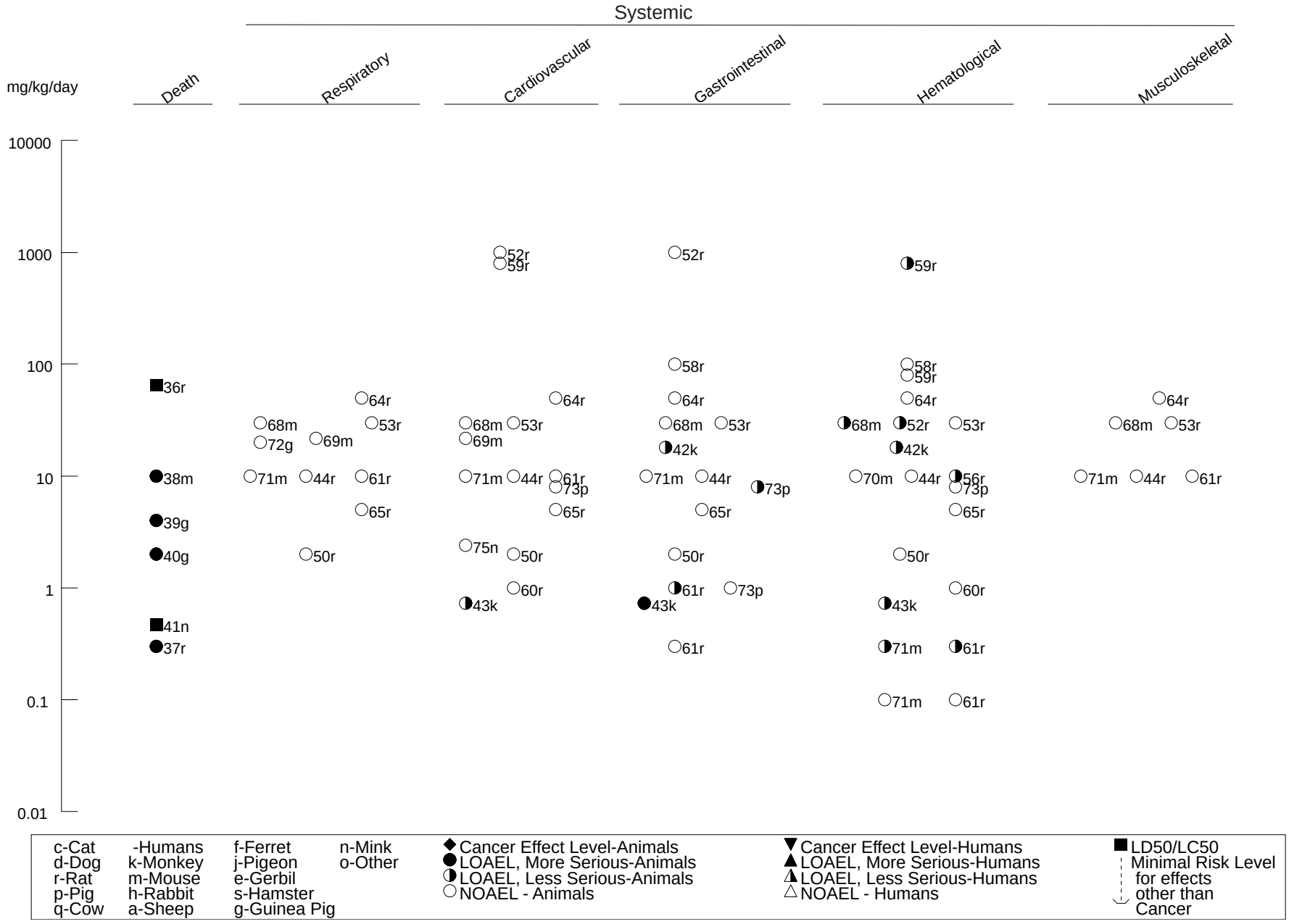


Figure 5-2. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

Intermediate (15-364 days)

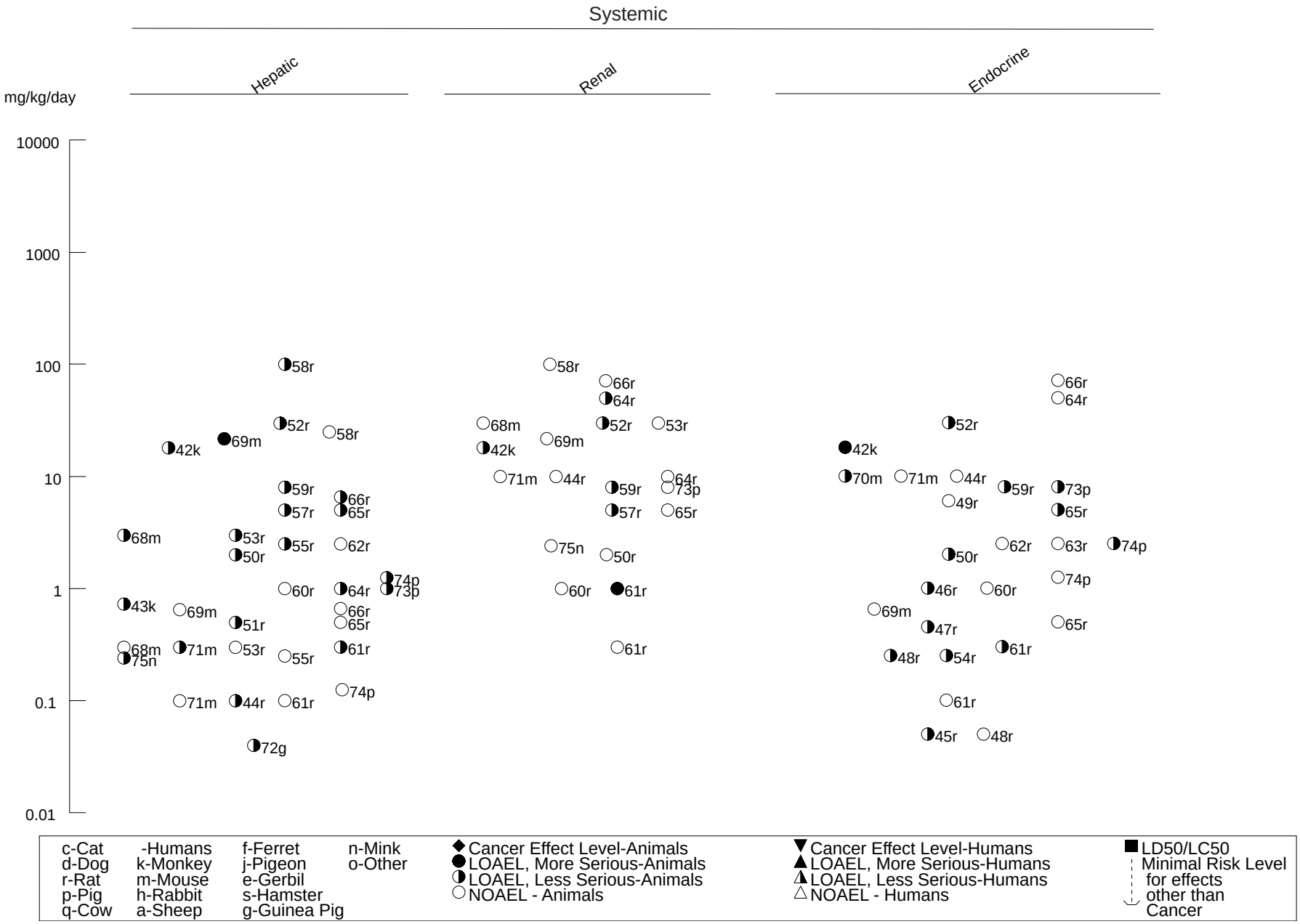


Figure 5-2. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

Intermediate (15-364 days)

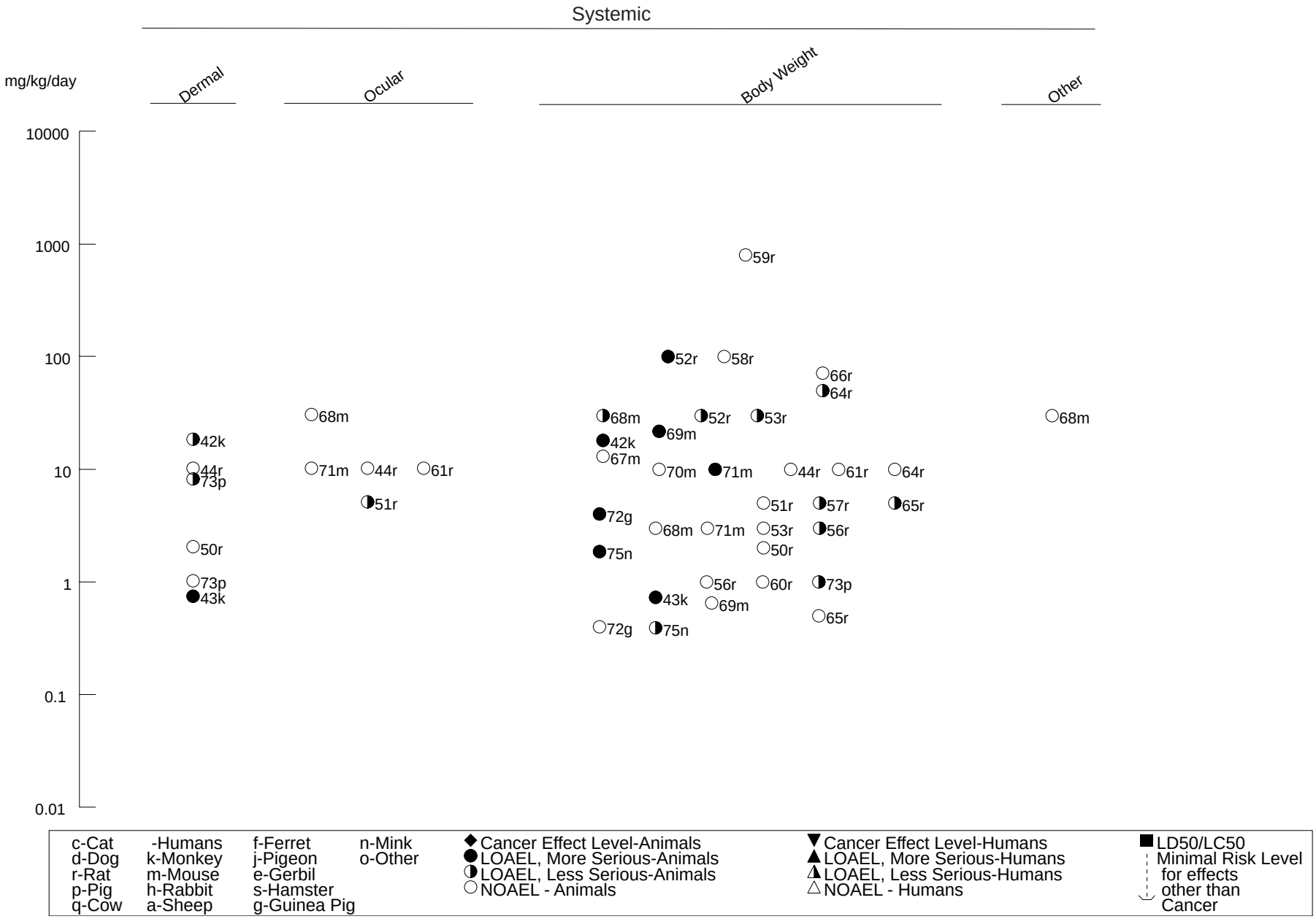


Figure 5-2. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

Intermediate (15-364 days)

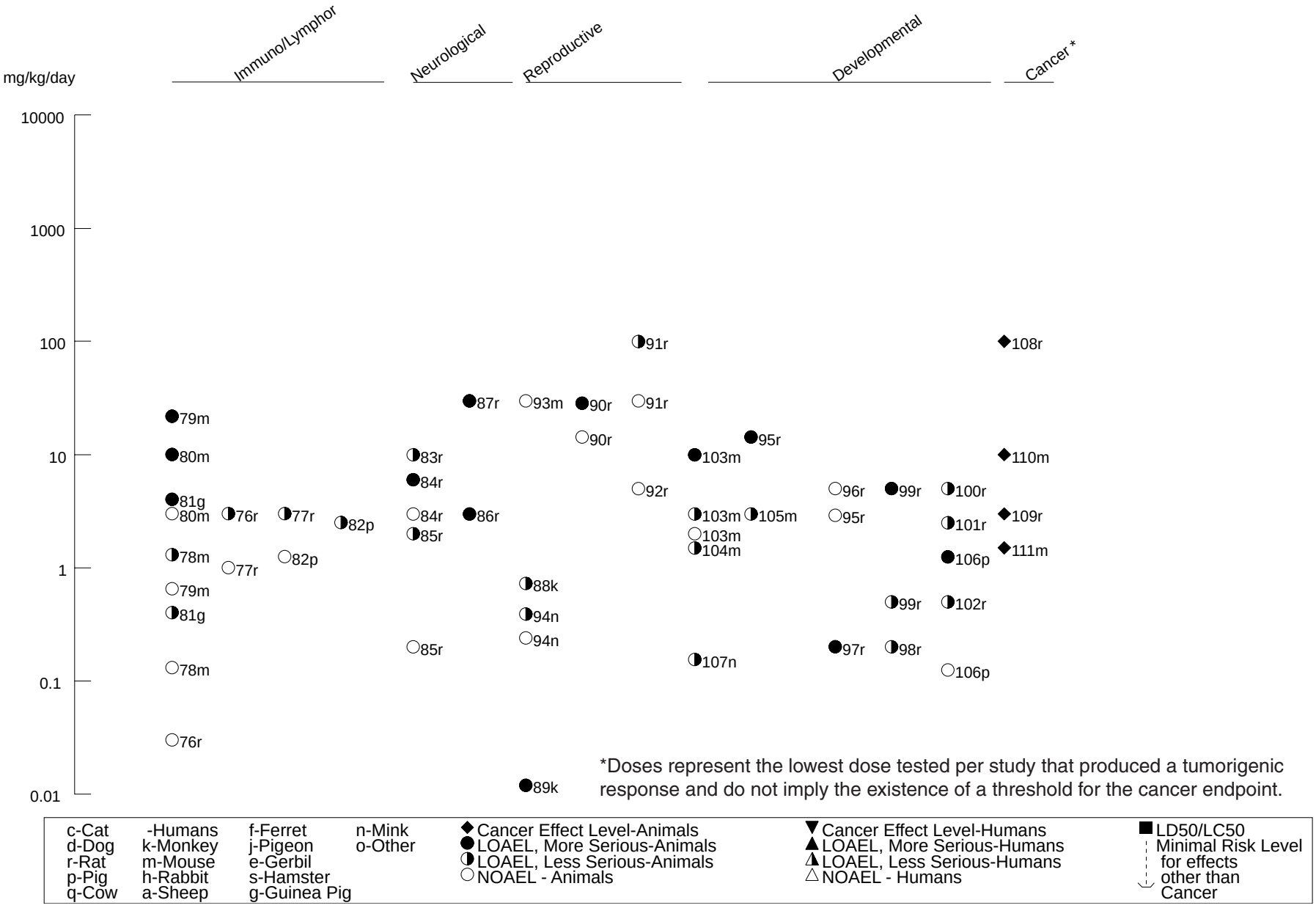


Figure 5-2. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

Chronic (≥365 days)

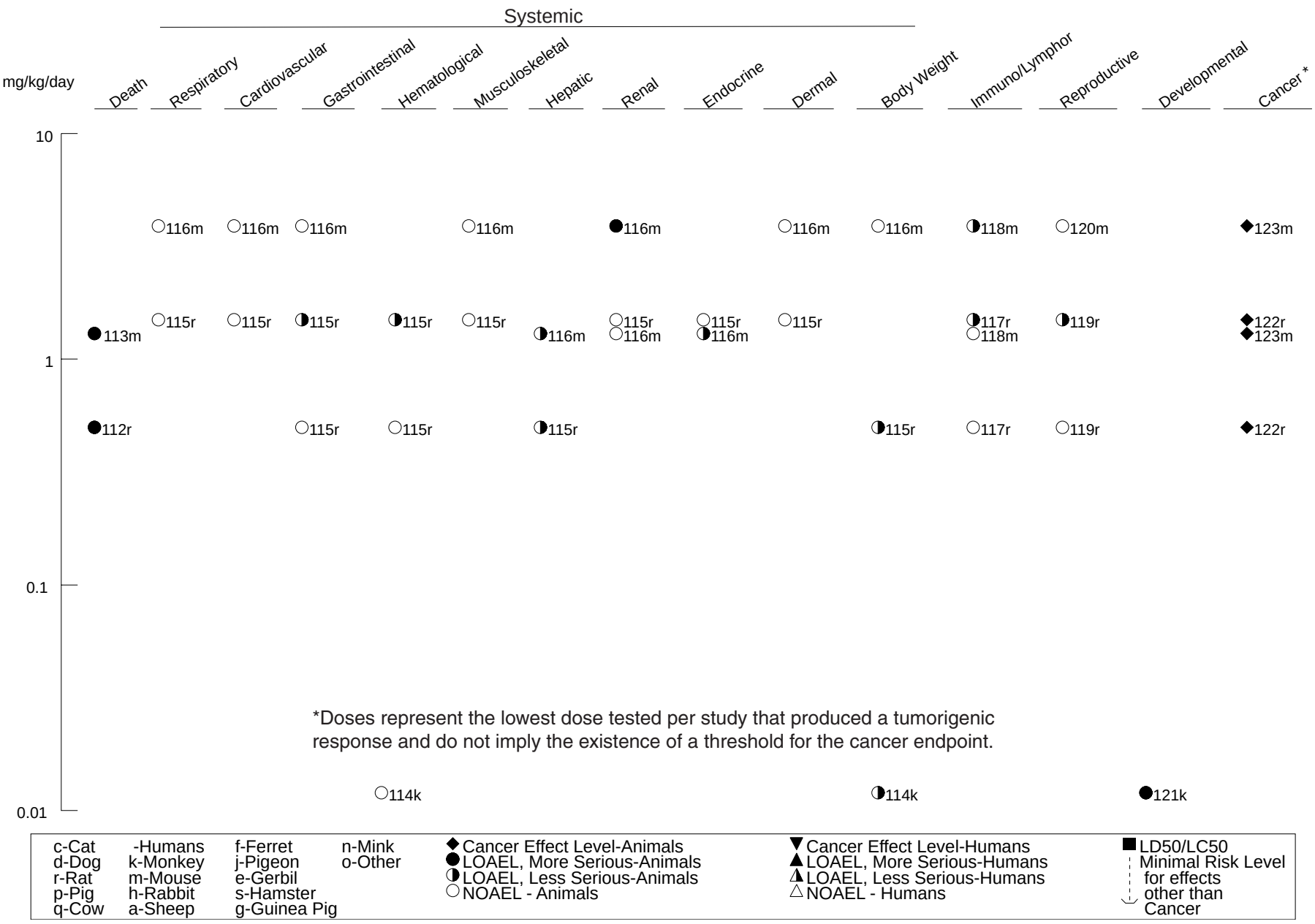


Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral

Key to figure[a]	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 (CD)	10 d Gd 6-15 (GO)	Bd Wt	10	100	(30% reduced maternal body weight gain)			Argus Research Laboratories 1985a PentaBDE
5	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic	76.6 M					Carlson, 1980b OctaBDE
6	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic	56.4 M					Carlson, 1980b PentaBDE

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to 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 (Sprague-Dawley)	14 d 1x/d (GO)	Endocr		18 (reduced serum T4)		Darnerud and Sinjari 1996 PentaBDE
8	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic		18 (reduced liver vitamin A)		Hallgren et al. 2001 PentaBDE
			Endocr		18 (reduced serum T4)		
9	Rat Spartan	once (GO)	Bd Wt	5000			IRCD 1975a OctaBDE
10	Rat Spartan	once (GO)	Bd Wt	500			IRCD 1975b PentaBDE
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

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - 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
13	Rat (Long-Evans)	4 d 1x/d (GO)	Endocr	10	30	(reduced serum T4)		Zhou et al. 2001 PentaBDE
14	Rat (Long-Evans)	4 d 1x/d (GO)	Endocr	3	10	(reduced serum T4)		Zhou et al. 2001 OctaBDE
15	Mouse (C57BL/6N)	14 d 1x/d (GO)	Endocr		18	(reduced serum T4)		Darnerud and Sinjari 1996 PentaBDE
16	Mouse C57BL/6J	once (GO)	Hepatic	500				Fowles et al. 1994 PentaBDE
			Endocr	100	500	(reduced serum T4)		
17	Mouse (C57BL/6N)	14d 1x/d (GO)	Hepatic	72				Fowles et al. 1994 PentaBDE
			Endocr		18	(reduced serum T4)		
			Bd Wt	72				

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - 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
18	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)		
	Immuno/ Lymphoret							
19	Rat (Sprague-Dawley)	14 d 1x/d (GO)		36				Darnerud and Thuvander 1998 PentaBDE
20	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
21	Mouse (C57BL/6N)	once (GO)		500				Fowles et al. 1994 PentaBDE
22	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

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - 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
	Developmental						
23	Rat (CD)	10 d Gd 6-15 (GO)		200			Argus Research Laboratories 1985a PentaBDE
24	Rat (CD)	10 d Gd 6-15 (GO)		10	25 (increased resorptions and reduced fetal body weight)		Argus Research Laboratories 1985b OctaBDE
25	Rat (CD)	10 d Gd 6-15 (GO)		2.5	10 (minimal increased post-implantation loss)		Life Science Research Israel Ltd. (1987) OctaBDE
26	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
27	Rat (Long-Evans)	14 d Gd 6-Gd 20 (GO)		1[b]	10 (reduced serum T4 in fetuses)		Zhou et al. 2002 PentaBDE
28	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

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Systemic						
29	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	1.77 M			Carlson 1980a PentaBDE
30	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	14.1 M			Carlson 1980a PentaBDE
31	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	2.4 M			Carlson, 1980a OctaBDE
32	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	19.2 M			Carlson, 1980a OctaBDE
33	Rat (CD)	28 d (F)	Hepatic		9 (increased liver weight and enlarged parenchymal cells)		IRDC 1976 PentaBDE
			Renal	90			
			Endocr	90			
			Bd Wt	90			

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - 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
34	Rat (CD)	28 d (F)	Hepatic		9 (increased liver weight and enlarged parenchymal cells)		IRDC 1976 OctaBDE
			Renal	90			
			Endocr	90			
			Bd Wt	90			

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - 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
35	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)		

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - 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
36	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 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to 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
37	Rat (Long-Evans)	36 d Gd 6-Pnd 21 (GO)	Endocr	10	30 (reduced maternal serum T4)		Zhou et al. 2002 PentaBDE
	Immuno/ Lymphoret						
38	Rat (CD)	13 wk (F)		750 F			IRDC 1977 OctaBDE
39	Rat (Sprague-Dawley)	90d (F)		100			WIL Research Laboratories 1984 PentaBDE
	Reproductive						
40	Rat (CD)	13 wk (F)		600 M[d] 750 F			IRDC 1977 OctaBDE
41	Rat (Sprague-Dawley)	90d (F)		100 M 100 F			WIL Research Laboratories 1984 PentaBDE

[a] Key to figure

Table 5-3 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - 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
	Developmental						
42	Rat (Long-Evans)	36 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 PentaBDE

a The number corresponds to entries in Figure 5- 3.

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 an 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 5-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); (DW) = drinking water; endocr = endocrine; (F)= feed; F = female; Gd = gestation day; (G) = gavage; gastro = gastrointestinal; (GO) = gavage in oil; hemato = hematological; hr = hour(s); LD50 = lethal dose; 50% kill; LOAEL = lowest observed adverse effect level;min = minute(s); M = male; Musc/skel = musculoskeletal; NOAEL = no observed adverse effect level; NS = not specified; pnd = post natal day; Resp = respiratory; T4 = thyroxine ; wk = week(s); x = time(s)

Figure 5-3. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers- Oral

Acute (≤14 days)

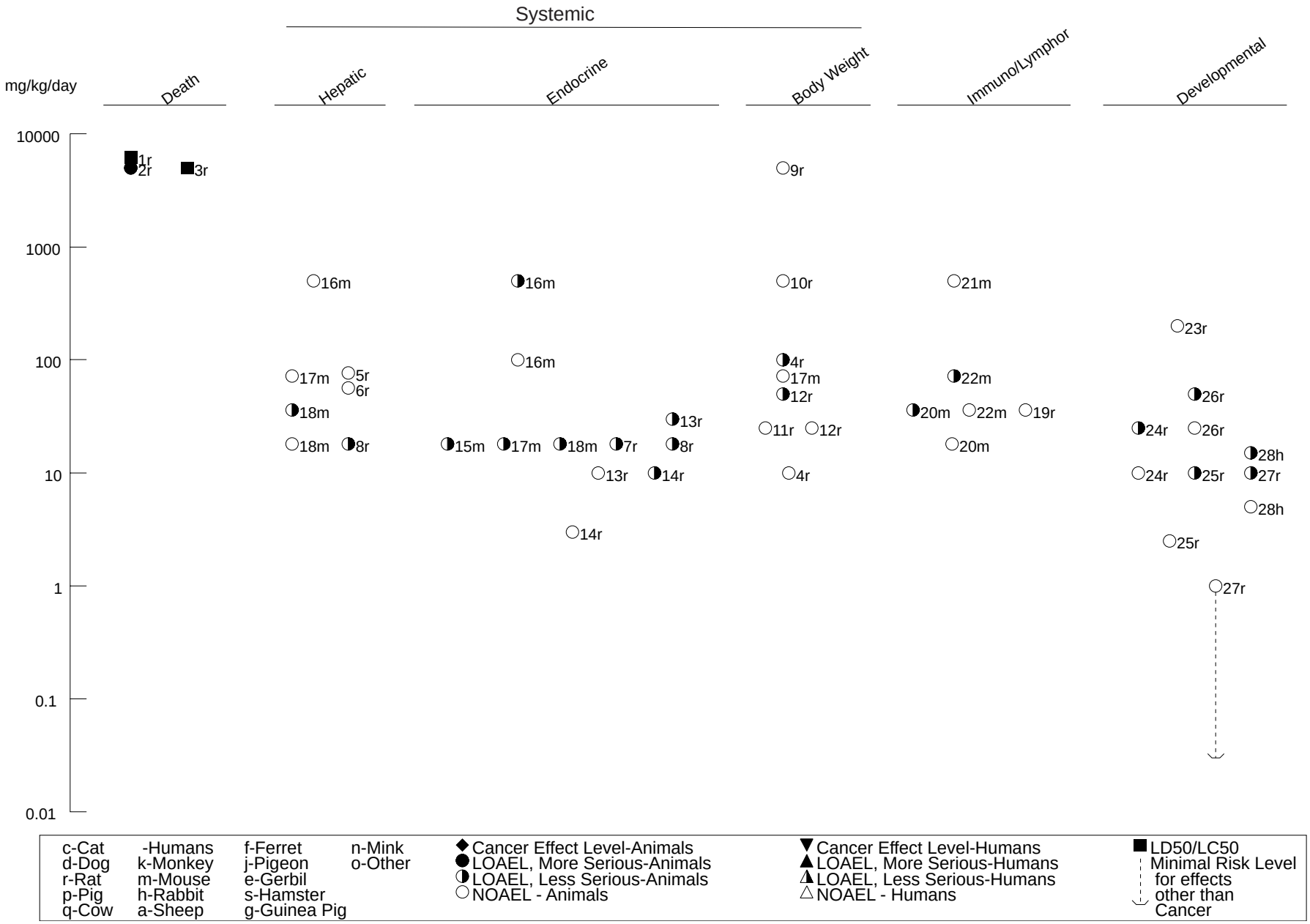


Figure 5-3. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers- Oral (*Continued*)

Intermediate (15-364 days)

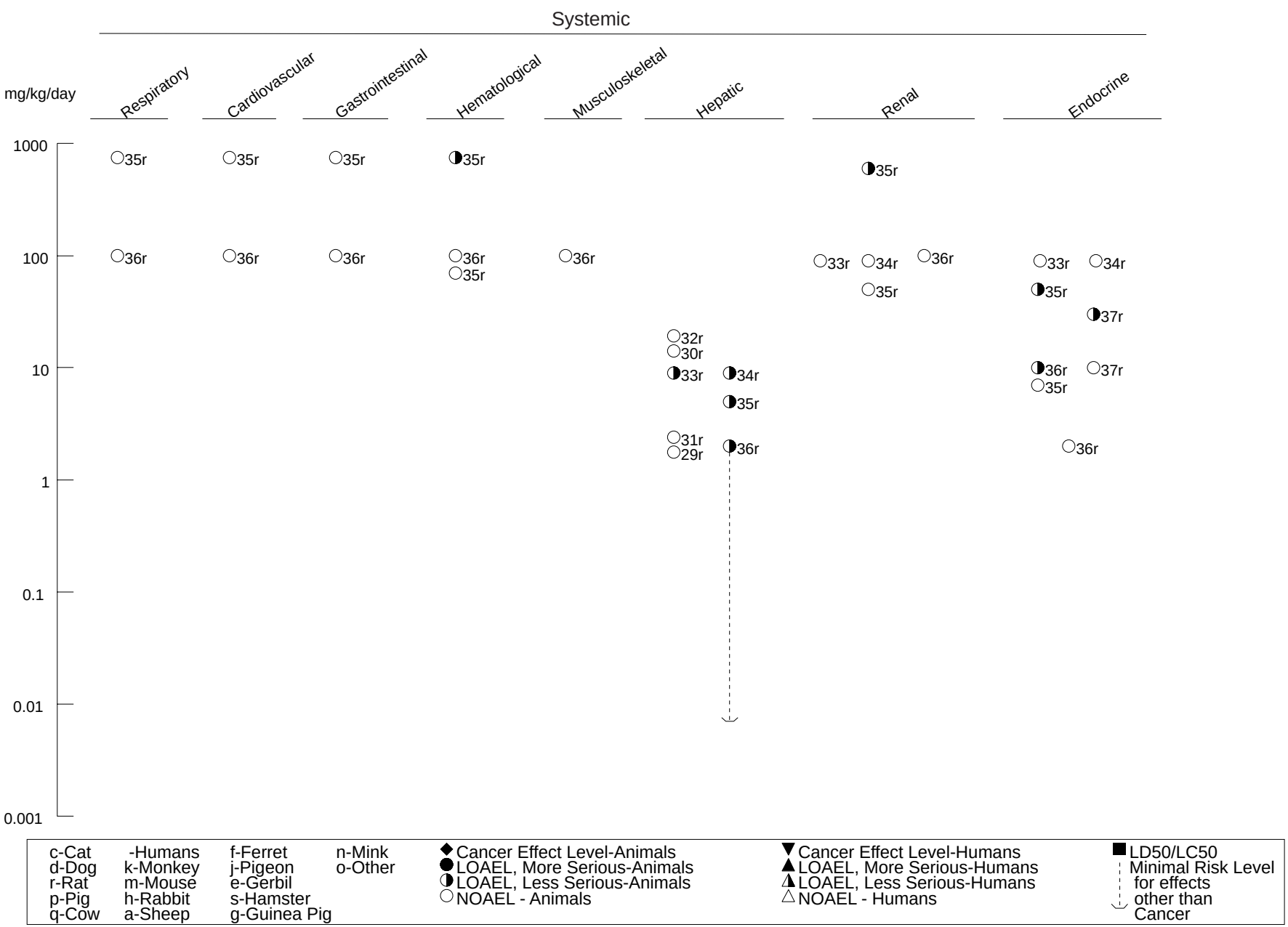


Figure 5-3. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers- Oral (*Continued*)

Intermediate (15-364 days)

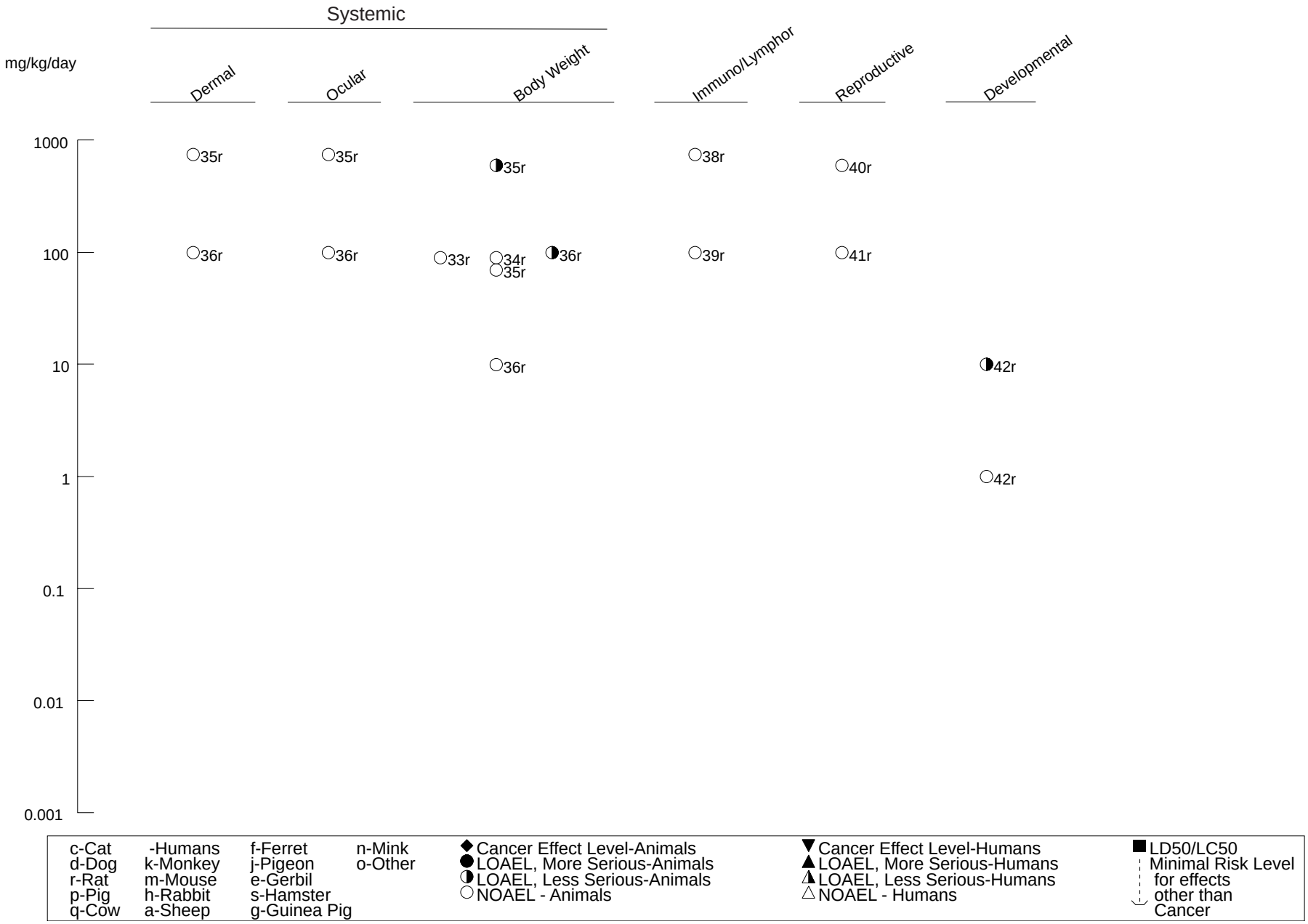


Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral

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
	ACUTE EXPOSURE						
	Systemic						
1	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic	95.9 M			Carlson 1980b DecaBDE
2	Rat Spartan	once (GO)	Bd Wt	5000			IRCD 1974 DecaBDE
3	Rat (Fischer- 344)	14d 1x/d (F)	Bd Wt	16000			NTP 1986 94-97% decaBDE
4	Rat (Long-Evans)	4 d 1x/d (GO)	Endocr	100			Zhou et al. 2001 DecaBDE
5	Mouse (B6C3F1)	14d 1x/d (F)	Bd Wt	19000			NTP 1986 94-97% decaBDE

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Systemic						
6	Rat (CD)	28 d (F)	Hepatic	90			IRDC 1976 DecaBDE
			Renal	90			
			Endocr	90			
			Bd Wt	90			

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - 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
7	Rat (Fischer- 344)	13 wk (F)	Resp	8000			NTP 1986 94-97% decaBDE
			Cardio	8000			
			Gastro	8000			
			Hemato	8000			
			Musc/skel	8000			
			Hepatic	8000			
			Renal	8000			
			Endocr	8000			
			Bd Wt	8000			

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - 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
8	Mouse (B6C3F1)	13 wk (F)	Resp	9500			NTP 1986 94-97% decaBDE
			Cardio	9500			
			Gastro	9500			
			Hemato	9500			
			Musc/skel	9500			
			Hepatic	9500			
			Renal	9500			
			Endocr	9500			
			Bd Wt	9500			
	Immuno/ Lymphoret						
9	Rat (Fischer- 344)	13 wk (F)		8000			NTP 1986 94-97% decaBDE

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - 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
10	Mouse (B6C3F1)	13 wk (F)		9500			NTP 1986 94-97% decaBDE
	Reproductive						
11	Rat (Fischer- 344)	13 wk (F)		8000			NTP 1986 94-97% decaBDE
12	Mouse (B6C3F1)	13 wk (F)		9500			NTP 1986 94-97% decaBDE
	Developmental						
13	Rat (Sprague-Dawley)	20 d Gd 0-19 (GO)		1000[b] F			Hardy et al. 2002 99% decaBDE

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - 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
	CHRONIC EXPOSURE						
	Systemic						
14	Rat (Sprague-Dawley)	2 yr (F)	Resp	1			Kociba et al. 1975; Norris et al. 1975b 77% decaBDE, 22% nonaBDE
			Cardio	1			
			Gastro	1			
			Hemato	1			
			Musc/skel	1			
			Hepatic	1			
			Renal	1			
			Endocr	1			
			Ocular	1			
			Bd Wt	1			

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - 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
15	Rat (Fischer- 344)	103 wk (F)	Resp	2550 F			NTP 1986 94-97% decaBDE
			Cardio	2550 F			
			Gastro	1120 M	2240 M		
			Hemato	2550 F			
			Musc/skel	2550 F			
			Hepatic	1200 M	1120 M		
					2250 F (pre-neoplastic nodules)		
			Renal	2550 F			
			Endocr	2550 F			
			Bd Wt	2550 F			

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - 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
16	Mouse (B6C3F1)	103 wk (F)	Resp	7780 F			NTP 1986 94-97% 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			
	Immuno/ Lymphoret						
17	Rat (Sprague-Dawley)	2 yr (F)		1			Kociba et al. 1975; Norris et al. 1975b 77% decaBDE, 22% nonaBDE

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - 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
18	Rat (Fischer- 344)	103 wk (F)			2240 M (splenic fibrosis and lymphoid hyperplasia) 1200 F (splenic hematopoiesis)		NTP 1986 94-97% decaBDE
19	Mouse (B6C3F1)	103 wk (F)		7780 F			NTP 1986 94-97% decaBDE
	Reproductive						
20	Rat (Sprague-Dawley)	2 yr (F)		1 M 1 F			Kociba et al. 1975; Norris et al. 1975b 77% decaBDE, 22% nonaBDE
21	Rat (Fischer- 344)	103 wk (F)		2240 M 2550 F			NTP 1986 94-97% decaBDE

Table 5-4 Levels of Significant Exposure to Decabromodiphenyl Ether - 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
22	Mouse (B6C3F1)	103 wk (F)		6650 M 7780 F			NTP 1986 94-97% decaBDE
	Cancer						
23	Rat (Fischer- 344)	103 wk (F)				1120 M (CEL: liver neoplastic nodules)	NTP 1986 94-97% decaBDE
24	Mouse (B6C3F1)	103 wk (F)				3200 M (CEL: hepatocellular adenomas and carcinomas)	NTP 1986 94-97% decaBDE

a The number corresponds to entries in Figure 5 4.

b Used to derive an intermediate-duration (15-364 days) oral minimal risk level (MRL) of 10 mg/kg/day for decaBDE. The MRL was derived by dividing the 1,000 mg/kg/day NOAEL by an uncertainty factor of 100 (10 for species to species extrapolation and 10 for human variability).

c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 5-4. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); (DW) = drinking water; endocr = endocrine; (F)= feed; F = female; Gd = gestation day; (G) = gavage; gastro = gastrointestinal; (GO) = gavage in oil; hemato = hematological; hr = hour(s); LOAEL = lowest observed adverse effect level; M = male; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no observed adverse effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s); yr = year(s)

Figure 5-4. Levels of Significant Exposure to Decabromodiphenyl Ether - Oral

Acute (≤14 days)

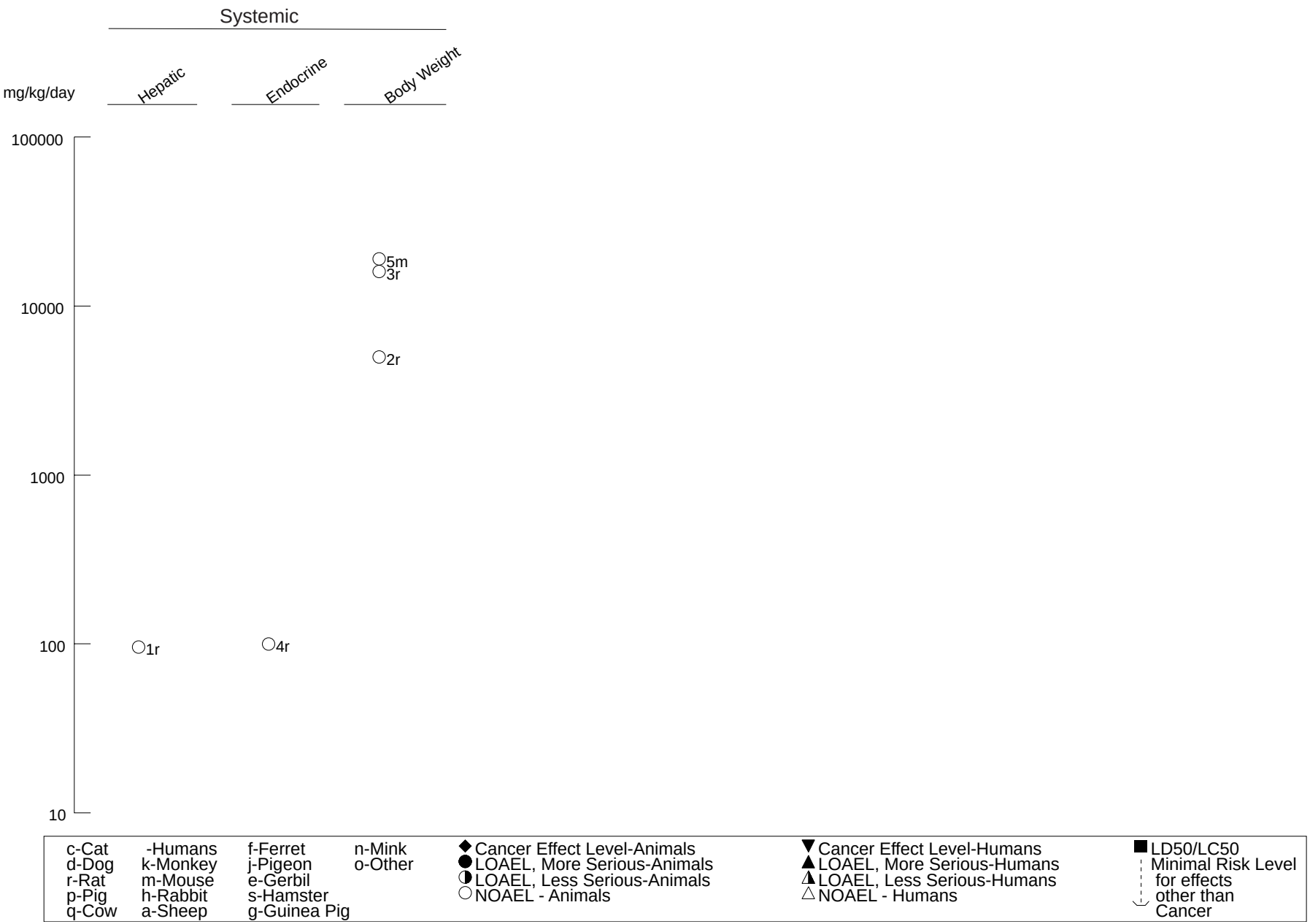


Figure 5-4. Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (*Continued*)

Intermediate (15-364 days)

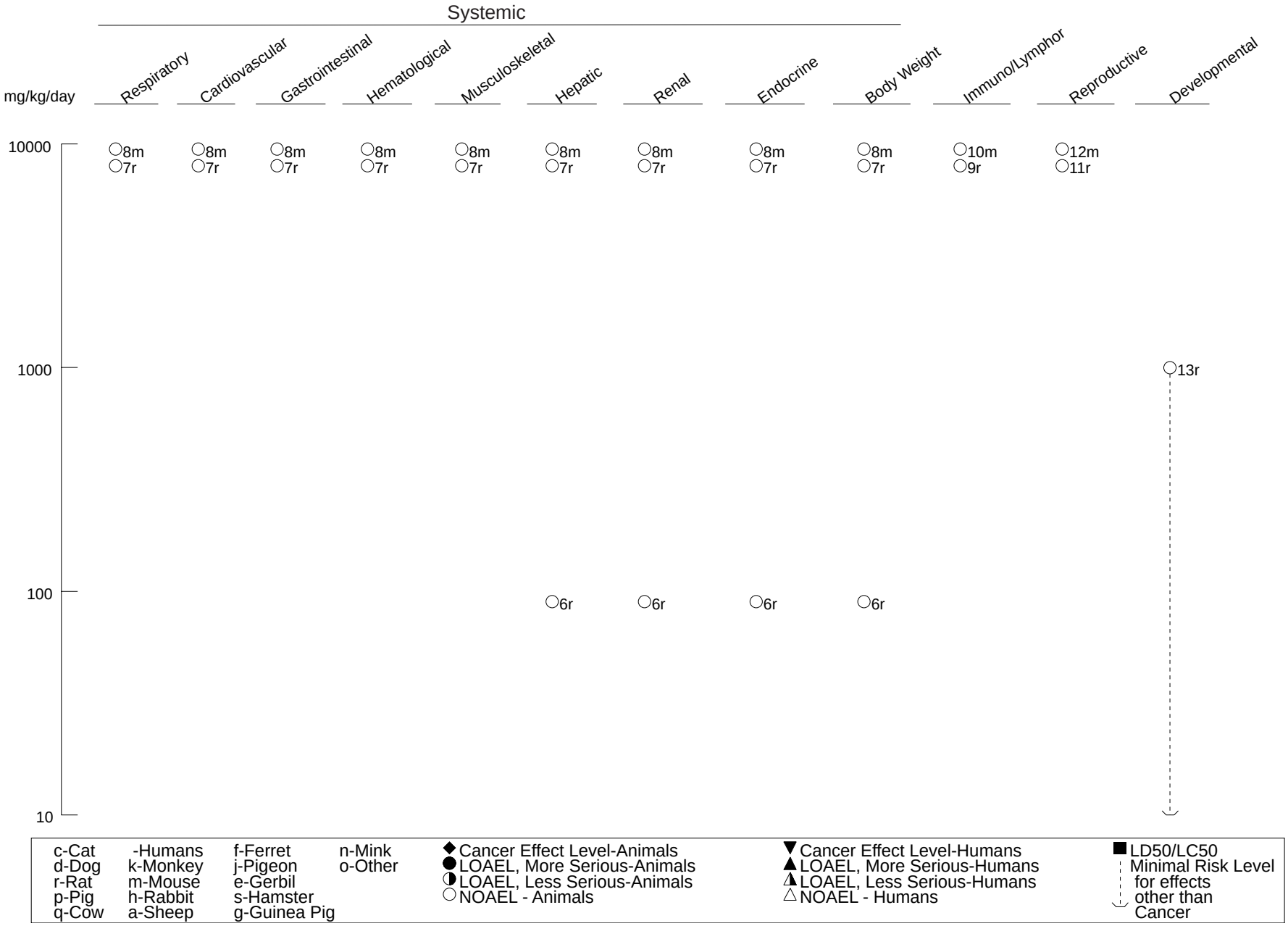
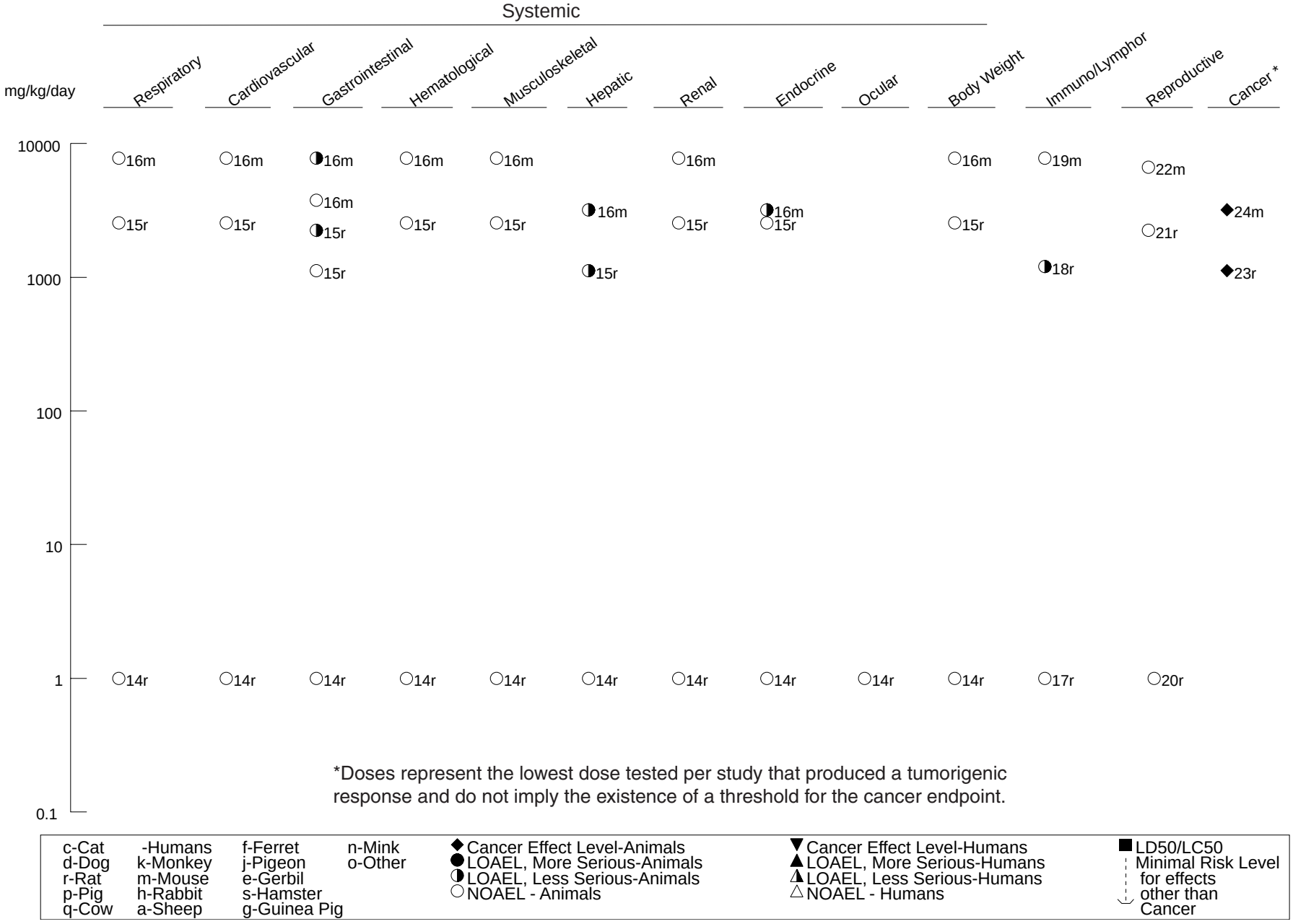


Figure 5-4. Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (*Continued*)

Chronic (≥365 days)



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 1978). 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 5-2 and plotted in Figure 5-2.

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, 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 BDE studies in rats are recorded in Tables 5-3 (lower BDEs) and 5-4 (decaBDE) and plotted in Figures 5-3 (lower BDEs) and 5-4 (decaBDE).

5.2.2.2 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 5-2 (PBBs), 5-3 (lower PDBEs), or 5-4 (decaBDE) and plotted in Figures 5-2 (PBBs), 5-3 (lower PDBEs), or 5-4 (decaBDE).

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

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 an intermediate-duration dietary studies in rats in which erythrocytes, hematocrit, and hemoglobin were reduced 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 in 4 of 23 (17%) Michigan residents with known PBB exposure and incapacitating health complaints and in 2 of 28 (7%) workers involved in the manufacture and distribution of PBBs,

respectively; however, these workers 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 5.8.2, 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 (AhR agonists), which elicit a well known pattern of toxic responses (see Chapters 3 and 4). 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. As discussed below, repeated dietary exposure to commercial PBDE products 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 and induced by lower doses with octaBDE and pentaBDE than decaBDE. Regarding decaBDE, the low purity former mixture (77.4% pure containing 21.8% nonaBDE and 0.8% octaBDE) was much more hepatotoxic than the current day commercial product (≈99% pure). In particular, hepatic effects included increased liver weights at ≥80 mg/kg/day with centrilobular cytoplasmic enlargement and vacuolation at 800 mg/kg/day in male rats exposed to 77% decaBDE for 30 days (Norris et al. 1973, 1975a, 1975b), whereas exposure to 94–97% decaBDE for 13 weeks caused no liver pathology in rats and mice exposed to estimated doses as high as 2,000–8,000 and 2,375–9,500 mg/kg/day, respectively (NTP 1986). The NOAEL for hepatic effects from the NTP (1986) 13-week study (8,000 mg/kg/day) was used as the basis for the intermediate-duration MRL for oral exposure to decaBDE, as indicated in a footnote to Table 5-4 and discussed in Chapter 4 and Appendix A. In chronic studies, exposure to 94–97% decaBDE for 103 weeks caused liver lesions that included neoplastic nodules in rats at ≥1,120 mg/kg/day, thrombosis and degeneration in rats at 2,240 mg/kg/day, and centrilobular hypertrophy and granulomas in mice at ≥3,200 mg/kg/day (NTP 1986). The thrombosis in the rats was characterized by a near total occlusion of a major heptatic blood vessel by a dense fibrin coagulum. A NOAEL was not identified in the rats or mice. The only other chronic study of decaBDE found that exposure to 1 mg/kg/day of the 77% pure mixture for 2 years caused no liver effects in rats; higher doses were not tested, precluding identification of a LOAEL (Kociba et al. 1975; Norris et al. 1975b). Unlike the decaBDE used in the NTP (1986) study, the composition of the mixture tested by Kociba et al. (1975) is substantially different than that of current-day commercial decaBDE products (≈99%).

OctaBDE caused increased liver weight and histopathological changes such as hepatocellular enlargement and vacuolation in rats exposed to doses as low as 5mg/kg/day (lowest tested dose) for 4–13 weeks (IRDC 1976, 1977). 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 to tetra- to heptaBDEs as indicated in the footnote to Table 5-3 and discussed in Chapter 4 and Appendix A. Liver vitamin A concentrations were increased in rats and mice exposed to a commercial pentaBDE mixture (Bromkal 70-5 DE) 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 for the pentaBDE and octaBDE commercial products, but has not been observed for decaBDE (Carlson 1980b; Zhou et al. 2001). 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-nitro-phenyl 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.

Dietary studies of PBDEs in animals observed kidney effects that are mainly attributable to octaBDE. Renal effects induced by octaBDE included 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 (tubule regeneration, intratubular casts, and cellular debris occurred in most 600 mg/kg/day males) suggested a compound-related effect (IRDC 1977). Another study of octaBDE found no histopathological changes in the kidneys of rats exposed to ≤90 mg/kg/day for 90 days (IRDC 1976). 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).

Studies of low purity (≈77%) commercial decaBDE mixtures found kidney pathology (hyaline degenerative cytoplasmic changes) in male rats exposed to 800 mg/kg/day for 30 days (Norris et al. 1973, 1975a, 1975b), but not in rats exposed to ≤90 mg/kg/day for 90 days (IRDC 1976) or ≤1.0 mg/kg/day for 2 years (Kociba et al. 1975; Norris et al. 1975b). Interpretation of this finding is complicated by the fact that hyaline degenerative cytoplasmic changes are not uncommon in adult male rats and might be induced by a mechanism specific to certain aged male rats. No renal histopathological changes were induced by 94–97% pure commercial decaBDE in rats exposed to ≤8,000 mg/kg/day for 13 weeks 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).

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 ($p \leq 0.05$) 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 indicated in the footnote to Table 5-2 and discussed in Chapter 3 and Appendix A. 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 the congener 2,2',4,4'-tetraBDE (BDE 47) 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 BDE 47 and plasma TSH after age adjustment, but the congener could not explain more than 10% of the variance in TSH (r^2=0.10, p<0.001). The fact that BDE 47 could only explain 10% of the variance in TSH is not surprising due to the occurrence of PCBs and other likely similarly acting compounds in the Baltic fisherman.

Hyperplasia of the thyroid was 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 ≥94% pure commercial 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 5.2.2.7, 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 low purity composition of the older commercial decaBDE mixture tested by Norris et al. (1973, 1975a, 1975b) (i.e., 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE, compared to the ≥94% decaBDE composition used in the NTP studies).

Thyroid function was not tested in any of the intermediate- and chronic-duration studies of decaBDE, although an acute study in rats (Zhou et al. 2001), summarized in the following paragraph, found that a >98% pure decaBDE product (DE-83R) caused no serum changes in thyroid hormones. Studies of commercial octa- and pentaBDE mixtures and individual constituent congeners of these mixtures, also summarized below, indicate that the rat and mouse thyroid is particularly sensitive to the lower brominated BDEs. The human relevance of the animal thyroid data is unclear due to evidence indicating that the main thyroid effect, decreased serum T_4, occurs by a mechanism that is not clearly relevant to humans (see Section 5.5.2 Mechanisms of Toxicity).

Thyroid hormone levels were determined in 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 (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 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. 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 the commercial pentaBDE mixture DE-71 that found reduced thyroid hormone levels 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 to tetra- to heptaBDEs as indicated in the footnote to Table 5-3 and discussed in Chapter 4 and Appendix A. The BMD and BMDL resulting in a 20% reduction in serum T_4 levels were reported to be 2.36 and 0.94 mg/kg/day, respectively. 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 5.2.2.6 (Developmental Effects).

Reduced serum T_4 levels additionally occurred in adult offspring of rats that were exposed to commercial pentaBDE mixture DE-71 during gestation and lactation in two studies incompletely reported as abstracts (Taylor et al. 2002, 2003). In one study, rats were orally dosed with 0, 1, 10, or 30 mg/kg/day of DE-71 in corn oil from GD 6 through PND 21 (Taylor et al. 2002). Evaluation of the offspring at various ages (not specified) showed effects that included reduced serum T_4 levels; specific data were not reported, although the BMD and BMDL for reduced T_4 were 2.3 and 0.9 mg/kg/day, respectively. In the other study, rats were similarly administered 1-100 mg/kg/day of DE-71 on GD 6 to PND 21 (Taylor et al. 2003). Measurement of serum levels of thyroid hormones in offspring showed dose-related decreases in T_4 at 5, 30, and 100 mg/kg/day on PND 5 (73.3, 49.3, and 43.5% of controls) and PND 14 (75.6, 33.6, and 29.9% of controls). The serum T_4 decreases in both studies were accompanied by increases in hepatic metabolism (EROD, PROD, UDPGT, and glucuronidation). Other effects included neuro-behavioral and reproductive developmental changes as summarized in Sections 5.2.2.4 (Neurological Effects) and 5.2.2.5 (Reproductive Effects).

Commercial pentaBDE mixture DE-71 was tested under EPA's Endocrine Disruptor Screening Program (EDSP) using male and female rat pubertal protocols for detecting thyroid active agents (Laws et al. 2003; Stoker et al. 2003). These studies are incompletely reported as abstracts. End points in both studies included pubertal development (time to preputial separation in males and vaginal opening in females), body and reproductive tissue weights, thyroid function (serum levels of T_4, T_3, and TSH), and liver microsomal enzyme induction (EROD, PROD, and UDPGT activity). Both sexes showed delays in reproductive development that were accompanied by changes in thyroid hormone levels and hepatic metabolism. In the study with males, Wistar rats were gavaged with 0, 3, 30, or 60 mg/kg/day doses in

corn oil for 5 days on PNDs 24–28, or for 31 days on PNDs 23–53 (Stoker et al. 2003). Pubertal development was delayed as shown by significant increases in the age of preputial separation at 30 and 60 mg/kg/day (2.0- and 2.3-day delay, respectively). Seminal vesical and ventral prostate weights were reduced at 60 mg/kg/day with no significant changes in testis or epididymal weights or serum testosterone levels. Thyroid hormone measurements showed reductions in serum T_4 at 30 and 60 mg/kg/day (74 and 81% lower than controls) after 5 days of exposure, serum T_4 at 3, 30, and 60 mg/kg/day (20, 80, and 86% lower) after 31 days, and serum T_3 at 30 and 60 mg/kg/day (25 and 20% lower) after 31 days, and increased serum TSH at 30 and 60 mg/kg/day (64 and 113% higher than controls) after 31 days. Hepatic effects included increased relative liver weight and microsomal EROD, PROD, and UDPGT activity at 30 and 60 mg/kg/day at both time points. In the study with females, Wistar rats were gavaged with DE-71 in corn oil in doses of 0, 3, 30, or 60 mg/kg/day for 5 days on PNDs 22–26, or for 20 days on PNDs 22–41 (Laws et al. 2003). The 60 mg/kg/day dose caused a small but statistically significant delay in the age of vaginal opening (1.8-day delay compared to controls). Other effects included a significant decrease in serum T_4 at ≥30 mg/kg/day at both time points, a linear trend for increased TSH (1.6-fold increase at 60 mg/kg/day) after 20 days of exposure, and increased relative liver weight and microsomal EROD, PROD, and UDPGT activity at ≥30 mg/kg/day after at both time points. The results of both studies indicate that the changes in thyroid hormone levels were related to induction of liver metabolic enzymes.

End points assessed in a comprehensive 90-day feeding study of a commercial pentaBDE (DE-71) mixture 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.

Serum total T_4 concentrations were significantly reduced in female C57BL/6J mice that were given a single gavage dose of commercial pentaBDE mixture 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). Another single-dose gavage study, this time in rats (Hakk et al. 2002), reported transient increases in total T4 plasma levels, but the small (n=3) number of animals per group and the lack of reported tests of statistical significance make the interpretation of the findings unclear. 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 these single-dose and 14-day mouse studies. Serum levels of total and free T_4 were also reduced in female Sprague-Dawley rats and female B6C3F1 mice that were exposed to ≥18 mg/kg/day of the commercial pentaBDE mixtures Bromkal 70 or Bromkal 70-5 DE, or the congener 2,2',4,4'-tetraBDE (BDE 47), by daily gavage for 14 days (Darnerud and Sinjari 1996; Hallgren and Darnerud 1998; Hallgren et al. 1998, 2001). Exposure to the mixtures or congener did not cause decreases in serum T_4 at doses ≤6 mg/kg/day, or any changes in serum TSH or thyroid histology at any tested level (≤36 mg/kg/day) in either species. The decreases in serum T_4 were associated with reduced *ex vivo* binding of T_4 to the plasma thyroid hormone transporter protein transthyretin, as well as with induction of hepatic microsomal enzymes (EROD, MROD, PROD, and UDPGT) (Hallgren and Darnerud 1998). A limited amount of information is available on hormonal effects of PBDEs other than thyroid. There were no clear chemical-related changes in serum corticosterone levels in female mice that were exposed to a commercial pentaBDE mixture (DE-71) in doses of 18, 36, or 72 mg/kg/day by daily gavage for 14 days (Fowles et al. 1994). As reported in a study abstract (Kuriyama and Chahoud 2003), serum levels of testosterone and LH were unchanged in adult male offspring of Wistar rats that were maternally exposed to a single 60 or 300 µg/kg oral dose of the penta congener BDE 99 on day 6 of gestation. Although there were no effects on these male reproductive hormones, spermatid and sperm numbers were reduced as summarized in Section 5.2.2.6 Developmental Effects.

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.

In animals, repeated exposures to PBBs produced characteristic dermal changes in certain species, particularly monkeys, but generally not in haired rodents. 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 1978; 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), 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).

5.2.2.3 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, and many studies administered the PBBs by gavage (exceptions noted below). Additionally, most studies were conducted in rats, a species that may be a poor model for investigating dioxin-like effects on the adult immune system. Identification of the most sensitive species is further complicated by 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 5.2.2.6.

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 1978). 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 1978). 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 5-2 and plotted in Figure 5-2.

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 (BDE 47) or 2,2',3,4,4'-pentaBDE (BDE 85) *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. The effects in both 14-day studies of commercial pentaBDE mixtures occurred only at the highest dose and are possibly due to contamination with PBDDs and PBDFs. Mice that were similarly tested with 18 mg/kg/day of the congener 2,2’,4,4’-tetraBDE (BDE 47) 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 5-3 and plotted in Figure 5-3.

5.2.2.4 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 5.2.2.6 (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 5-2 and plotted in Figure 5-2.

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

A limited amount of information is available on neurological effects of PBDE mixtures in animals. None of the commercial decaBDE, octaBDE, and pentaBDE products have been screened for neurotoxicity using comprehensive test batteries that typically include functional observational, motor activity, and neuropathology evaluations.

There were no indications of neurotoxicity for commercial decaBDE, as assessed by overt clinical signs and nervous system histopathology, in rats and mice in lifetime feeding studies of the 94–97% pure mixture (NTP 1986). These animals were exposed to high dietary levels of the decaBDE product (estimated doses as high as 2,550 mg/kg/day in rats and 7,780 mg/kg/day in mice) for 103 weeks. There also were no overt signs of neurotoxicity in rats and mice exposed to decaBDE in estimated dietary doses

of ≤16,000 and ≤19,000 mg/kg/day, respectively, for 14 days, or ≤8,000 and ≤9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986). Histological examinations of the nervous system were not performed in these 14-day and 13-week studies. Although the high doses and extended exposure durations in the NTP (1986) studies provided opportunities for the induction and/or development of effects, neurotoxicity is incompletely evaluated due to the lack of testing for subtle behavioral and other sensitive neurological end points.

Three studies, reported in limited detail as abstracts, assessed neurobehavioral development in offspring of rats that were perinatally exposed to commercial pentaBDE mixture DE-71 in corn oil by gavage on GD 6 through PND 21, in dose ranges of 1–30 mg/kg/day (Taylor et al. 2002), 1–100 mg/kg/day (Taylor et al. 2003), or 5–100 mg/kg/day (MacPhail et al. 2003). Behavioral end points included motor activity (MacPhail et al. 2003; Taylor et al. 2002, 2003), auditory startle (Taylor et al. 2002, 2003), and fear conditioning (Taylor et al. 2003). Evaluation of adult offspring showed no alterations in motor or sensory development as assessed by overall levels of motor activity, within-session habituation of activity, or auditory startle response, although tests of fear conditioning revealed decreases in cue-based (but not context-based) performance. The lack of motor activity changes in the DE-71 mixture-exposed rats differs from attenuating effects on habituation of motor activity observed in mice exposed to individual PBDE congeners, as summarized below.

Neurobehavioral effects of postnatal or perinatal exposure to individual PBDE congeners have been evaluated in a number of mouse studies. As detailed below, these studies collectively indicate that the developing nervous system is a target of particular congeners, as shown by mild performance impairments in tests of spontaneous motor behavior and learning and memory in adult mice. The aberrations in spontaneous behavior generally appeared to persist and worsen with age, and were induced during a defined critical phase of neonatal brain development.

In a series of congener studies using similar experimental designs, single doses of 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',5,5'-hexaBDE (BDE 153), or 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209) were postnatally administered to male NMRI mice in a 20% fat emulsion vehicle by gavage (Eriksson et al. 1999, 2001a, 2002a; Viberg et al. 2001a, 2001b, 2002a, 2002b, 2003a). Evaluations included spontaneous motor behavior at 2, 4, and/or 6 months of age (BDEs 47, 99, 153, and 209), and Morris swim maze performance at 5 or 6 months of age (BDEs 47, 99, and 153). The spontaneous behavior test measured open-field locomotion (horizontal movements), rearing (vertical movements), and total activity (all types of vibrations within a test cage). The measurements were

performed during three consecutive 20-minute periods to assess habituation, defined as a decrease in the motor activities in response to diminishing novelty of the test chamber over 60 minutes. The water maze test assessed spatial learning ability and memory by evaluating the ability to locate a submerged platform. Cognition was tested 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.

In the study with 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209), the mice were dosed once with 0, 2.22, or 20.1 mg/kg on PNDs 3 or 19, or 0, 1.34, 13.4 or 20.1 mg/kg on PND 10, and evaluated for spontaneous behavior at 2, 4, and 6 months of age (Viberg et al. 2001b, 2003a). A non-habituating behavior profile was observed in the mice exposed on PND 3, but not in those exposed on PND 10 or 19. In particular, following exposure on PND 3, aberrations in spontaneous motor behavior were manifested at 6 months of age in the mice exposed to 2.22 mg/kg, and at 2, 4, and 6 months of age in those exposed to 20.1 mg/kg. The aberrations were more pronounced in the older animals, indicating that the effects worsened with age. The findings are consistent with tissue distribution data in this study, suggesting that brain uptake of ^{14}C-BDE 209 was more efficient in the younger animals and that the amount of radioactivity reaching the brain increased with time (see Section 5.4.2). Additional information on the behavioral results of this study, including quantitative data, was not reported.

In the study with 2,2',4,4',5,5'-hexaBDE (BDE 153), mice were dosed once with 0, 0.45, 0.9, or 9.0 mg/kg on PND 10, and evaluated for spontaneous behavior at 2, 4, and 6 months of age, and swim maze performance at 6 months of age (Viberg et al. 2001b, 2002a). Non-habituating behavior occurred in mice exposed to 0.45 mg/kg at 6 months of age, and 0.9 and 9.0 mg/kg at 2, 4, and 6 months of age. The effect worsened with age and was most pronounced at 9.0 mg/kg. The swim maze test found that all mice improved their ability to locate the platform during the acquisition period, although those exposed to ≥0.9 mg/kg had significantly longer latencies to locate the platform on days 2 and 3 during the acquisition period. Additional information on the behavioral results of this study, including quantitative data, was not reported.

Mice were also exposed once to 2,2',4,4'-tetraBDE (BDE 47) in doses of 0, 0.7, or 10.5 mg/kg, or 2,2',4,4',5-pentaBDE (BDE 99) in doses of 0, 0.8, or 12.0 mg/kg, on PND 10 (Eriksson et al. 1998, 2002b). Spontaneous behavior was tested at 2 and 4 months of age in all dose groups, and swim maze

performance was tested at 5 months of age in the groups given the high dose of each congener. A disruption of habituation was observed in mice exposed to both congeners. During the first of the three consecutive 20-minute test periods, at both 2 and 4 months, animals treated with 10.5 mg/kg BDE 47 and ≥0.8 mg/kg BDE 99 were significantly less active than controls as shown by dose-related decreases in all three activity measures. 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 BDE 47 and ≥0.8 mg/kg BDE 99 caused significantly more activity than controls at 2 and 4 months as shown by dose-related increases in the test measures. 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 same non-habituating behavior at 2 and 4 months of age (hypoactivity followed by hyperactivity) seen in mice exposed to an 8 mg/kg dose of BDE 99 on PND 10 (Viberg et al. 2002b). The only exposure-related effect in the Morris water maze test was found in the mice exposed to BDE 99 at 12.0 mg/kg; performance in finding a new platform location did not improve as it did in controls and mice exposed to BDE 47(Eriksson et al. 1998, 2001a).

Other reports further characterized effects of postnatal exposure to 2,2',4,4',5-pentaBDE (BDE 99) on spontaneous motor behavior in mice. In a study designed to ascertain if NMRI male mice are susceptible during a critical phase of neonatal brain development (i.e., during the period of rapid brain growth), spontaneous behavior was evaluated in adult mice that were administered a single 8 mg/kg dose of BDE 992 on PNDs 3, 10, or 19 and tested at 4 months of age (Eriksson et al. 1999, 2002b). A non-habituating behavioral pattern similar to that observed in the studies summarized above (i.e., decreased locomotion, rearing, and total activity over time in response to diminished novelty of the test chambers) was seen in the mice treated at either 3 or 10 days of age. There were no significant changes in the three spontaneous activity measures in the mice exposed at 19 days of age, suggesting that there was a critical window for the induction of the behavioral disturbances. In an assessment of sex and/or strain dependency (i.e., whether mice other than NMRI males were affected), male and female C57 Bl/J mice were exposed to BDE 99 as a single gavage dose of 0.4, 0.8, 4.0, 8.0, or 16.0 mg/kg on PND 10, and tested at 2, 5, and 8 months of age (Viberg et al. 2003a). Spontaneous motor behavior was significantly impaired at ≥0.8 mg/kg in both sexes at all three ages. The effect was dose-related and appeared to worsen with age, showing a pattern of response similar to that observed for BDE 99 and other congeners in the various studies with NMRI male mice.

In a study of perinatal exposure to 2,2',4,4',5-pentaBDE (BDE 99), groups of two male and two female CD-1 Swiss female mice were gavaged with 0, 0.6, 6, or 30 mg/kg/day in corn oil from GD 6 to PND 21 (Branchi et al. 2001, 2002). Somatic development (body weight gain, hair growth, day of eyelid and ear opening, day of incisor eruption) and neurobehavioral development (righting reflex, forelimb stick grasping reflex, forelimb placing reflexes, negative geotaxis, screen grasping and climbing, pole grasping, ultrasonic vocalizations, homing test) were assessed during PNDs 2–20. Spontaneous activity, including locomotion (horizontal movement), rearing (vertical movement), and thigmotaxis (time and distance traveled close to walls, an index of emotionality), was assessed on PNDs 22, 34, 60, and 120. There were no clear exposure-related indications of prenatal toxicity as shown by maternal weight gain and pregnancy and litter indices. The testing during PNDs 2–22 suggested a delay in sensorimotor development at 30 mg/kg/day, as indicated by approximately 2 days delayed maturation in screen climbing response. The spontaneous behavior testing showed changes suggestive of an age-dependent alteration in activity at ≥6 mg/kg/day; effects included hyperactivity (increased locomotion and rearing) and impaired habituation at PNDs 34 and 60, altered thigmotaxis (reduced time near walls) at PND 60, and a tendency to hypoactivity (reduced locomotion) at PND 120.

5.2.2.5 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 90^{th} 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 5-2 and plotted in Figure 5-2.

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).

Exposure to lower brominated PBDEs has been reported to cause reproductive effects in developing rats. As summarized in Section 5.2.2.6 Developmental Effects, postnatal exposure to the commercial pentaBDE mixture DE-71 caused delayed onset of puberty in male and female rats (Laws et al. 2003; Stoker et al. 2003). Additionally, testicular and ovarian effects occurred in male and female adult offspring of rats that were gestationally exposed the pentaBDE congener BDE 99 (Kuriyama and Chahoud 2003; Talsness et al. 2003).

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 5-3 and plotted in Figure 5-3.

5.2.2.6 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 5.2.2.8 (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 suppressed 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 5-2 and plotted in Figure 5-2.

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 commercial mixtures of deca-, octa- and pentaBDE (Argus Research Laboratories 1985b; Breslin et al. 1989; Dow Chemical Co. 1975, 1985; Hardy et al. 2001, 2002; Life Science Research Israel Ltd. 1987; Norris et al. 1975b; WIL Research Laboratories 1986). None of the commercial BDE mixtures have been shown to be overtly teratogenic in animals, although neurobehavioral tests, summarized in Section 5.2.2.4 (Neurological Effects), indicate that the developing nervous system is a potential target of some individual lower brominated congeners, including 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).

No prenatal developmental toxicity was found in a comprehensive study of commercial decaBDE product (Hardy et al. 2001, 2002). The test material was a composite of current commercial decaBDE mixtures produced by three manufacturers and had a composition of 97.34% decaBDE and 2.66% nona-

and octaBDE congeners. The mixture was administered to groups of 25 mated female Sprague-Dawley rats by gavage in corn oil in daily doses of 0, 100, 300, or 1,000 mg/kg/day on GDs 0 through 19. All females were necropsied following sacrifice on GD 20. Maternal end points included clinical observations, body weight and food consumption, gravid uterine and liver weights, gross lesions, and uterine implantation indices (e.g., numbers of corpora lutea, implantations, and early and late resorptions). Fetal end points included viability, body weights, sex distribution, gross malformations (all fetuses), skeletal/cartilaginous malformations and ossification variations (approximately half of each litter), and visceral malformations (remaining fetuses). There were no treatment-related effects on any of the maternal or fetal end points, indicating that 1,000 mg/kg/day was a NOAEL for developmental toxicity of decaDBE.

A lower purity commercial decaBDE product (77% decaDBE, 22% nonaBDE, 0.8% octaBDE) used in the 1970s was fetotoxic in rats at high dose levels that were not maternally toxic. Developmental effects 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 5.2.2.5 (Reproductive Effects), a one-generation study of the 77% commercial decaBDE mixture 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).

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 overt 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 commercial 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, $p\leq0.05$), 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 ($p\leq0.05$) 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 ($p\leq0.01$) 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 the rat 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 5.2.2.2. There were no clear effects on pregnancy and birth indices in mice that were gavaged

with the congener 2,2',4,4',5-pentaBDE (BDE 99) in oral doses of 0.6–30 mg/kg/day from GD 6 to PND 21 (Branchi et al. 2001, 2002).

A limited amount of information is available on neurodevelopmental effects of commercial pentaDBE mixture DE-71 in mice in two studies incompletely reported as abstracts (Taylor et al. 2002, 2003). These studies assessed effects in adult offspring of rats that were orally exposed during gestation and lactation (GD 6 to PND 21). In one study, the maternal rats were dosed with 0, 1, 10, or 30 mg/kg/day and offspring were evaluated at various ages (not specified) for end points that included motor activity development, auditory startle response, and age at eye opening. There were no alterations in any of these indices. The second study also found no changes in motor activity, auditory startle response, or eye opening in the offspring following exposure to 1–100 mg/kg/day, although fear conditioning performance was altered (Taylor et al. 2003). Other effects of DE-71 in both studies included decreased serum T_4 levels in the offspring and dams (see Section 5.2.2.2 Endocrine Effects).

Delays in reproductive development occurred in male and female Wistar rats that were exposed to the pentaBDE commercial mixture DE-71 in studies that are incompletely reported as abstracts (Laws et al. 2003; Stoker et al. 2003). Male rats were gavaged with 0, 3, 30, or 60 mg/kg/day doses of DE-71 in corn oil for 5 days on PNDs 24–28, or for 31 days on PNDs 23–53 (Stoker et al. 2003). Pubertal development was delayed as indicated by significant increases in the age at preputial separation at 30 and 60 mg/kg/day (2.0 and 2.3 days delay, respectively). Seminal vesical and ventral prostate weights were reduced at 60 mg/kg/day, although there were no significant changes in testis or epididymal weights or serum testosterone levels. Female rats were gavaged with DE-71 in corn oil in doses of 0, 3, 30, or 60 mg/kg/day for 5 days on PNDs 22–26, or for 20 days on PNDs 22–41 (Laws et al. 2003). Pubertal development was delayed as indicated by a small but statistically significant delay in the age of vaginal opening (1.8 days delay compared to controls) at 60 mg/kg/day. There were no treatment-related changes in weights of female reproductive tissues, and information on levels of female reproductive hormones was not reported. As summarized in Endocrine Effects in Section 5.2.2.2, the delays in male and female reproductive development were accompanied by changes in serum levels of thyroid hormones (decreased T_3 and T_4, increased TSH). The onset of puberty was also delayed in female offspring (vaginal opening), but not in male offspring (preputial separation), of Long Evans rats that were subcutaneously exposed to 1 or 10 mg/kg/day doses of the congener 2,2',4,4',5-pentaBDE (BDE 99) on days 10–18 of gestation (Lichtensteiger et al. 2003b).

Testicular and ovarian effects were observed in male and female adult offspring of Wistar rats that were maternally exposed to a single 60 or 300 µg/kg oral dose of the pentaBDE congener BDE 99 in peanut oil on day 6 of gestation (Kuriyama and Chahoud 2003; Talsness et al. 2003). Evaluations of the male offspring were performed on PND 140 and included reproductive tissue weights (testis, epididymis, ventral prostate, and seminal vesicle), spermatid and sperm numbers, and serum levels of testosterone and LH (Kuriyama and Chahoud 2003). Effects in the male offspring occurred at 60 and 300 µg/kg, including significantly decreased ($p<0.05$) spermatid number (31 and 34% less than controls), sperm number (29 and 18% less than controls), and daily sperm production (31 and 34% less than controls). The female offspring were necropsied in estrus on approximately postnatal day 90, at which time, ovaries were examined by electron microscopy (Talsness et al. 2003). Ultrastructural alterations were observed in ovaries at both dose levels, particularly degenerative changes that included vacuolization and accumulation of vesicules in the cytoplasm of the stromal cells and necrosis in the serosal epithelial cells. The single congener dose levels in this study are much lower than the LOAEL of 2 mg/kg/day for liver effects in rats exposed to a commercial mixture of pentaBDE in the 90-day study used to derive the intermediate oral MRL.

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 5-3 and plotted in Figure 5-3.

5.2.2.7 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 90^{th} and 95^{th} 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 biphenyls (PCBs) 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 ($p \leq 0.055$). 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 ($p\leq0.002$) 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 ($p\leq0.05$) 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 ($p\leq0.01$) and 37 of 50 ($p\leq0.01$) in males and 17 of 50 ($p>0.05$) and 27 of 50 ($p\leq0.01$) in females. In the 0.5:1.5 mg/kg/day groups, the incidences were 37 of 50 ($p\leq0.01$) in males and 25 of 50 ($p\leq0.05$) 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 ($p\leq0.05$ in males; $p\leq0.01$ in females). For males, there was also a marginally significant ($p\leq0.05$) 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 5-2 and plotted in Figure 5-2.

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-nitroso-pyrrolidine (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 diethyl-nitrosamine 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 (BB 77) (≈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 (BB 153) (≈0.5 mg/kg/day in the diet for 180 days) or 3,3',4,4',5,5'-hexa-bromobiphenyl (BB 169) (≈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 BB 153 for 480 days similarly promoted hepatic development of altered foci and neoplastic nodules in rats, whereas ≈0.05 mg/kg/day of BB 169 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 5.5.2.

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 (BB 77) 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 (BDE 47) (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 BDE 47 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 carcinogenicity" in both sexes. However, although it was concluded that there was some evidence of carcinogenicity in male and female rats based on "neoplastic nodules", this is a poorly defined and understood term that is no longer used by NTP to characterize hepatoproliferative lesions in rats. 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 5.2.2.2. 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 5-3 and plotted in Figure 5-2.

5.2.3 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 5.2.1. Dermal exposure may not be an important route of concern for PBDEs because dermal absorption is likely to be low, particularly for the highly brominated congeners.

5.2.3.1 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 5-5. 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.

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

Table 5-5 Levels of Significant Exposure to Polybrominated Biphenyls - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
ACUTE EXPOSURE								
Death								
Rabbit (NZW)	24 hr		10000 mg/kg/day					Waritz et al. 1977 (OBB)
Rabbit (NZW)	24 hr					5000 mg/kg/day	(4/4 died)	Waritz et al. 1977 (HBB)
Systemic								
Rabbit (Albino)	once	Dermal	658 mg/kg/day					Millischer et al. 1980 (DBB)
Rabbit (NZW)	5 d 1x/d	Dermal		0.19 mg/kg/day	(hyperkeratosis)			Needham et al. 1982 (FF-1)
Rabbit (NZW)	24 hr	Hepatic	100 M mg/kg/day	1000 mg/kg/day	(increased liver weight; necrotic foci)			Waritz et al. 1977 (HBB)
		Bd Wt	1000 M mg/kg/day	5000 mg/kg/day	(11% weight loss)			
Rabbit (NS)	2 wk 5 d/wk 1x/d	Hepatic		1 mg/kg/day	(increased liver weight)			Waritz et al. 1977 (OBB)
		Dermal	1 mg/kg/day					
		Bd Wt	1 mg/kg/day					

Table 5-5 Levels of Significant Exposure to Polybrominated Biphenyls - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
INTERMEDIATE EXPOSURE						
Systemic						
Gn Pig (Albino Hartley)	3 wk 3x/wk	Dermal	62 M mg/kg/day			Waritz et al. 1977 (OBB)

Bd Wt = body weight; d = days; DBB = deca-brominated biphenyl; Derm = dermal; FF-1 = FireMaster FF-1; HBB = hexa-brominated biphenyl; hr = hour(s); M = male; OBB = octa-brominated biphenyl; wk = week(s); x = time(s)

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.

5.2.3.2 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 Tables 5-5 and 5-6.

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).

Table 5-6 Levels of Significant Exposure to Polybrominated Diphenyl Ethers - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rabbit (New Zealand)	24 hr	Bd Wt	2000 mg/kg			IRDC 1974 DecaBDE
Rabbit (New Zealand)	24 hr	Bd Wt	2000 mg/kg			IRDC 1975a OctaBDE
Rabbit (New Zealand)	24 hr	Bd Wt	2000 mg/kg			IRDC 1975b PentaBDE

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

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 5.2.1.2, 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 5.2.1.2.

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

Dermal Effects.

Polybrominated Biphenyls. As discussed in Section 5.2.1.2, 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 a former commercial decaBDE mixture (500 mg as dry solid was applied to clipped skin and occluded for 24 hours) (IRCD 1974). A 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). A similar single application of solid 77.4% decaBDE (21.8% nonaBDE and 0.8% octaBDE) to abraded skin caused a slight erythematous and edematous response in rabbits, although repeated applications of the same decaBDE mixture to intact skin (5 days/week for 2 weeks) or abraded skin (3 days) was non-irritating to rabbits (Norris et al. 1975a). All skin sites returned to normal appearance following cessation of exposure. (Norris et al. 1975a).

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) 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.

5.2.3.3 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.

5.2.3.4 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.

5.2.3.5 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.

5.2.3.6 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.

5.2.3.7 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.

5.3 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 5-7. 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 5-8, 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).

Table 5-7. 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 commercial mixture; decaBDE = decabromodiphenyl ether; DNA = deoxyribonucleic acid; FF-1 = FireMaster FF-1; nonaBDE = nonabromodiphenyl ether; PBBs = polybrominated biphenyls; PBDEs = polybrominated diphenyl ethers

Table 5-8. Genotoxicity of PBBs and PBDEs *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
PBBs				
Prokaryotic organisms:				
Salmonella typhimurium (plate incorporation)	Gene mutation	–	–	NTP 1983 (FF-1)
Salmonella typhimurium (plate incorporation)	Gene mutation	–	–	Haworth et al. 1983 (HBB)
Salmonella 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 5-8. Genotoxicity of PBBs and PBDEs *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
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

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 bsence 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 5-7 and 5-8, 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 (BDE 47), 3,4-diBDE (BDE 12), and 2-monoBDE (BDE 1) caused increased recombinogenic activity at the HGPRT locus in Chinese hamster SPD8 and Sp5 V79 cells (Helleday et al. 1999).

5.4 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. As discussed in Section 5.3.2, 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 some effects of PCBs and PCDDs.

5.4.1 Absorption

5.4.1.1 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 after inhalation exposure. Evidence for the inhalation absorption of lower-brominated PBDEs in animals was provided by observations of systemic toxicity in rats that were intermittently exposed to a commercial octaBDE product (bromine content 78.7%) as dust aerosol for 13 weeks (Great Lakes

Chemical Corporation 2001a, 2001b). The absorption of the lower brominated BDE congeners was indicated by the occurrence of hepatic, thyroid, and ovarian effects in rats following exposure to 16 or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks.

5.4.1.2 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 5.2.2) and increased residue levels in tissues following oral administration of these compounds (Section 5.4.2.2); however, few quantitative data exist. By comparing the amount of radioactivity in the feces of rats administered a single 1 mg/kg oral dose of ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl (BB-155) 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 with PBB-155 later confirmed these results (Tuey and Matthews 1980). It was also demonstrated that absorption of this 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, a commercial octabromobiphenyl mixture (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. Information regarding oral absorption in animals is available from studies of commerical PBDE mixtures and individual PBDE congeners. As summarized below, absorption of decaBDE is poor, whereas the lower brominated PBDEs are readily absorbed .

Studies with ^{14}C-labeled decaBDE (BDE 209) in rats consistently indicate that gastrointestinal absorption of this congener is low at 10% or less in rats (El Dareer et al. 1987; Klasson Wehler et al. 2001; Morck and Klasson Wehler 2001; Morck et al. 2003; Norris et al. 1973, 1975c). Following treatment with a

single 1 mg/kg dose of ^{14}C-decaBDE, administered as a former low purity commercial mixture (77.4% decaBDE, 21.8% nonaBDE, 0.8% octaBDE) by gavage, 90.6 and >99% of the dose was eliminated in the feces within 24 and 72 hours post-dosing, respectively (Norris et al. 1973, 1975b). Two feeding studies were conducted in which rats were exposed to a higher purity commercial mixture as unlabeled decaBDE (92% pure) on days 1–7 and ^{14}C-decaBDE (98.9% pure) on day 8, followed by unlabelled decaBDE on days 9, 9–10 or 9–11 (El Dareer et al. 1987; NTP 1986). In the first study, dietary concentrations ranged from 238 to 51,100 ppm (six levels) (≈20–4,500 mg/kg/day). Recovery of radioactivity in the feces ranged from 91.3±4.0% to 101±4% of the amount ingested in the 72 hours following ^{14}C-decaBDE intake and was not related to dose level. In the second study, rats were exposed to dietary concentrations of 277 or 48,000 ppm (≈20 or 4,300 mg/kg/day). Recovery of radioactivity in the feces ranged from 82.5±4.7% to 86.4±8.5% of the dose and was not related to dose level or time of sacrifice (24, 48, or 72 hours after ^{14}C-decaBDE intake). For both dose levels, the percent of ^{14}C dose remaining in the gut contents (<4%) and gut contents (<0.04%) decreased with time. Of the radioactivity recovered, >99% was in the feces and gut contents. Based on a comparison of average tissue concentrations following intravenous and oral administration, NTP (1986) estimated that oral absorption was 0.33±0.19% at the highest dietary level (50,000 ppm).

A study of laboratory synthesized ^{14}C-decaBDE (>98% pure) was conducted in which a single 3 µmol/kg (≈3 mg/kg) dose was administered to normal or bile duct-cannulated male Sprague-Dawley rats by gavage (Klasson Wehler et al. 2001; Morck and Klasson Wehler 2001; Morck et al. 2003). The compound was suspended in a novel vehicle, Lutrol F127/soya phospholipone (34:16, w/w)/water, that was formulated to enhance solubility and improve absorption in comparison with previous studies of decaBDE, including those summarized above. In the normal rats, approximately 90% (86–93%, n=8) of the dose was found in the feces after 3 days; cumulative recovery after 7 days was 91% (87–95%, n=4). For the two bile duct-cannulated rats, an average of 88 and 9.5% of the dose was recovered in the feces and bile, respectively, within 3 days. There was a large variation in the fecal excretion of the two cannulated rats, which might have been due to the fact that no bile salts were added to compensate for the collected bile; the investigators concluded that this likely affected absorption. Because the biliary excretion of decaBDE was approximately 10% of the dose, it appears that at least this much of the decaBDE was absorbed. The investigators could not exclude that more than 10% of the dose had been absorbed because 65% of the radioactivity excreted in the feces was metabolites.

Information on oral absorption of the commercial pentaBDE mixture DE-71 and the commercial octaBDE mixture DE-79 is available from studies in which male Sprague-Dawley rats were fed diets

containing 0 or 32-33 ng/day (≈120 ng/kg/day) of either mixture in peanut oil for 21 days (Hakk et al. 2001; Huwe et al. 2002b). The doses were designed to mimic environmental exposure levels. Liver, carcass, and feces were analyzed for major congeners in the penta- and octaBDE formulations 24 hours after the final feeding; urine was not evaluated. The study of the pentaBDE mixture assessed the following six congeners: 2,2',4,4'-tetraBDE (BDE 47), 2,2',3,4,4'-pentaBDE (BDE 85), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',6-pentaBDE (BDE 100), 2,2',4,4',5,5'-hexaBDE (BDE 153), and 2,2',4,4',5,6'-hexaBDE (BDE 154) (Hakk et al. 2001). Based on liver, carcass, and unrecovered levels of congeners, and assuming that excretion in the urine was negligible, absorption is estimated to have been 44.3% for penta congener BDE 85 and 84.3–92.4% for the other tetra- to hexaBDE congeners. The study of the octaBDE mixture assessed the following eight congeners: 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), 2,3,3',4,4',5,6-hepta-BDE (BDE 190), an unknown heptaBDE, and three unknown octaBDEs (Huwe et al. 2002b). Based on liver, carcass, and unrecovered levels of congeners, and assuming that excretion in the urine was negligible, absorption is estimated to have been 84.2–95.1% for the hexaBDEs, 68.5–79.1% for the heptaBDEs, and 55.7–83.3% for the octaBDEs.

A single 14.5 mg/kg (30 µmol/kg) gavage dose of ^{14}C-2,2',4,4'-tetraBDE (BDE 47) in corn oil was well absorbed by rats and mice (Örn and Klasson-Wehler 1998). Approximately 5% of the dose in rats and 7% of the dose in mice was excreted as parent congener in the feces in 24 hours. The investigators concluded that these values represented the non-absorbed doses, indicating that absorption was 93–95%.

5.4.1.3 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.

5.4.2 Distribution

5.4.2.1 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 (Great Lakes Chemical Corporation 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.

5.4.2.2 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 8.4.

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 (Agency for Toxic Substances and Disease Registry 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 (BB 153), 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-BB 153 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 5.4.5 (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 5.8.1).

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 5.2).

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. Results of tissue distribution studies of decaBDE are consistent with the poor absorption and rapid fecal elimination of this congener. In male rats administered a single

gavage dose of 1 mg/kg of a ^{14}C-labeled former commercial decaBDE mixture (77.4% pure containing 21.8% nonaBDE and 0.8% octaDBE), radioactivity could be detected on day 1 in all sampled tissues (adipose, skin, liver, heart, adrenals, spleen, pancreas) (Norris et al. 1975b). On day 16 after dosing radioactivity was only detected in adrenals and spleen (0.01 and 0.06% of the administered dose per gram of tissue, respectively). Norris et al. (1975b) also examined the bromine content of tissues from rats administered 1 mg/kg/day doses of the 77.4% decaBDE mixture 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, serum and kidneys had the same amounts of bromine as the controls, although adipose levels were increased approximately 4-fold and remained essentially unchanged over the 90-day recovery period. In the liver, the bromine content was elevated on day 0 of the recovery period, but decreased and stabilized near control values after recovery day 10. Tissue analyses in rats that were similarly exposed to 0.01-1 mg/kg/day of 77% decaBDE for 12 months showed adipose bromine levels that were slightly increased during the first 180 days and not significantly different than controls at the end of the year; no significant bromine accumulation occurred in serum, liver, kidneys, skeletal muscle, or testes (Norris et al. 1975b). Pregnant rats that were administered the 77% commercial decaBDE mixture by gavage on GDs 6–15 showed no significant increase in bromine content in the liver of fetuses on gestation day 21 compared to controls (Norris et al. 1975b). Placental transfer cannot be totally ruled out since no other fetal tissues were examined.

Two feeding studies were conducted in which rats were exposed to a higher purity commercial mixture as unlabeled decaBDE (92% pure) on days 1–7 and ^{14}C-decaBDE (98.9% pure) on day 8, followed by unlabelled decaBDE on days 9, or 9–10, or 9–11 (El Dareer et al. 1987; NTP 1986). The compound was poorly absorbed in both studies. In the first study, dietary concentrations ranged from 238 to 51,100 ppm (≈20–4,500 mg/kg/day), and ≈91–100% of the ^{14}C was recovered in the feces dose in 72 hours. In the second study, rats were exposed to dietary concentrations of 277 or 48,000 ppm (≈20 or 4,300 mg/kg/day), and fecal recovery of ^{14}C ranged from ≈83 to 86% of the dose. Both studies found only trace levels of radioactivity in any organ or tissue at any time point, and the maximum total ^{14}C activity detected in the body at any time was only ≈1% of the dose. In general, the highest amounts of ^{14}C were found in the liver, and there was a tendency for rats fed the lower amounts of decaBDE to retain more radiolabel in tissues than rats fed higher amounts. Analysis of all major organs and tissues in the second study found the highest levels of ^{14}C in the gastrointestinal tract, followed by liver, kidney, lung, skin, and adipose.

A study of laboratory synthesized ^{14}C-decaBDE (>98% pure) was conducted in which a single 3 µmol/kg (≈3 mg/kg) dose was administered to male Sprague-Dawley rats by gavage (Klasson Wehler et al. 2001; Morck and Klasson Wehler 2001; Morck et al. 2003). The compound was suspended in a novel vehicle, Lutrol F127/soya phospholipone (34:16, w/w)/water, that was formulated to enhance solubility and optimize absorption. The amount of the ^{14}C dose remaining in the body after 3 and 7 days was approximately 9% (calculated by subtracting total urine and feces output from 100%). The highest concentrations of radioactivity on a fresh weight basis were in adrenals, kidneys, heart, and liver after both 3 and 7 days. Based on lipid weight, plasma and liver had the highest concentrations and adipose tissue had the lowest concentrations at both time points. The data indicate that the highest concentrations were in plasma and blood-rich tissues and that decaBDE is not readily distributed to adipose. The investigators speculated that decaDBD does not partition into lipids and is transported through aqueous compartments (e.g., serum and bile) due to binding to transport proteins. As discussed below, PBDEs with fewer numbers of bromine preferentially accumulate in adipose. The accumulation of lower brominated congeners appears to be due to their partitioning and retention in lipid-rich tissues, as well as rates of metabolism and elimination that are likely lower than for decaBDE.

The tissue half-life of a commercial pentaBDE product (Bromkal 70) was investigated in male and female Wistar rats following gavage administration of a single high dose (300 mg/kg) in corn oil (von Meyerinck et al. 1990). Groups of four rats/sex were sacrificed at weekly intervals until 10 weeks post-dosing for congeneric analysis of unspecified organs and perirenal fat. Distribution from extra-adipose tissues into the fat was essentially complete after 4 days. Five congeners were detected in the fat and incompletely characterized as a tetraBDE, two pentaBDEs, and two hexaBDEs. The half-life of the congeners generally increased with increasing bromination. The mean half-life of the tetraBDE congener was 19.1 days in males and 29.9 days in females and significantly ($p=0.01$) different between the sexes. The mean half-lives of the penta- and hexaBDE congeners did not significantly differ between the sexes, ranging from 36.8–47.4 days for pentaBDE congener 1, 24.9–25.2 days for pentaBDE congener 2, 44.6–55.1 days for hexaBDE congener 1, and 90.9–119.1 days for hexaBDE congener 2. Although the congeners were not fully identified (likely due to a lack of analytical standards), it is relevant to note that the predominant congeners in Bromkal 70 are 2,2',4,4'-tetra BDE (BDE 47) and 2,2',4,4',5-penta BDE (BDE 99).

Information on the tissue distribution of the commercial pentaBDE mixture DE-71 and the commercial octaBDE mixture DE-79 is available from studies in which male Sprague-Dawley rats were fed diets containing 0 or 32–33 ng/day (≈120 ng/kg/day) of either mixture in peanut oil for 21 days (Hakk et al.

2001; Huwe et al. 2002b). The doses were designed to mimic environmental exposure levels. Liver, carcass, and feces were analyzed for major congeners in the penta- and octaBDE formulations 24 hours after the final feeding. The study of the pentaBDE mixture assessed the following six congeners: 2,2',4,4'-tetraBDE (BDE 47), 2,2',3,4,4'-pentaBDE (BDE 85), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',6-pentaBDE (BDE 100), .2,2',4,4',5,5'-hexaBDE (BDE 153), and 2,2',4,4',5,6'-hexaBDE (BDE 154) (Hakk et al. 2001). An average of 0.4–1.2 and 27.4–45.2% of the dosed congeners occurred in the liver and carcass, respectively, and 11.7–59.1% of the doses were not recovered. The congener distribution patterns in the liver and carcass resembled that of the commercial pentaBDE mixture, suggesting that there was no preferential tissue accumulation of the tested congeners. The study of the octaBDE mixture assessed the following eight congeners: 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), 2,3,3',4,4',5,6-heptaBDE (BDE 190), an unknown heptaBDE, and three unknown octaBDEs (Huwe et al. 2002b). Four of congeners (BDE 90, the unknown heptaBDE, and two of the unknown octaBDEs) were not detected in the liver, and one congener (an unknown octaBDE) was not detected in the carcass. Of the detected congeners, an average of 1.1–1.7% and 16.2–62.9% of the dose occurred in the liver and carcass, respectively. Unlike the lower brominated congeners (tetra- to hexaBDEs) in the study of the pentaBDE mixture, tissue accumulation generally decreased with increasing bromination; total retentions in the liver and carcass were 64.4% for one of the hexaBDEs (BDE 153), 27.0–37.1% for the three heptaBDEs, and 16.2–22.8% for two of the octaBDEs. An average of 19.6–83.3% of the congener doses were not recovered. The brain uptake and retention of PBDE congeners was studied in neonatal NMRI male mice that were given a single 1.5 mg/kg dose of ^{14}C-2,2',3,3',4,4',5,5',6,6'-decaDBE (BDE 209), or 0.8 mg/kg of ^{14}C-2,2',4,4',5-pentaDBE (BDE 99), by gavage in a 20% fat emulsion vehicle, on PNDs 3, 10, or 19 and killed 24 hours or 7 days after exposure (Eriksson et al. 2002b, Viberg et al. 2001b, 2003a). In the study with BDE 209, after 24 hours, the mice exposed on PND 3 or 10 had 4.8 or 4.0% of the total administered radioactivity in the brain, respectively, whereas the brain of those exposed on PND 19 had only 0.6% of administered amount (Viberg et al. 2001b, 2003a). Seven days after exposure, the amount of radioactivity in the brain had increased approximately 2-fold in the mice exposed on PND 3 or 10 (to 7.4 or 10.5% of the administered amount), whereas those exposed on PND 19 showed the same amount as at 24 hours post-exposure. These findings suggest that brain uptake of ^{14}C-BDE 209 was more efficient in the younger animals and that the amount of radioactivity reaching the brain increased with time. The pattern of brain retention for BDE 209 was different than that for BDE 99, which showed a decrease over the 7-day period (Eriksson et al. 2002a). In particular, 24 hours after exposure to ^{14}C-BDE 209, the amount of radioactivity in the brain was between 3.7 and 5.1% of the total administered

amount in the three different age categories, whereas the amount declined to 1.3–2.8% of the administered dose after 7 days.

Rats that were administered a single 2.2 mg (≈10 mg/kg) gavage dose of ^{14}C-2,2',4,4'-5-pentaBDE (BDE 99) in corn oil and examined after 72 hours had the largest amounts of radioactivityin the carcass, adipose (epididymal), and gastrointestinal tract (38.8, 3.8, and 6.1% of the dose, respectively (Hakk et al. 1999, 2002). No other tissues contained contained >1% of the radioactivity. Fractionation of the carcass into skin, bone, brain, eyes, and muscle showed that the majority of the ^{14}C was in the skin. When deposition was expressed on a concentration basis, the highest levels of radioactivity.occurred in the most lipid-rich tissues, i.e., adipose, adrenals, gastrointestinal tract, and skin.

A single 14.5 mg/kg dose of ^{14}C-2,2',4,4'-tetraBDE (BDE 47) in corn oil was administered by gavage to rats and mice (Örn and Klasson-Wehler 1998). Approximately 86% of the absorbed dose in rats and 80% of the dose in mice remained in tissues (liver, lung, kidney, brain) at 5 days, mainly in the adipose. In rats, adipose tissue had an approximately 70 times higher concentration of label than the other tissues on a fresh weight basis and 3.5-fold higher on a lipid weight basis. The lungs had the second highest concentration of radiolabel with approximately twice that in the liver and kidneys. In mice, adipose tissues had an approximately 10-fold higher level of label 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.

5.4.2.3 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.

5.4.2.4 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 (BB-153) 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 (BB 153) and 2,2',3,4,4',5,5'-heptabromobiphenyl (BB 180) (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.

5.4.3 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). The concentration of two pentabromobiphenyls was lower in the farmers than in the chemical workers. Both farmers and workers had a significantly lower amount of 2,2',3,4,4',5,5'-heptabromobiphenyl than 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 whould not be expected since the temperatures reached during these processes is probably not high enough. As discussed in Chapter 6, temperatures must exceed ≈500 °C 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 (BB 15) 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 BB 15 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 (BB 153).

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 (BB 3). 2-Bromobiphenyl (BB 1) was metabolized to 2-bromo-4,4'-biphenyldiol and 2-bromo-4',5-biphenyldiol; 2-bromo-5-biphenylol was a minor metabolite. 3-Bromobiphenyl (BB 2) 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 BB 1 and BB 2; 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'-hexa-bromobiphenyl (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 (BB 153) with liver microsomes of rats induced with either BB 153 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 (BB 101) and a hexabromobiphenyl were metabolized by microsomes from PB- or PBB-treated rats. Of seven structurally identified PBB components, only BB 101 had a bromine-free *para* position. Although BB 101, 2,3',4,4',5-pentabromobiphenyl (BB 118), and 2,2',3,4,4',5'-hexabromobiphenyl (BB 138) have two adjacent unsubstituted carbons, only BB 101 was metabolized. No significant metabolism occurred when the PBB mixture was incubated with microsomes of control rats or MC-induced rats. When 2,2'-dibromobiphenyl (BB 4) and 4,4'-dibromobiphenyl (BB 15) were incubated with liver microsomes of PB-treated rats, only BB 4 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. DecaBDE (BDE 209) is predominantly excreted in the feces as unabsorbed parent molecule. Data are available indicating that the small amount of decaBDE that is absorbed can be metabolized (El Dareer et al. 1987; Morck et al. 2003; NTP 1986). A feeding study was conducted in which rats were exposed to a high purity mixture as unlabeled decaBDE (92% pure) on days 1–7 and ^{14}C-decaBDE (98.9% pure) on day 8, followed by unlabelled decaBDE on days 9, or 9–10, or 9–11, at dietary concentrations of 277 or 48,000 ppm (El Dareer et al. 1987; NTP 1986). Recovery of radioactivity in the feces ranged from 82.5±4.7 to 86.4±8.5% of the dose, and was not related to decaBDE dose level or time of sacrifice (24, 48, or 72 hours after consumption of ^{14}C-decaBDE). For both dose levels, the percent of ^{14}C dose remaining in the gut contents (<4%) and gut contents (<0.04%) decreased with time. Of the radioactivity recovered, >99% was in the feces and gut contents. HPLC and UV spectral analyses of extracts of feces collected on days 9–11 indicated the presence of decaBDE (81% of recovered radioactivity) and three main unidentified metabolites. The total radioactivity present as the metabolites tended to increase with increasing dietary level of decaBDE (1.5 and 27.9% of total recovery at the low and high dose, respectively). Since absorption of decaBDE was minimal, El Dareer et al. (1987) speculated that the greater extent of metabolism in the high dose rats may be due to induction of hepatic metabolizing enzymes, or gastrointestinal tract bacteria, during the period of feeding unlabeled decaBDE. Analysis of feces from rats following a single 1.07 mg/kg intravenous dose of ^{14}C-decaBDE similarly indicated that the excreted material was predominantly unchanged compound and three main unidentified metabolites (El Dareer et al. 1987; NTP 1986). Unchanged decaBDE comprised 36.5 and 40.4% of the totals for the 0–48-hour and 48–72-hour collection periods, respectively. The HPLC retention times of the metabolites were similar in the oral and intravenous studies. A single metabolite was detected in the bile of rats following a single 0.9 mg/kg intravenous dose of ^{14}C-decaBDE (El Dareer et al. 1987). Approximately 7% of the administered dose appeared in the bile in 4 hours, and <1% of this amount was unchanged decaBDE.

A study of laboratory synthesized ^{14}C-decaBDE (>98% pure) was conducted in which a single 3 µmol/kg (≈3 mg/kg) dose was administered to normal or bile duct-cannulated male Sprague-Dawley rats by gavage (Morck and Klasson Wehler 2001; Morck et al. 2003). The compound was emulsified in a novel vehicle, Lutrol F127/soya phospholipone (34:16, w/w) in water, that was formulated to enhance solubility

and optimize absorption. Feces, bile, and several tissues (liver, kidney, lung, small intestine wall, and adipose) were qualitatively analyzed for metabolites using gel permeation chromatography (GPC) and gas chromatography-mass spectrometry (GC-MS). In the normal rats, approximately 90% of the dose was excreted in the feces in 3 days, mainly as metabolites (65% of dose). In the the two bile duct-cannulated rats, an average of 9.5% of the dose was excreted via the bile in 3 days, almost all of which represented metabolites. Metabolites were characterized as nonextractable, water-soluble, lipid-bound, phenolic metabolites, and parent compound/neutral metabolites. Feces from normal rats showed formation of phenolic and neutral metabolites. Metabolites in the nonconjugated phenolic fraction included six penta- to heptaBDEs containing a guaiacol structure (a hydroxy and a methoxy group) on one of the rings (proposed to be on vicinal carbons), as well as traces of monohydroxylated diphenyl ethers with at least six bromine atoms and uncharacterized metabolites having eight bromine atoms. DecaBDE was the main component in the neutral fraction of the feces, but trace amounts (<0.5% of the decaBDE) of three nonaBDEs also formed. The mechanism by which decaBDE was debrominated to the methoxy-hydroxylated penta- to hepatBDEs was not clear, but was inferred to include a catechol (dihydroxy compound) and/or other reactive intermediates. Analysis of bile showed metabolites that were mainly lipid-bound on day 1 and subsequently water soluble. Neutral compounds in the bile consisted mainly of parent decaBDE and traces of the three nonaBDEs that were found in the feces. Phenolic metabolites in the bile included eight compounds that were the same as those found in the feces. The tissue evaluations showed a high concentration of radioactivity in the liver and small intestine wall (27 and 61%, respectively) that was largely nonextractable, and therefore was assumed to be bound covalently to macromolecules and indicative of adducts formed by metabolism via reactive metabolites. The metabolites identified in the feces of the rats were probably due to debromination of decaBDE, followed by metabolic substitution of vicinal carbons by methoxy or hydroxy groups. The authors did not rule out that the intestinal endoderm or gut microflora could play a role in some of this metabolism. PBDEs with fewer bromines probably have lower rates of metabolism (and elimination) than decaBDE because lower brominated PBDEs partition into, and are retained in, lipid-rich tissues, whereas decaBDE does not partition into lipids.

Information on the metabolism of the commercial pentaBDE mixture DE-71 and the commercial octaBDE mixture DE-79 is available from studies in which male Sprague-Dawley rats were fed diets containing 0 or 32–33 ng/day (≈120 ng/kg/day) of either mixture in peanut oil for 21 days (Hakk et al. 2001; Huwe et al. 2002b). The doses were designed to mimic environmental exposure levels. The predominant congeners in the pentaBDE formulation were 2,2’,4,4’-tetraBDE (BDE 47) and 2,2’,4,4’,5-pentaBDE (BDE 99). The octaBDE formulation was mainly comprised of hexaBDE through

nonaBDE congeners and only contained tetra- and pentaBDEs as minor components. Liver, carcass, and feces were analyzed for major congeners in the penta- and octaBDE formulations 24 hours after the final feeding. Urine was not analyzed because the lipophilic nature of the compounds and previous studies indicated that PBDEs are not excreted in the urine.

The study of the pentaBDE mixture assessed the following six congeners: 2,2',4,4'-tetraBDE (BDE 47), 2,2',3,4,4'-pentaBDE (BDE 85), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',6-pentaBDE (BDE 100), 2,2',4,4',5,5'-hexaBDE (BDE 153), and 2,2',4,4',5,6'-hexaBDE (BDE 154) (Hakk et al. 2001). An average of 0.4–1.2 and 27.4–45.2% of the dosed congeners occurred in the liver and carcass, respectively. The congener distribution patterns in the liver and carcass resembled that of the commercial pentaBDE mixture, suggesting that there was no preferential tissue accumulation of the tested congeners. An average of 11.7–59.1% of the congener doses was not recovered, suggesting that significant metabolism of some of the congeners occurred. The study of the octaBDE mixture assessed the following eight congeners: 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), 2,3,3',4,4',5,6-heptaBDE (BDE 190), an unknown heptaBDE, and three unknown octaBDEs (Huwe et al. 2002b). Four of congeners (BDE 90, the unknown heptaBDE, and two of the unknown octaBDEs) were not detected in the liver, and one congener (an unknown octaBDE) was not detected in the carcass. Of the detected congeners, an average of 1.1–1.7% and 16.2–62.9% of the dose occurred in the liver and carcass, respectively. Unlike the lower brominated congeners (tetra- to hexaBDEs) in the study of the pentaBDE mixture, tissue accumulation generally decreased with increasing bromination; total retentions in the liver and carcass were 64.4% for one of the hexaBDEs (BDE 153), 27.0–37.1% for the three heptaBDEs, and 16.2–22.8% for two of the octaBDEs. An average of 19.6–83.3% of the congener doses were not recovered, indicating that most of the congeners were metabolized to some extent

The metabolism of ^{14}C-2,2',4,4'-5-pentaBDE (BDE 99) was investigated in normal and bile duct-cannulated rats that were administered a single 2.2 mg (≈10 mg/kg) dose in corn oil by gavage (Hakk et al. 1999, 2002). The feces was the major route of elimination as shown by fecal recovery of 43 and 86% of the administered ^{14}C in 72 hours in the normal and bile-duct cannulated rats, respectively. The feces from the normal rats contained predominantly parent compound and minor amounts of metabolites (>90 and <10% of the extracted radioactivity, respectively). The fecal metabolites were incompletely identified as two mono-OH-pentaBDEs and two mono-OH-tetraBDEs, indicating that some debromination occurred. Metabolites found in the bile included two mono-OH-pentaBDEs, three di-OH-pentaBDEs, and two possible thiol-substituted pentaBDEs. The possible thiol-substituted pentaBDEs

could have been formed through the mercapturic acid pathway, but no glucuronide or sulfate conjugates were found in the bile. Evidence for reactive intermediates in the feces of normal rats was indicated by high nonextractable fractions ranging from 18–52%. Cumulative excretion of radiolabel in the urine at 72 hours, consisting exclusively of uncharacterized metabolites, was 1 and 0.3% of the dose in the normal and bile duct-cannulated rats, respectively. Absorbed BDE 99 was preferentially distributed to lipophilic tissues, in which it accumulated as parent compound; the only tissue in which metabolites were detected was the liver, which contained only trace amounts of OH-metabolites.

Rats given a single gavage dose of 14.5 mg/kg dose of ^{14}C-2,2',4,4'-tetraBDE (BDE 47) in corn oil excreted 14% of the dose in the feces and <0.5% in the urine over a 5-day period (Örn and Klasson-Wehler 1998). The majority of the fecal ^{14}C (≈85% of the parent compound/metabolite fraction) was parent compound. Six metabolites were detected in the feces, but were not precisely identified; the metabolites were tentatively characterized as hydroxlated derivatives (two *ortho*-, one *meta*-, and two *para*-OH-tetraBDEs) and a trace amount of a thiol-tetraBDE. Mice treated in the same manner excreted 20% of the dose in the feces and 33% in the urine over 5 days, indicating that the mouse is more capable of metabolizing BDE 47 than rats. The majority of the fecal ^{14}C in mice (≈70% of the parent compound/metabolite fraction) was the metabolite fraction, which contained the same six metabolites characterized in the rat feces. Approximately 20% of the mouse urinary ^{14}C was characterized as parent compound; the remainder could not be identified, but was speculated to arise from decomposition of a labile metabolite(s). Unchanged tetraBDE was the major compound in all tissues analyzed in both species; minor amounts of hydroxylated tetraBDE metabolites were also detected. A water-soluble metabolite was detected in urine from mice, but could not be isolated.

Following oral exposure of male Sprague-Dawley rats to decaBDE (BDE-209), 13 phenolic metabolites were determined in the plasma (Sandholm et al. 2003). The major metabolites were characterized as a hydroxyl-octaBDE, a hydroxyl-nonaBDE, and a hydroxyl-methoxy-hexaBDE. In addition to the debromination reactions, the presence of a methoxy group is suggestive of methylation, and possibly other metabolic processes, by bacteria of the gut.

5.4.4 Elimination and Excretion

5.4.4.1 Inhalation Exposure

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

5.4.4.2 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 (Blanck et al. 2000b; Lambert et al. 1990; 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 (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 5.4.2.2.

There is limited information regarding excretion of PBBs in experimental animals. Rats dosed once with ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl (BB 153) 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. Oral studies with ^{14}C-labeled decaBDE consistently show that this PBDE is rapidly and predominantly eliminated in the feces (El Dareer et al. 1987; Klasson Wehler et al. 2001, Morck and Klasson Wehler 2001; Morck et al. 2003; Norris et al. 1973, 1975c). In rats treated by

gavage with a single 1 mg/kg dose of a low purity former commercial mixture (77.4% ^{14}C-decaBDE, 21.8% nonaBDE, 0.8% octaBDE) in corn oil, 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. 1973, 1975c). No significant differences in excretion patterns were observed between males and females. 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. Two feeding studies were conducted in which rats were exposed to a higher purity commercial mixture as unlabeled decaBDE (92% pure) on days 1–7 and ^{14}C-decaBDE (98.9% pure) on day 8, followed by unlabelled decaBDE on days 9, or 9–10, or 9–11 (El Dareer et al. 1987; NTP 1986). In the first study, dietary concentrations ranged from 238–51,100 ppm (six levels) (≈20–4600 mg/kg/day). Recovery of radioactivity in the feces ranged from 91.3±4.0 to 101±4% of the amount ingested in the 72 hours following ^{14}C-decaBDE intake and was not related to dose level. In the second study, rats were exposed to dietary concentrations of 277 or 48,000 ppm (≈25 or 4,300 mg/kg/day). Recovery of radioactivity in the feces ranged from 82.5±4.7 to 86.4±8.5% of the dose and was not related to dose level or time of sacrifice (24, 48, or 72 hours after ^{14}C-decaBDE intake). For both dose levels, the percent of ^{14}C dose remaining in the gut contents (<4%) and gut contents (<0.04%) decreased with time. Of the radioactivity recovered, >99% was in the feces and gut contents. Urinary excretion of ^{14}C accounted for ≤0.01% of the dose.

In a study of laboratory synthesized ^{14}C-decaBDE (>98% pure), a single 3 µmol/kg (≈3 mg/kg) dose was administered to normal or bile duct-cannulated male Sprague-Dawley rats by gavage (Klasson Wehler et al. 2001; Morck and Klasson Wehler 2001; Morck et al. 2003). The compound was suspended in a novel vehicle, Lutrol F127/soya phospholipone (34:16, w/w)/water, that was formulated to enhance solubility and optimize absorption. In the normal rats, approximately 90% (86–93%, n=8) of the dose was found in the feces after 3 days; cumulative recovery after 7 days was 91% (87-95%, n=4). For the two bile duct-cannulated rats, an average of 88 and 9.5% of the dose was recovered in the feces and bile, respectively, within 3 days. There was a large variation in the fecal excretion of the two cannulated rats that might have been due to the fact that no bile salts were added to compensate for the collected bile. Urinary excretion of ^{14}C was negligible for all groups at <0.1% of the dose. DecaBDE was speculated to have higher rates of metabolism and elimination than PBDEs with fewer numbers of bromines because it is unlikely to partition into lipids and is transported through aqueous compartments (e.g., serum and bile), whereas lower brominated congeners preferentially accumulate in the body due to their partitioning and retention in lipid-rich tissues.

Information on oral absorption of the commercial pentaBDE mixture DE-71 and the commercial octaBDE mixture DE-79 is available from studies in which male Sprague-Dawley rats were fed diets containing 0 or 32–33 ng/day (≈120 ng/kg/day) of either mixture in peanut oil for 21 days (Hakk et al. 2001; Huwe et al. 2002b). The doses were designed to mimic environmental exposure levels. Liver, carcass, and feces were analyzed for major congeners in the penta- and octaBDE formulations 24 hours after the final feeding; urine was not evaluated. The study of the pentaBDE mixture assessed the following six congeners: 2,2',4,4'-tetraBDE (BDE 47), 2,2',3,4,4'-pentaBDE (BDE 85), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',6-pentaBDE (BDE 100), 2,2',4,4',5,5'-hexaBDE (BDE 153), and 2,2',4,4',5,6'-hexaBDE (BDE 154) (Hakk et al. 2001). One of the penta congeners, BDE 85, occurred at a relatively high level in the feces (55.8% of the adminstered amount). Fecal excretion of the five other tetra- to hexaBDE congeners ranged from 7.6 to 15.8% of the dose. The study of the octaBDE mixture assessed the following eight congeners: 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), 2,3,3',4,4',5,6-heptaBDE (BDE 190), an unknown heptaBDE, and three unknown octaBDEs (Huwe et al. 2002b). Fecal excretion ranged from 4.9 to 15.9% of the dose for the hexaBDE congeners, 20.9–31.5% of the dose for the heptaBDE congeners, and 16.7–44.3% of the dose for the octaBDE congeners.

The elimination of ^{14}C-2,2',4,4'-5-pentaBDE (BDE 99) was investigated in normal and bile duct-cannulated rats that were administered a single 2.2 mg (≈10 mg/kg) dose in corn oil by gavage (Hakk et al. 1999, 2002). The main route of elimination was via the feces as shown by cumulative fecal recovery of 43 and 86% of the administered radiolabel in 72 hours in the normal and bile-duct cannulated rats, respectively. The difference in the excreted amounts of radioactivity suggests that bile salts are needed for the intestinal uptake of BDE 99. Cumulative urinary excretion of radiolabel over 72 hours was ≈1% and ≈0.3% of the dose in the normal and bile duct-cannulated rats, respectively. The cumulative biliary excretion of radiolabel in cannulated rats was ≈4%.

Rats given a single gavage dose of 14.5 mg/kg dose of ^{14}C-2,2',4,4'-tetraBDE (BDE 47) in corn oil 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).

5.4.4.3 Dermal Exposure

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

5.4.4.4 Other Routes of Exposure

Polybrominated Biphenyls. Rats given a single intravenous dose of ^{14}C-2,2',4,4',5,5'-hexabromobiphenyl (BDE 153) 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.

5.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

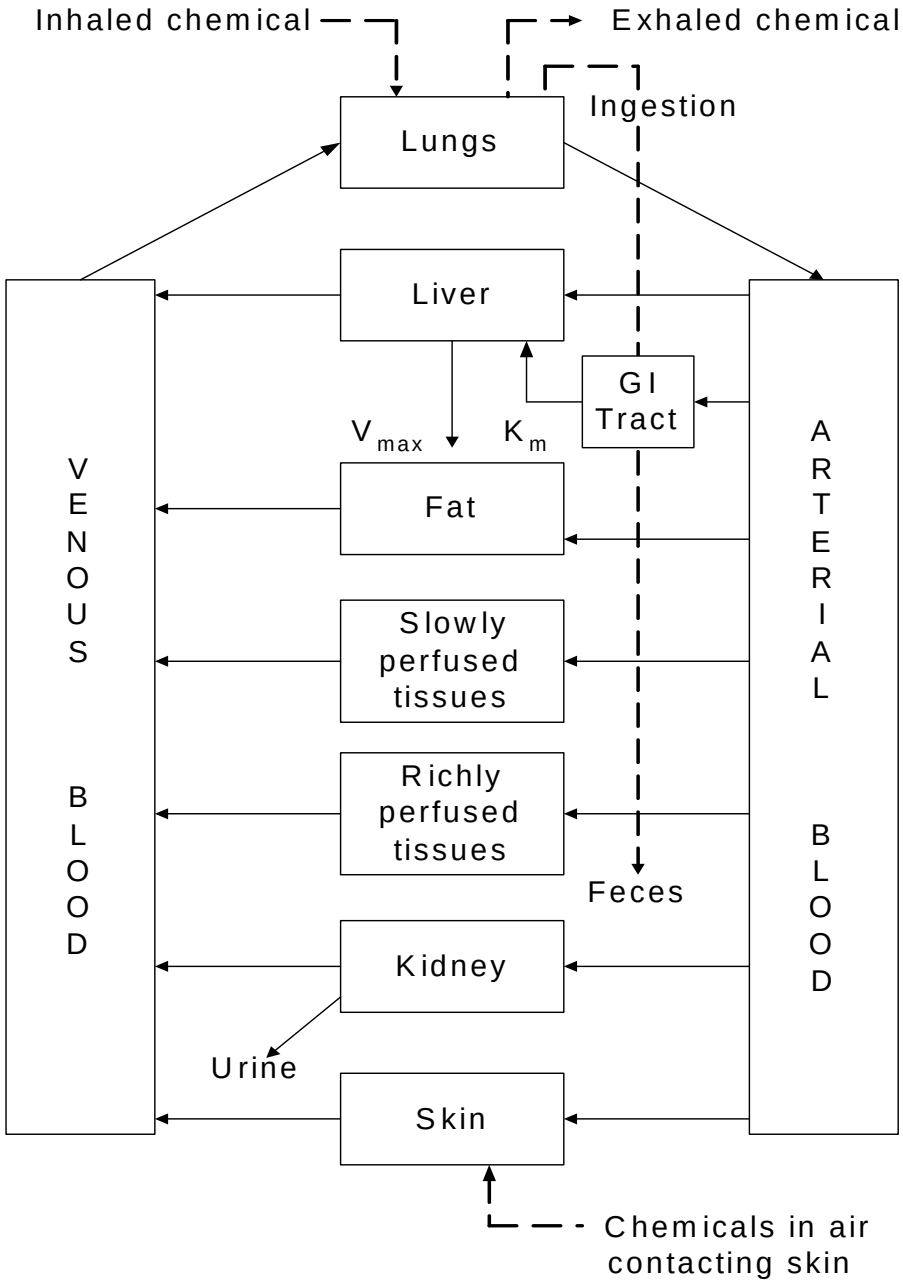
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 5-5 shows a conceptualized representation of a PBPK model.

Figure 5-5. Conceptual Representation of a Physiologically Based Pharma cokinetic (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.

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 (BB 153), 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 BB 153) 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 would be years. The half-life of 6.5 years predicted using the rat-based PBPK model is shorter than mean half-life values of ≈10-15 years estimated using human sera data from the Michigan PBB cohort (Blanck et al. 2000b; Lambert et al. 1990; Rosen et al. 1995), as discussed in Section 5.4.4 (Elimination and Excretion). The shorter predicted half-life from the rat model compared to estimated values based on human sera might be due to differences in adipose content between rats and man; fat acts as a depot for these chemicals, and most rat studies use young animals with a fat content less than in many people.

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

5.5 MECHANISMS OF ACTION

5.5.1 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 were 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 (BB 153) 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 BB 153, 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.

5.5.2 Mechanisms of Toxicity

PBBs and PBDEs share some toxicological properties with other structurally similar polyhalogenated aromatic compounds, particularly PCBs, chlorinated dibenzo-*p*-dioxins (CDDs), and chlorinated dibenzofurans (CDFs) (Agency for Toxic Substances and Disease Registry 1994, 1998, 2000). However, although these chemicals are structurally similar in two dimensions, PBDEs (and PCDEs) differ from the other classes on a three dimensional basis. In particular, the oxygen bridge of the ether linkage in the diphenyl oxide molecule increases the distance between the biphenyl rings. This apparently reduces steric interactions between *ortho* substituents on the adjacent rings, such that the presence of *ortho* bromines is unlikely to present a barrier to rotation that would prevent the two aromatic rings from assuming a fully coplanar configuration (Chen et al. 2001; Hardy 2002; Howie et al. 1990). In other words, the ether bridge makes PBDEs more non-coplanar in nature, and introducing *ortho* substitutions into PBDEs 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 PBBs or PCBs. Therefore, for PBDEs, the influences of the ether bridge and bromine position preclude clearly classifying the congeners as either dioxin-like (coplanar) or non-dioxin-like (non-coplanar). This has implications not only for dioxin-type toxicities, which are

mediated by the Ah (aryl hydrocarbon) receptor (AhR) pathway, but also for non-dioxin-type effects. For example, Chen et al. (2001) found that the induction of CYP1A1 by PBDEs is AhR-mediated, as it is for numerous organochlorines, even though PBDEs do not readily adopt the planar conformation usually considered characteristic of AhR ligands. Structure-activity relationships have been incompletely examined for non-dioxin-like effects of PBDEs such as neurotoxicity. However, based on limited available data, it can be speculated that di-*ortho*-substituted PBDEs might follow the neurotoxic potency of *ortho*-PCBs (Eriksson et al. 2002b; Kodavanti and Derr-Yellin 2002a; Mariussen and Fonnum 2002, 2003).

There are also geometrical differences in PCBs, PBBs, and PBDEs due to the higher atomic weight and considerably larger molecular volume of bromine compared 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), AhR 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). The geometrical differences in bromine and chlorine also have implications for understanding the mechanism(s) of effects for nondioxin-like PBB congeners, which are not as well characterized as for PCBs. In particular, it cannot necessarily be assumed, on the basis of two-dimensional structure, that the mechanisms and effects for nondioxin-like PBBs and PCBs are similar.

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 the cellular AhR, 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 (BB 126), the monoortho substituted congener 2,3,3',4,4',5-hexabromobiphenyl (BB 156), and the diortho substituted analog 2,2',5,5'-tetrabromobiphenyl (BB 52) 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 AhR protein, the monoortho analog partially displaced the radiolabel, and 2,2',5,5'-tetrabromobiphenyl (BB 52) 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 (BB 77) 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 AhR 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'-tribromobiphenyl (BB 37), 3,4,4',5-tetrabromobiphenyl (BB 81), 3,3',4,4'-tetrabromobiphenyl (BB 77), 3,3',4,4'5-pentabromobiphenyl (BB 126), and 3,3',4,4',5,5'-hexabromobiphenyl (BB 169) 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'-tetrabromobiphenyl (BB 66), 2,3',4,4',5-pentabromobiphenyl (BB 118), and 2,3',4,4',5,5'-hexabromobiphenyl (BB 167), 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'-tetrabromobiphenyl (BB 52), 2,2',4,5,5'-pentabromobiphenyl (BB 101), 2,2',4,4',5,5'-hexabromobiphenyl (BB 153), 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 (BB 15) resembled PB in its mode of induction (Robertson et al. 1982), whereas 2,2'-dibromobiphenyl (BB 4) 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 (BB 169) (MC-type) and 2,2',4,4',5,5'-hexabromobiphenyl (BB 153) (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 (BB 77) (MC-type) and 2,2'5,5'-tetrabromobiphenyl (weak PB-type) were compared in rats (Robertson et al. 1983a). Only BB 77 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 AhR 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 [BB 169] and 3,3',4,4'-tetrabromobiphenyl [BB 77]) and PB-type (2,2',4,4',5,5'-hexabromobiphenyl [BB 153]) congeners showed hepatic promoting activity with varying potencies. FireMaster BP-6 was a more effective promoter than its major constituent congener BB 153 (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 BB 169 were effective skin tumor promoters, but BB 153 showed no activity, suggesting that, unlike rat liver tumor promotion, promoter activity in the mouse skin tumor model is AhR-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 (CB 153) in a dose-dependent manner, but not by the coplanar congener 3,3',4,4',5,5'-hexaCB (CB 169). 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 dioxin-type toxic response, which is species and strain dependent, is initiated by the binding of individual congeners with the AhR. 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 AhR 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 AhR binding affinity. 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 (BB 77), 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 BB 77, thymic atrophy was only observed in the responsive strain (Robertson et al. 1984a). In general, studies summarized in Section 5.2 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 AhR 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. Newly synthesized enzymes and macromolecules resulting from the pleiotropic response to the ligand-receptor complex are believed to be responsible for many of the effects caused by PBBs and other halogenated aromatic hydrocarbons. In other words, the binding of a congener to the AhR initiates a transcriptional upregulation of a battery of genes that modulates biochemical and endocrine pathways, cell cycle regulation (e.g., apoptosis, proliferation, and differentiation), morphogenesis, oxidative stress response, and other processes, and is ultimately expressed as a diverse spectrum of well characterized toxic responses.

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

Polybrominated Diphenyl Ethers. As discussed in the introduction to this section, bromination at the *ortho* position does not appear to significantly change the planarity of PBDE molecules or their biological effects. Structure-activity studies have shown that some PBDE congeners can bind to the AhR, although binding affinities and induction of AhR-mediated responses are very weak or negligible, particularly for commercial PBDE mixtures and environmentally relevant congeners.

For example, Meerts et al. (1998) indirectly examined the AhR-mediated (dioxin-like) properties of 17 PBDE congeners in a recombinant H4II rat hepatoma cell line showing AhR 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 (BDE 15)and 3,3',4,4'-tetraBDE (BDE 77), all had at least one *ortho* substitution. Seven of the congeners showed luciferase expression, indicating their ability to activate the AhR. 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. Another study also examined the AhR induction potency of PBDE congeners using the *in vitro* luciferase assay with H4IIE-luc recombinant rat hepatoma cells (Villeneuve et al. 2002). Only 1 of 10 tested congeners, 3,3’,4,4’,5-pentaBDE (BDE 126), induced a significant AhR-mediated gene expression response in the H4IIE-luc cells, but the magnitude of induction was only 13% of that caused by TCDD. With the exception of 2,3,3’,4,4’-pentaBDE (BDE 105), which induced a response of 1.7% of the TCDD maximum, no other congener, including the environmentally prominent congeners 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), yielded a response greater than 1% of TCDD. Overall, the tested PBDE congeners were at least 200,000 times less potent than TCDD for inducing AhR-mediated gene expression in this test system.

Chen et al. (2001) studied the affinities of a series of 18 PBDE congeners and 3 commercial PBDE mixtures for rat hepatic AhR by using competitive AhR-ligand and EROD induction assays. The analysis showed that both the congeners and octa- and pentaBDE commercial 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 (BDE 85), although its relative binding affinity was only 2% that of 2,3,7,8-TCDD. No binding activity could be determined for the 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 receptor binding site. The dioxin-like activity of the PBDE congeners and commercial mixtures was subsequently more completely characterized, by determining whether they act as AhR agonists or antagonists at sequential stages of the AhR signal transduction pathway leading to CYP1A1 in rat hepatocytes (Chen and Bunce 2001).

Congeners 3,3’,4,4’-tetraBDE (BDE 77), 2,3’,4,4’,6-pentaBDE (BDE 119), and 3,3’,4,4’,5-pentaBDE (BDE 126) were moderately active towards DRE (dioxin response element) binding and induced responses of both CYP1A1 mRNA and CYP1A1 protein equivalent to the maximal response of TCDD, although at concentrations 3–5 orders of magnitude greater than TCDD. These congeners showed additive behavior towards DRE binding with TCDD (i.e., an increased response compared to TCDD alone), whereas most of the other congeners antagonized the action of TCDD. Congeners 2,2’,4,4’,6-pentaBDE (BDE 100), 2,2’,4,4’,5,5’-hexaBDE (BDE 153), and 2,2’,3,4,4’,5’,6-heptaBDE (BDE 183) were very weak activators of DRE binding, and other congeners and the three commercial BDE mixtures were inactive. In particular, the environmentally prominent congeners 2,2’,4,4’-tetraBDE (BDE 47) and 2,2’,4,4’,5-pentaBDE (BDE 99) were among the least active with respect to dioxin-like behavior (i.e., were inactive at all stages of signal transduction), and the commercial pentaBDE mixture had negligible EROD induction activity. The PBDE congeners that bound most strongly to the AhR were also the strongest inducers of CYP1A1 mRNA and CYP1A1 protein, indicating that the induction of CYP1A1 was AhR-mediated. Considering all end points evaluated in the Chen et al. (2001) and Chen and Bunce (2003) studies, it was concluded that the relative induction potencies (REPs) of the most active PBDEs toward CYP1A1 are $\approx 10^{-4}$ that of TCDD (similar to some mono-*ortho*-PCBs and two orders of magnitude less than those of coplanar PCBs), and the REPs for the environmentally prominent congeners are essentially zero.

The enzyme induction properties of PBDEs have been less studied than for other structurally similar chemicals. Existing information suggests that PBDEs can be classified as mixed-type inducers of hepatic microsomal monooxygenases, although the mixed induction properties of the commercial mixtures are likely due to contamination with PBDDs/PBDFs (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 (BDE 77), 2,2',4,4',6-pentaBDE, 2,3',4,4'-tetraBDE (BDE 66), and 3,3',4,4',5-penta-BDE (BDE 126) were the strongest inducers. Congeners 2,2',4,4',5,5'-hexaBDE (BDE 153) and 2,2',3,4,4',5',6-heptaBDE were weak inducers in all cell types, whereas BDE 66 and 2,2',3,4,4'-pentaBDE (BDE 85) were very weak inducers in rat hepatocytes and inactive in the other cells. Congeners 2,2',4,4'-tetraBDE (BDE 47) 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 (BDE 28), 2,2',4,4',5,6'-hexaBDE, 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 AhR binding with the notable exception of 2,2',3,4,4'-pentaBDE (BDE 85), which despite its relatively strong AhR binding affinity (see above), showed no evidence of activating the AhR to its dioxin-response element (DRE) binding form and was only a weak EROD inducer.

Relevant information on structure-toxicity relationships 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 AhR-mediated, such as the inhibition of the PFC response to challenge with SRBC antigen. For example, the laterally substituted congeners 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 5.2.2.2, Endocrine Effects). DecaBDE appears to be much less potent than the lower brominated mixtures and the main effects 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 accompanying 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 is hypothesized 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 T_4 levels is is unclear. The apparent lack of effect of PBDEs on serum TSH suggests that direct effects on the thyroid leading to inhibition of T_4 synthesis are

unlikely. PBDEs are hepatic microsomal enzyme inducers, but there is little evidence that increased enzyme activity leads to greater clearance of thyroid hormones. 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 also 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; however, this mechanism is not fully elucidated.

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 (BDE 15), 2,4,4'-triBDE (BDE 28), 2,4,6-triBDE (BDE 30), 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,6'-tetraBDE (BDE 51), 2,4,4',6-tetraBDE (BDE 75), 3,3,4,4'-tetraBDE, 2,2',4,4',6-pentaBDE, and 2,3',4,4',6-pentaBDE (BDE 119). No T_4-TTR inhibition occurred with the higher brominated diphenyl ethers (i.e., 2,2',3,4,4',5'-hexaBDE (BDE 138), 2,2',4,4',5,5'-hexaBDE (BDE 153), 2,3,4,4',5,6-hexaBDE (BDE 166), 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. Studies with PCBs and hydroxylated derivatives similarly showed that the congener patterns most closely resembling the diiodophenolic ring of thyroxine had the highest TTR binding activity (Chauhan et al. 2000; McKinney et al. 1987; Rickenbacher et al. 1986).

Although the findings discussed above suggest that hydroxylation of PBDEs could be involved in the mechanism of thyroid toxicity, there are indications that hydroxylated metabolites might not play a large role for commercial penta- and octaBDE products. For example, of the *in vitro*-generated metabolites displacing T_4 from TTR (Meerts et al. 1998, 2000), only two (2,2',4,4'-tetraBDE [BDE 47] and 2,2',4,4',6-pentaBDE [BDE 100]) are known to be present in a commercial product (pentaBDE). An *in vivo* study in rats (Om and Klasson-Wehler 1998) showed that BDE 47 is well absorbed (~95%), but poorly metabolized, because (1) only 3% of the amount excreted in feces over a 5-day period was in the form of metabolites, (2) the parent molecule was the major compound detected in all tissues analyzed (and the only brominated compound detectable in kidney, brain, and adipose tissue), and (3) plasma levels were low and mainly due to the parent molecule. Additionally, the three pure hydroxylated PBDEs synthesized by Meerts et al. (1998, 2000) for their structural similarity to thyroid hormones are not based on congeners known to be present in commercial penta- or octaBDE mixture; this suggests that the congeners in these mixtures do not share close structural relationships with thyroid hormones. It is relevant to note that high concentrations of hydroxy and methoxy metabolites of PBDEs have been detected in fish from the Baltic Sea (Asplund et al. 1999), indicating that these compounds can potentially directly impact thyroid function in humans consuming fish.

Three hydroxylated PBDEs, the 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 was speculated that other hydroxylated PBDE congeners will have even lower potential for receptor binding. DecaBDE (not hydroxylated) had no effect on thyroid hormone receptor-mediated transcriptional activation by T_3 in HeLaTRDR4-luc human cells; no other congeners were tested in this assay (Sakai et al. 2003).

The extent that PBDEs affect circulating levels of T_4 or T_3 is likely to vary with species and rats are generally regarded as more sensitive than humans. As discussed in Section 5.5.3, this is thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid, and to a more rapid clearance of secreted hormone in the rat; that latter being, in part, related to the absence of thyroid binding globulin (TBG) in rats (Capen 1997). Transthyretin (TTR) is the major thyroid hormone binding protein in rats, whereas TBG is the main binding protein in man and most other mammals. However, although TTR is a minor thyroid hormone binding protein in humans, it is the principal protein involved in T_4 transport to the brain in both rats and man (Blay et al. 1993; Sinjari et al. 1998). TTR does not transport T_4 from the bloodstream to the brain, but rather is the main T_4 binding protein in cerebrospinal fluid (CSF) in both rats and humans. In the rat, T_4 is transported to the brain primarily through the blood-brain barrier, and not via the choroid plexus and CSF (Blay et al. 1993). 2,2',4,4'-TetraBDE (BDE 47) competitively inhibited binding of T_4 to sites in rat choroid plexus following *in vivo* (but not *in vitro*) exposure (Sinjari et al. 1998). 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. At least one group of mammals is known to exist without TTR (Palha et al. 1997; Schussler 2000). The TTR-nul mouse has decreased protein-bound and total T_4, normal free T_4, and has apparent good health (Palha et al. 1997, 2000). Interference with the blood-choroid-plexus-CSF-TTR-mediated route of T_4 to the brain caused by the absence of TTR did not produce measurable features of hypothyroidism (Palha et al. 2000).

Neurobehavioral developmental alterations have been induced in mice that were neonatally or perinatally exposed to individual PBDE congeners, including 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',5,5'-hexaBDE (BDE 153), and 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209) (Branchi et al. 2001, 2002; Eriksson et al. 1999, 2001a, 2002a; Viberg et al. 2001a, 2001b, 2002a, 2002b, 2003). As detailed in Section 5.2.2.4 Neurological Effects, the main effects were observed at adulthood and included reduced spontaneous motor activity, impaired habituation capability, and learning impairment in a maze task. The mechanisms for these behavioral and cognitive effects have not been elucidated. One possibility involves the well-documented key role of thyroid hormones in brain development. As discussed above, *in vivo* and *in vitro* exposure to PBDEs has caused changes in hormone levels and other thyroid end points in animal models. Some studies suggest that the effects might be related to alterations in cholinergic functions. For example, neonatal exposure to a single 8 mg/kg oral dose of BDE 99 on PND 10 altered the behavioral response to nicotine, a cholinergic agent, in adult mice (Viberg et al. 2002b). Neonatal exposure to nicotine and adult exposure to BDE 99 (single 8 mg/kg oral dose at age 5 months) also affected behavior in mice; the change was not seen in mice only exposed to BDE 99 as

adults or mice only exposed to nicotine as neonates (Ankarberg et al. 2001). Adult mice that were exposed to single 9 mg/kg oral dose of BDE 153 on PND 10 had a decrease in specific α-Bungarotoxin binding sites (cholinergic nicotinic receptors) in the brain hippocampus (Viberg et al. 2001b, 2002a).

Effects of PBDEs on intracellular signaling processes in rat neuronal cultures and cerebellar fractions have been reported. *In vitro* exposure to commercial pentaBDE mixture DE-71 or tetra congener BDE 47 stimulated arachidonic acid release in rat cerebellar granule neurons; this effect was not seen with the commercial octaBDE product DE-79 (Kodavanti 2003; Kodavanti and Derr-Yellin 2002). The release of arachidonic acid appeared to be mediated by the activation of both Ca^{+2}-dependent and Ca^{+2}-independent cytosolic phospholipase A_2. *In vitro* exposure to penta mixture DE-71and tetra congener BDE 47 also caused translocation of protein kinase C, as indicated by increased phorbol ester binding; octaBDE mixture DE-79 did not induce this effect (Kodavanti and Derr-Yellin 2002; Rao et al. 2003). Other effects of penta mixture DE-71 and tetra congener BDE 47 included decreases in intracellular calcium buffering by microsomes and mitochondria (Kodavanti and Derr-Yellin 2002). The tetra congener BDE 47 was generally more potent than the DE-71 mixture (mainly comprised of tetra and penta congeners) in these tests. Another study found that DE-71 was more toxic than octa and deca congeners in inducing cell death and free radical formation in cerebellar granule cells (Reistad et al. 2002). The *in vitro* uptake of the neurotransmitter dopamine into rat brain synaptic vesicles was inhibited by penta mixture DE-71 mainly tetra and penta congeners), but not by commercial mixtures of octaBDE (DE-79) or decaBDE (DE-83R) (Mariussen and Fonnum 2002, 2003).

The ability of PBDE congeners to induce estrogen receptor (ER)-mediated gene expression in MVLN recombinant human breast carcinoma cells, or displace steroid hormones (^{3}H-testosterone or ^{3}H-estradiol) from carp serum proteins, was assessed by Villeneuve et al. (2002). Of 10 tested congeners, including the environmentally prominent congeners 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), induced a significant response in either *in vitro* assay. Another study found that a hydroxylated metabolite of BDE 47, 6-OH-2,2',4,4'-tetraBDE, did not inhibit aromatase (CYP 19) enzyme activity in human H295R adrenocortical cells (Canton et al. 2003). Aromatase is a steroidogenic enzyme that mediates the conversion of androgens to estrogens. No other PBDEs were tested in this *in vitro* study.

The estrogenic and antiestrogenic activities of several PBDE congeners and three hydroxylated PBDEs were also assessed *in vitro* using human breast cell line assays based on 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-tribromophenoxy)phenol, have bromine substitution patterns similar to those of the thyroid hormones T_2 (3,5-diiodothyronine), T_3 (3,3',5-triiodothyronine), and T_4 (3,3',5,5'-tetraiodothyronine), 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 [BDE 100] > 2,4,4',6-tetraBDE [BDE 75] > 2,2',4,6'-tetraBDE [BDE 51] > 2,4,6-triBDE [BDE 30] > 2,3',4,4',6-pentaBDE [BDE 119]) 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 (BDE 153), 2,3,4,4',5,6-hexaBDE (BDE 166), 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 (BDE 30), 2,2',4,4',6-pentaBDE (BDE 100), 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 (BDE 30) (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).

The predominant congeners in biological samples, 2,2',4,4'-tetraBDE (BDE 47) and 2,2',4,4',5-pentaBDE (BDE 99), did not demonstrate estrogenic activity in the Meerts et al. (2001) study. The hydroxy-PBDE derivatives that showed minimal activity were *para*-substituted with a hydroxyl group, whereas the *para* position of the predominant isomers in biological samples is occupied by bromine atom, suggesting that the relevance of the results to commercial BDE mixtures is unclear. Additionally, all of the available estrogenicity studies were *in vitro*, and there is, as yet, no evidence either for estrogenicity or anti-estrogenicity of PBDEs and/or PBDE metabolites *in vivo*.

5.5.3 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 8, 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. The wildlife residue data also indicate that different species have different tissue ratios of congeners, possibly reflective of interspecies differences in metabolic capabilities as well as potential differences in exposure. The likelihood of interspecies differences in the quantitative disposition of PBBs and PBDEs is illustrated by the observation that metabolism and urinary excretion of a single oral dose of BDE 47 was significantly slower in rats than in mice (Orn and Klasson-Wehler 1998).

Humans are possibly less sensitive than rats to effects of PBDEs on circulating levels of thyroid hormones. This difference is thought to derive from the rat thyroid having a smaller store of iodinated thyroglobulin that is more easily depleted when the availability of iodide is limited, and from a more rapid clearance of T_4 from the rat circulation; the latter resulting from rats not having a high affinity binding protein for T_4 in serum analogous to thyroid-binding globulin (TBG) in humans (Capen 1997). If the production of T_4 and T_3 is impaired sufficiently to deplete the thyroid of stored iodinated thyroglobulin, the thyroid cannot produce or secrete amounts of T_4 and T_3 needed to support physiological demands, circulating levels of T_4 (free T_4) and T_3 decrease, and a state of thyroid hormone insufficiency ensues. Transthyretin (TTR) is the major thyroid hormone binding protein in rats, but not in man. In most mammals, including humans, thyroxin binding globulin (TGB) is the principal thyroid hormone binding protein; 74% of the total bound-T_4 is bound to TGB, and TTR and albumin bind only 11 and 15%, respectively, of the total (Schussler 2000). In contrast to most mammals, the rat utilizes TTR as the major T_4 plasma binding protein; approximately 75% of T_4 in rat serum is bound to TTR and only 25% to albumin. Both circulating T_3 and T_4 are highly protein bound with only a small fraction of their total present as free hormone, and this high degree of protein binding serves to maintain equilibrium between the extracellular and intracellular pools of these hormones (O'Connor et al. 1999). The increased metabolic clearance of serum T_4 is thought to involve the induction of hepatic microsomal enzymes. Although it is well documented that PBDEs are microsomal enzyme inducers, there is little evidence that induction of hepatic enzymes leads to greater clearance of thyroid hormones, indicating that it is

misleading to assume that PBDEs are unlikely to affect thyroid function in humans, or that humans are less sensitive to these effects than rats.

Less is known about the relative sensitivities of humans and experimental animals to developmental effects of PBDEs. Outstanding uncertainties include potential differences in kinetics of maternal-fetal and maternal-infant transfer of PBDEs, as well as potential differences in the degree to which the fetus of the human, in comparison to experimental animals, is dependent on maternal thyroid hormone for development, particularly during the period of gestation prior to the onset of fetal hormone production.

5.6 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 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), and in 1998, the EDSTAC 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 1997a). As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. 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 (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 (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 5.8.1. 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 5.2.2.5.

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, as well as *in vivo* thyroid hormone homeostasis studies in animals, suggest that there is a potential for some PBDEs to disrupt thyroid and other endocrine system functions in humans.

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 [BDE 75] > 2,2',4,6'-tetraBDE [BDE 51] > 2,4,6-triBDE [BDE 30] > 2,3',4,4',6-pentaBDE [BDE 119]) 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 [3,5-diiodothyronine] and T_3 [3,3’,5-triiodothyronine], 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 (BDE 30), 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 BDE 30 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. However, no estrogenic activity was demonstrated by the predominant congeners in biological samples, 2,2’,4,4’-tetraBDE (BDE 47) and

2,2',4,4',5-pentaBDE (BDE 99). The hydroxy-PBDE derivatives that showed minimal activity were *para*-substituted with a hydroxyl group, whereas the *para* position of the predominant isomers in biological samples is occupied by bromine atom, suggesting that the relevance of the results to commercial PBDE mixtures is unclear. Additionally, because all of the available estrogenicity data are *in vitro*, there is, as yet, no evidence either for estrogenicity or anti-estrogenicity of PBDEs and/or PBDE metabolites *in vivo*.

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 (BDE 15), 2,4,4'-triBDE (BDE 28), 2,4,6-triBDE (BDE 30), 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,6'-tetraBDE (BDE 51), 2,4,4',6-tetraBDE (BDE 75), 3,3,4,4'-tetraBDE, 2,2',4,4',6-pentaBDE, and 2,3',4,4',6-pentaBDE (BDE 119). 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 T_4; 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). Studies with hydroxylated derivatives of PBBs similarly showed that the congener patterns most closely resembling the diiodophenolic ring of thyroxine had the highest TTR binding activity (Chauhan et al. 2000; McKinney et al. 1987; Rickenbacher et al. 1986).

Because PBDEs were able to compete with T_4-TTR binding only after metabolic conversion, and considering that thyroid hormones are also hydroxy-halogenated diphenyl ethers, the results of the Meerts et al. (1998, 2000) study suggest that hydroxylation of PBDEs could be involved in the mechanism of thyroid toxicity. However, there are indications that hydroxylated metabolites might not play a large role for thyroid effects of commercial penta- and octaBDE mixtures. For example, of the *in vitro*-generated metabolites displacing T_4 from TTR (Meerts et al. 1998, 2000), only two (2,2',4,4'-tetraBDE (BDE 47) and 2,2',4,4',6-pentaBDE) are known to be present in a commercial mixture (pentaBDE). An *in vivo* study in rats (Om and Klasson-Wehler 1998) showed that BDE 47 is well absorbed (~95%), poorly metabolized (only 3% of the amount excreted in feces was in the form of metabolites), and occurs in

blood and other tissues mainly as the parent compound. Additionally, the three pure hydroxylated PBDEs synthesized by Meerts et al. (1998, 2000) for their structural similarity to thyroid hormones are not based on congeners known to be present in commercial penta- or octaBDE mixtures; this suggests that the congeners in these mixtures do not share close structural relationships with thyroid hormones. In another study, 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.

Studies of serum hormone levels and organ histology indicate that the thyroid is a sensitive target for some 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 commercial 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).

As summarized above, 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. The main effects 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 accompanying 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), and decaBDE appears to be much less potent than the lower brominated mixtures. Considering these data, the structural resemblance of some PBDEs to T_4, and information from binding studies of individual congeners as summarized above, it is hypothesized that, depending on dose, duration, and mixture/congener, PBDEs can disrupt the production, transport, and disposition of thyroid hormones.

The extent that PBDEs affect circulating levels of T_4 or T_3 is likely to vary with species, and rats are generally regarded as more sensitive than humans. This is thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid, and to a more rapid clearance of secreted hormone in the rat; that latter being, in part, related to the absence of thyroid binding globulin (TBG) in rats (Capen 1997). Transthyretin (TTR) is the major thyroid hormone binding protein in rats, whereas TBG is the main binding protein in man and most other mammals. However, although TTR is a minor thyroid hormone binding protein in humans, it is the principal protein involved in T_4 transport to the brain in both rats and man (Blay et al. 1993; Sinjari et al. 1998). TTR does not transport T_4 from the bloodstream to the brain, but rather is the main T_4 binding protein in cerebrospinal fluid (CSF) in rats and humans. In the rat, T_4 is transported to the brain primarily through the blood-brain barrier, and not via the choroid plexus and CSF (Blay et al. 1993). 2,2',4,4'-TetraBDE (BDE 47) competitively inhibited binding of T_4 to sites in rat choroid plexus homogenates following *in vivo* exposure (Sinjari et al. 1998).

5.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 8.6 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 effects 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 (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 5.8.1. 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 5.2.2.5.

Polybrominated Diphenyl Ethers. No specific information was located on health effects of PBDEs in newborn or older children. Thyroid and neurobehavioral alterations have been observed in developing animals following pre- and/or postnatal exposure to lower brominated BDEs, indicating that infants and children might be particularly susceptible to these effects. The potential for thyroid and neurodevelopmental effects of decaBDE is expected to be relatively low due to differences in the toxicokinetics and toxicity of decaBDE compared to lower brominated BDEs.

Thyroid hormones regulate cell proliferation, migration, and differentiation during development, and maintenance of normal levels is essential to normal growth and development. Disruption of circulating hormone levels can have markedly different effects, depending on the stage of development, and even transient disruptions can produce permanent effects. Effects can include mental retardation, impaired motor skills, and hearing and speech impediments (Boyages 2000; Fisher and Brown 2000). Several factors might contribute to a high vulnerability of the fetus and neonate to lower brominated PBDEs. Relatively brief periods of thyroid hormone insufficiency (e.g., 14 days) can produce measurable neurological deficits in newborn infants (van Vliet 1999). Furthermore, unlike the adult thyroid gland, which contains a relatively large store of T4 that is sufficient to support circulating levels of hormone for several months, the neonatal thyroid contains only enough hormone to support circulating levels of hormone for ≥1 day (van den Hove et al. 1999; Vulsma et al. 1989). Thus, even acute exposures to a dose of lower brominated PBDEs sufficient to suppress thyroid hormone production could potentially result in thyroid insufficiency in the neonate. The absorbed dose of lower brominated PBDEs per unit of body mass is also likely to be higher in infants compared to adults exposed to similar levels of PBDEs because of higher intakes per unit of body mass and exposure from breast milk. It should be noted that screening of all newborn children for hypothyroidism is already a widely accepted and legislatively mandated practice (LaFranchi 1999; Landenson et al. 2000); newborns are tested for thyroid hormone levels within the first few days of life in the United States and most other developed countries; and treatment is started immediately if indicated (LaFranchi 1999; Landenson et al. 2000).

Although there is no evidence that exposure to PBDEs causes thyroid effects in humans, the thyroid is a well-documented target of lower brominated commercial mixtures and single congeners in adult and neonatal rats and mice. The main effects in animals are reduced serum T_4 hormone levels and follicular cell hyperplasia, with no accompanying changes in serum T_3 or TSH levels. In adult animals, acute-duration oral exposure caused 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 and Darnerud 1998; Hallgren et al. 2001; Zhou et al. 2001). Effects observed in intermediate-duration oral studies included 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).

Other animal studies have shown reduced serum levels of thyroid hormones in offspring of rats exposed to lower brominated PBDEs during gestation and lactation, as well as in rats orally 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. 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 octaBDE and pentaBDE at doses as low as 10 mg/kg/day (Darnerud and Sinjari 1996; Hallgren et al. 2001; WIL Research Laboratories 1984).

Although alterations in thyroid hormone homeostasis can cause neurodevelopmental effects, little specific information is currently available on the potential neurotoxic effects of PBDEs. Data are mainly 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 (BDE 47) or 2,2',4,4',5-pentaBDE (BDE 99) (Eriksson et al. 1998, 1999, 2001, 2002a). Effects on spontaneous activity were observed in adult mice treated at either 3 or 10 days of age, but not at 19 days of age, suggesting that there is a critical phase of neonatal brain development for the induction of behavioral disturbances (Eriksson et al. 1999, 2002a). No studies were located that sufficiently evaluated neurological effects of PBDEs in animals exposed as adults. None of the commercial decaBDE,

octaBDE, and pentaBDE products have been screened for neurotoxicity using comprehensive test batteries that typically include functional observational, motor activity, and neuropathology evaluations. There were no indications of neurotoxicity in rats and mice fed high dietary dose levels of a 94–97% pure commercial decaBDE mixture for 14 days (≤19,000 mg/kg/day), 13 weeks (≤9,500 mg/kg/day), or 103 weeks (≤7,780 mg/kg/day), as assessed by overt clinical signs (all exposures) and nervous system histopathology (chronic exposure only) (NTP 1986). Although the high doses and extended exposure durations in the NTP (1986) studies provided opportunities for the development of effects, neurotoxicity is only incompletely evaluated due to the lack of testing for subtle behavioral and other sensitive neurological end points.

The human relevance of the thyroid and neurodevelopmental effects of lower brominated BDEs in animals is unclear. Humans are generally regarded as being less sensitive than rats to effects of PBDEs on circulating thyroid hormones. This is thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid, and to a more rapid clearance of secreted hormone in the rat; the latter being, in part, related to the absence of thyroid binding globulin (TBG) in rats (Capen 1997). Transthyretin (TTR) is the major thyroid hormone binding protein in rats, whereas TBG is the main binding protein in man and most other mammals. However, although TTR is a minor thyroid hormone binding protein in humans, it is the principal protein involved in T_4 transport to the brain in both rats and man (Blay et al. 1993; Sinjari et al. 1998). TTR does not transport T_4 from the bloodstream to the brain, but rather is the main T_4 binding protein in cerebrospinal fluid (CSF) in rats and humans. In the rat, T_4 is transported to the brain primarily through the blood-brain barrier, and not via the choroid plexus and CSF (Blay et al. 1993). Also, mechanism by which lower brominated BDEs cause decreased serum T4 might involve hepatic microsomal enzyme induction and consequent increased metabolic formation of hydroxy-metabolites, but humans are not particularly sensitive to this effect. Additionally, the animal studies in which neurobehavioral alterations were observed were performed using an atypical design that has not been validated, and used exposure levels much higher than those likely to be experienced by humans.

The potential for induction of thyroid and neurodevelopmental effects by decaBDE is low in comparison to commercial penta- and octaBDE mixtures due to toxicokinetic and toxicity differences. The lower brominated BDEs preferentially accumulate in the body due to their partitioning and retention in lipid-rich tissues and lower rates of metabolism and elimination relative to decaBDE (Hardy 2002b; Morck et al. 2001, 2003). These characteristics seem to be a function of the number and location of bromines on the diphenyl oxide molecule . The tetra- and pentaBDEs appear to be relatively well absorbed, whereas the fully brominated decaBDE, a large poorly soluble molecule, is very poorly absorbed (≈1% or less of

an oral dose) and rapidly eliminated (≈99% of the dose within 72 hours). Further, decaBDE is significantly less toxic than lower brominated BDE mixtures. For example, a study in weanling rats showed that acute oral exposure to commercial decaBDE had no effect on thyroid hormones, while similar exposures to commercial octaBDE or pentaBDE mixtures caused decreases in serum T_4 and T_3 levels (Zhou et al. 2001). Similarly, acute postnatal oral exposure to pure decaBDE congener (BDE 99) was less potent than BDE 47, BDE 99, and 2,2',4,4',5,5'-hexaBDE (BDE 153) in inducing behavioral effects in adult mice (Eriksson et al. 1999, 2001a, 2002a; Viberg et al. 2001a, 2001b, 2002a, 2002b, 2003). Chronic (103-week) exposure to a high-purity (≥97%) commercial decaBDE mixture induced thyroid follicular cell hyperplasia in mice, but the dose levelwas very high (2,240 mg/kg/day) and no thyroid histological changes occurred in similarly exposed rats (NTP 1986).

No information is available regarding the immunosuppressive potential of PBDEs in young animals, and data on immune function in adult animals are mainly 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 (BDE 47) caused significantly reduced numbers of total lymphocytes and CD4+, CD8+, and CD45R+ subtypes in spleen (Darnerud and Thuvander 1998). Histological examinations of spleen, thymus, lymph node, and/or bone marrow tissues in systemic toxicity studies 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). None of these studies reported changes in clinical condition that could be indicative of reduced immunocompetence. Although the high doses and extended exposure durations provided opportunities for the development of histopathology in immune system tissues and relevant clinical signs, no comprehensive immunotoxicity evaluations of PBDEs have been performed.

Information on the reproductive toxicity of PBDEs mainly consists of a one-generation study of decaBDE in rats that found no exposure-related functional effects (Dow Chemical Co. 1975; Norris et al. 1975a, 1975b). No histopathological changes were observed in male or female reproductive tissues from rats that were exposed to PBDEs in dietary systemic toxicity studies, including decaBDE in rats at doses ≤8,000 mg/kg/day for 13 weeks or ≤2,550 mg/kg/day for 103 weeks (NTP 1986), decaBDE in mice at doses ≤9,500 mg/kg/day for 13 weeks or ≤7,780 mg/kg/day for 103 weeks (NTP 1986); octaBDE in rats at ≤750 mg/kg/day for 13 weeks (IRDC 1977); or pentaBDE in rats at doses ≤100 mg/kg/day for 90 days (WIL Research Laboratories 1984). Developmental toxicity studies showed 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).

Results of *in vitro* estrogen receptor assays suggest that there is a potential for some PBDEs to disrupt endocrine system functions in humans. 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 [BDE 75] > 2,2',4,6'-tetraBDE [BDE 51] > 2,4,6-triBDE [BDE 30] > 2,3',4,4',6-pentaBDE [BDE 119]) 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 [3,5-diiodothyronine] and T_3 [3,3’,5-triiodothyronine], 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 (BDE 30), 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 BDE 30 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. However, no estrogenic activity was demonstrated by the predominant congeners in biological samples, 2,2’,4,4’-tetraBDE (BDE 47) and 2,2’,4,4’,5-pentaBDE (BDE 99). The hydroxy-

PBDE derivatives that showed minimal activity were *para*-substituted with a hydroxyl group, whereas the *para* position of the predominant isomers in biological samples is occupied by bromine atom, suggesting that the relevance of the results to commercial PBDE mixtures is unclear. Additionally, because all of the available estrogenicity data are *in vitro*, there is no evidence for estrogenicity or anti-estrogenicity of PBDEs or PBDE metabolites *in vivo,* including possible effects on reproductive development in children.

Lower brominated 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 accumulation of decaBDE in breast milk does not appear to be appreciable, in large part because the amount in the maternal bloodstream and available for transfer to breast milk is low due to poor gastrointestinal absorption and rapid elimination in the feces (Hardy 2002b). 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.

Assessments of potential health risks to children were performed for commercial pentaBDE, octaBDE, and decaBDE products by industry as part of the EPA Voluntary Children's Chemical Evaluation Program (VCCEPP) (BFRIP 2002; ENVIRON 2003a, 2003b). Based on evaluations of toxicity and potential exposure data, the reports concluded that none of the three commercial mixtures were expected to be harmful to children. These assessment documents have been independently reviewed as part of the VCCEP Peer Consultation process, but final reports reflecting peer review findings and EPA conclusions are not yet available (EPA 2004a, 2004b, 2004c).

5.8 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 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 5.8.1.

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 5.8.2.

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 5.10 “Populations That Are Unusually Susceptible”.

5.8.1 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 larger number of people with measured exposure when adipose tissue results were included reflects the higher fat content of adipose compared to serum and the lipophilicity of the chemicals. 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 (BB 153) 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, indicating that $t_{1/2}$ increases with increasing fat content. 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 (Blanck et al. 2000b; Lambert et al. 1990; 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 (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).

Polybrominated Diphenyl Ethers. Lower brominated PBDEs are persistent environmental contaminants that accumulate in adipose tissue, serum, and breast milk serum of the general population, whereas decaBDE does not appear to be bioaccumulative. The accumulation of lower brominated congeners is likely due to ease of absorption, metabolism, and elimination compared to decaDBE (i.e., related to each molecule's specific structure and not solely due to lipophilicity). Serum, adipose, and breast milk levels are indicators of exposure for lower brominated PBDEs. Lower brominated congeners in breast milk are useful as 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.

5.8.2 Biomarkers Used to Characterize Effects Caused by PBBs and PBDEs

Polybrominated Biphenyls. Biomarkers of effects for PBBs are likely to be common to the general class of halogenated aromatic hydrocarbons, rather than specific for PBBs, because PCBs, PBDEs, and other structurally similar chemicals cause generally similar effects. A potential biomarker for PBBs is related to their effect on the thyroid gland. As discussed in Sections 5.2.2.2, Endocrine Effects, the thyroid gland is a sensitive and 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). Therefore, serum levels of T_4 and/or other thyroid hormones are potential biomarkers of effects for PBBs. 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, including information on the specific amount of change in the biomarkers associated with a demonstrably adverse effect. These potential biomarkers are not specific to PBBs because PBDEs and other antithyroid agents can have similar effects.

Caffeine has been used 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 is significantly induced by PBBs in animals (Safe 1984). The caffeine breath test (CBT) is primarily useful for detecting induction of CYP1A2 activity in human liver. Because the

induction of CYP1A enzymes is AhR mediated, the test 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).

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 5.2.

Polybrominated Diphenyl Ethers. Biomarkers of effects for PBDEs are likely to be common to the general class of halogenated aromatic hydrocarbons, rather than specific for PBDEs, because PBBs, PCBs, and other structurally similar chemicals cause generally similar effects. The thyroid is a critical target for lower brominated PBDEs in animals. As discussed in Sections 5.2.2.2, Endocrine Effects, exposure to commerical penta- and octaBDE products caused thyroid changes in rats and mice, particularly reduced serum T_4 levels (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998; WIL Research Laboratories 1984; Zhou et al. 2001, 2002). The potential for induction of thyroid effects by decaBDE appears to be low in comparison to penta- and octaBDE mixtures due to toxicokinetic and toxicity differences. In particular, lower brominated BDE congeners preferentially accumulate in the body compared to decaBDE, apparently due to their greater partitioning and retention in lipid-rich tissues and lower rates of metabolism and elimination (Hardy 2002b; Morck et al. 2001, 2003), and decaBDE only affected the thyroid in animals following lifetime exposure to dose levels several orders of magnitude higher than effect levels of penta- and octaBDE in acute-duration studies (NTP 1986; Zhou et al. 2001).

Serum T_4 may not be a reliable biomarker in humans because the extent that PBDEs affect circulating levels of T_4 (or T_3) possibly varies with species. As discussed in Section 5.5.3, Animal-to-Human Extrapolations, humans are generally regarded as less sensitive than rats to thyroid effects of PBDEs due to differences in the binding of T_4 to serum transport proteins. In particular, in humans, the binding of T_4 to thyroxine binding globule (TBG) protects the hormones from metabolism and excretion, resulting in relatively long serum half-lives. Rats lack a high-affinity binding protein (i.e., TBG) and consequently have lower serum levels of T_4 due to increased availability of the hormone for metabolism and elimination. The clearance of T_4 in rats is enhanced by the induction hepatic microsomal enzymes, particularly UDP-glucuronyl transferase, which catalyzes the conjugation of free T_4 and enhances its excretion in the bile. Effects of PBDEs on thyroid status via induction of hepatic enzymes are therefore unlikely to occur in humans. However, because PBDE-induced decreases in T_4 appear to involve multiple mechanisms in addition to increased thyroid hormone metabolism (Zhou et al. 2001), serum T_4 level is a potential biomarker of effects for lower brominated PBDEs in humans. Additional studies would be useful to characterize the applicability of the biomarker to humans and develop possible correlations between levels and duration of exposure and changes in serum T_4. This biomarker is not specific to PBDEs because other antithyroid agents can have similar effects. Additionally, screening of newborn children for hypothyroidism is a widely accepted and legislatively mandated practice (LaFranchi 1999; Landenson et al. 2000).

5.9 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 a group of 209 congeners that display biological activity involving different potential mechanisms, and share some toxicological properties with structurally similar polyhalogenated aromatic compounds, particularly PBBs, PCBs, polychlorinated- and poly-brominated dibenzo-*p*-dioxins (PCDDs and PCBDs), and chlorinated and brominated dibenzofurans (PCDFs and PBDFs). However, although these chemicals are structurally similar in two dimensions, PBDEs differ from the other classes on a three-dimensional basis. In particular, as discussed Section 5.5.2 Mechanisms of Toxicity, the influences of the ether bridge in the PBDE molecule preclude clearly classifying the congeners as either dioxin-like (coplanar) or non-dioxin-like (non-coplanar). This has implications for both dioxin-type toxicities (mediated by the AhR pathway) and non-dioxin-type effects. For example, structure-activity studies of PBDEs have shown that binding affinities and induction of AhR-mediated responses are very weak or negligible (Chen et al. 2000; Meerts et al. 1998), suggesting that there is a low potential for effects and interactions involving Ah-receptor-mediated mechanisms (e.g., induction of hepatic CYP1A oxygenases and Phase II enzymes, body wasting, thymic atrophy, and porphyria). Because of the diversity of PBDE activities involving Ah-receptor-independent mechanisms (e.g., induction of CYP2B and CYP3A oxygenases, induction of changes in brain dopamine levels, and disruption of calcium homeostasis), or possibly both Ah-receptor-dependent and -independent mechanisms (e.g., liver hypertrophy, disruption of steroid hormone homeostasis, thyroid hormone homeostasis, disruption of immune functions), there is a large potential for PBDEs to alter the toxicity of other chemicals, or other chemicals to alter the toxicity of PBDEs. For example, lower brominated PBDE mixtures and congeners 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.

5.10 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 8.7, Populations with Potentially High Exposures.

Information was located on a small part of the U.S. population that might be unusually susceptible to PBBs and PBDEs. As indicated in Section 5.4.4.2, breast milk constitutes the most important route of excretion of PBBs in lactating females, and this is likely to be the case for lower brominated PBDEs as well. DecaBDE has not been reported in breast milk and is unlikely to accumulate in the milk due to poor absorption and rapid elimination in the feces (Hardy 2002b). Therefore, women with high body burdens of PBBs and/or lower brominated PBDEs who breast-feed may be placing their infants at a higher risk of potential health effects. However, in most cases, the benefits of breast-feeding are expected to outweigh any risk to infants from exposure to these chemicals in the maternal milk.

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 possibly sensitive populations for exposure to PBBs and lower brominated PBDEs as they are for 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 lower brominated 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 5.2.2.2 (Endocrine Effects subsection). The potential for induction of thyroid and neurodevelopmental effects by decaBDE is low in comparison to commercial penta- and octaBDE mixtures due to toxicokinetic and toxicity differences, as discussed in .Section 5.7 (Children's Susceptibility).

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. However, the potential for induction of thyroid effects by PBDEs in humans appears to be low, based on mechanistic data as discussed Section 5.5.3 (Animal-to-Human Extrapolations).

5.11 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. Specific treatment methods have not been developed for exposures to PBBs or PBDEs.

The treatment methods discussed below are general methods that would apply to any persistent, lipophilic chemical, and have not been tested for efficacy, indicating that they might not be effective in reducing the toxic effects of PBBs and PBDEs. There is no indication of hazards associated with the treatments. The methods are particularly appropriate for trying under conditions of acute exposure, but PBBs and PBDEs are not acutely toxic chemicals. Scenarios where life-threatening acute exposure would occur are unlikely, although accidental or intentional ingestion of the commercial products is a conceivable concern. The relevance of the methods to common background environmental exposures to these chemicals is unclear, and it is questionable whether current exposure and tissue levels in the general population are a health concern.

5.11.1 Reducing Peak Absorption Following Exposure

Ingested PBBs and PBDEs are absorbed by the gastrointestinal tract of humans and animals (see Section 5.4). Although there are no specific recommendations for clinical treatment of acute intoxication from ingested PBBs and PBDEs, 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 be absorbed by the lungs,skin, and/or orally by hand-to-mouth contact. 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). Personal protective equipment (e.g., long sleeves, gloves, safety glasses, respiratory protection) and industrial hygiene programs generally help to limit occupational exposures.

5.11.2 Reducing Body Burden

PBBs and lower brominated PBDEs tend to accumulate in lipid-rich tissues and are slowly metabolized and eliminated from the body (see Section 5.4). DecaBDE differs from the lower brominated PBDEs in that it is unlikely to preferentially accumulate in body tissues due to poor oral absorption and metabolism and rapid elimination in the feces (Hardy 2002b). Several methods to enhance the elimination of PBBs from the body have been examined in animals and are applicable to PBDEs, although the relevance of the methods is questionable because it is unclear whether current tissue levels are a health concern for the

general population. Methods for increasing the elimination of these chemicals include 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 5.8.1, 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. Based on information for PCBs, mobilization of PBBs or PBDEs from adipose tissue is not recommended in individuals with hepatic or renal disease (Lemesh 1992).

5.11.3 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 congeners exert toxic actions by a process involving several steps (Safe 1984). This process begins with the binding of particular congeners to the AhR and leads ultimately to enhancement of the CYP1A1 gene expression (see Section 5.5). 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. Several compounds have been identified that partially antagonize one or more AhR-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 AhR activator (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) (Bannister et al. 1989). Therefore, the potential for interfering with the mechanism of AhR-mediated effects of PBBs after exposure has occurred is largely untested. For PBDEs, the ether bridge precludes congeners from readily adopting the coplanar (dioxin-like) conformation characteristic of AhR ligands (see Section 5.5.2 Mechanisms of Toxicity). Because PBDE congeners are not clearly classifiable as either dioxin-like (coplanar) or non-dioxin-like (non-coplanar), AhR antagonists might not effectively antagonize effects of PBDEs.

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. PBDE-induced decreases in thyroid T_4 hormone, which can affect neurobehavioral development, are likely to involve multiple mechanisms (see Section 5.5.3). These include induction of hepatic microsomal enzymes, particularly UDPGT, which can increase the rate of T_4 conjugation and excretion, and metabolic formation of hydroxy-metabolites of PBDEs. PBDEs and their hydroxy metabolites can bind with high affinity to thyroid transport proteins because they are structurally similar to T_4 hormone (i.e., are also hydroxy-halogenated diphenyl ethers) (see Section 5.5.2). Effects of PBDEs on thyroid status via induction of hepatic enzymes, however, are unlikely to occur in humans, and the impact of hydroxy-metabolites on serum T_4 needs further clarification. Effects of PBDEs on the function and development of the nervous system could also involve disruption of calcium homeostatic mechanisms and intracellular signalling events (Kodavanti 2003; Kodavanti and Derr-Yellin 2001, 2002; Smolnikar et al. 2001; Wiegand et al. 2001), effects on dopamine uptake into synaptic vesicles and synaptosomes (Mariussen and Fonnum 2002, 2003; Mariussen et al. 2003a) and cholinergic functions (Viberg et al. 2001b, 2002a, 2002b), and/or free radical-induced neuronal death (Reistad et al. 2002). Clinical interventions designed to interfere with the aforementioned mechanisms have yet to be developed.

5.12 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.

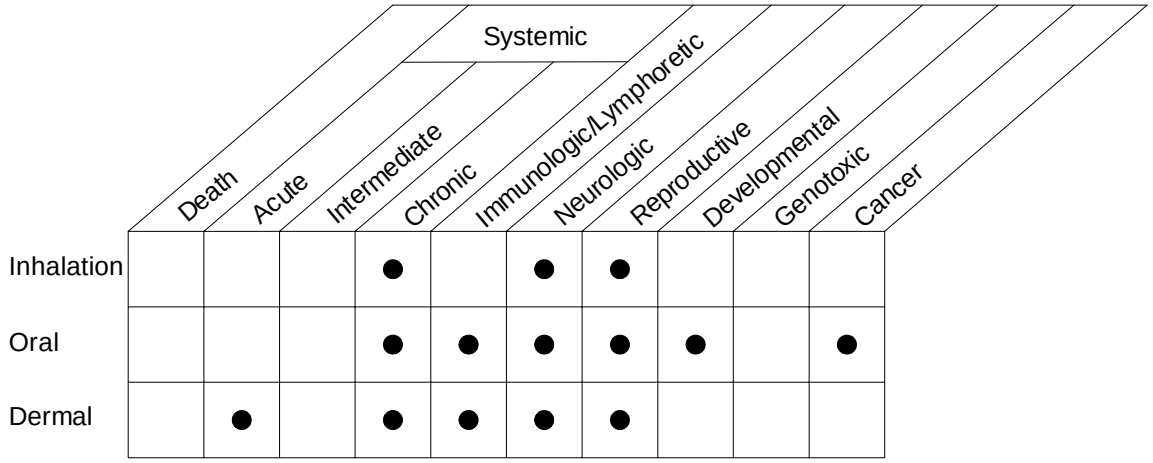
5.12.1 Existing Information on Health Effects of PBBs and PBDEs

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PBBs and PBDEs are summarized in Figures 5-6 and 5-7. 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.

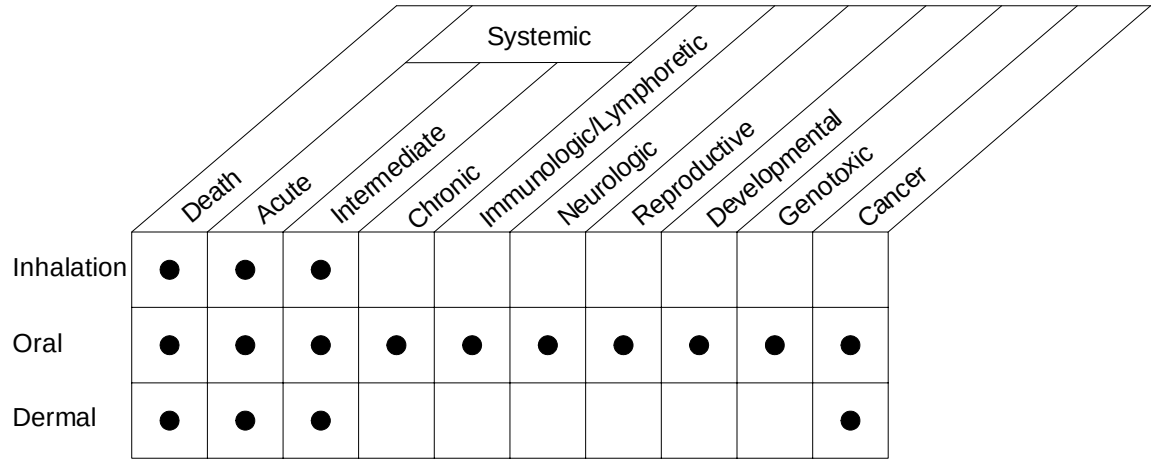
As indicated in Figure 5-6, information is available regarding systemic, immunological, neurological, developmental, reproductive, and carcinogenic effects of PBBs in humans. The information on effects in humans is derived from the Michigan contamination episode that involved chronic-duration oral exposure 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.

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.

Figure 5-6. Existing Information on Health Effects of PBBs



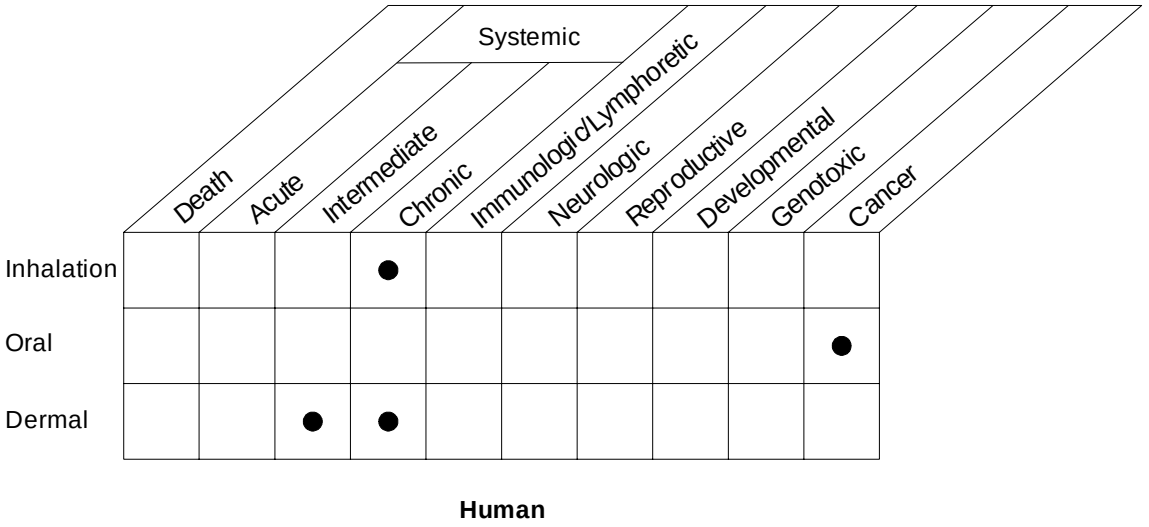
Human



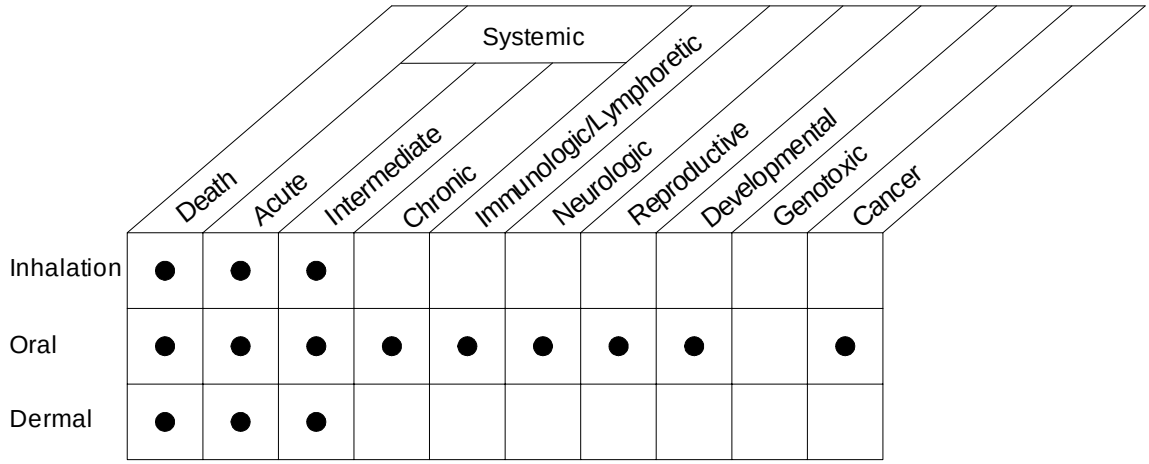
Animal

● Existing Studies

Figure 5-7. Existing Information on Health Effects of PBDEs



Human



Animal

● Existing Studies

A limited amount of information is available on the systemic and carcinogenic effects of PBDEs in humans (Figure 5-7). 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 animals. In general, the health effects of PBDEs are less adequately studied than for PBBs (and PCBs), and a prominent limitation of the PBDE database is a lack of adequate human studies.

5.12.2 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. Limitations in the animal database include inadequate reporting (e.g., numbers of animals not reported), limited number of exposure levels, and lack of studies of PBB mixtures likely to be most toxic (i.e., Firemaster PBBs). 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 and thyroid 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 on lower brominated PBDEs 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 lower brominated 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 lower brominated 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 of lower brominated PBDEs..

Data on decaBDE are insufficient for derivation of an acute-duration oral MRL. Information is available on effects of acute oral exposure to decaBDE on body and liver weights, microsomal enzyme induction in the liver, and serum thyroid levels in weanling rats (Carlson 1980b; NTP 1986; Zhou et al. 2001), but the database is limited by lack of LOAELs and/or sufficiently sensitive end points for estimation of an MRL.

Acute-duration inhalation exposure toxicity studies of decaBDE were not located. The inhalation database for acute-duration exposure to lower brominated PBDEs is essentially limited to two 14-day unpublished industry-sponsored studies of octaBDE in rats (Great Lakes Chemical Corporation 1978, 2000). Liver and nasal effect levels were identified in these studies, but MRL estimation is precluded by inconsistencies between the studies and a lack of information on thyroid hormone levels. Additional dose-response studies are needed to provide an adequate basis for derivation of an acute inhalation MRL for lower brominated PBDEs.

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 PBBs 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 lower brominated 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; 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 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 for lower brominated PBDEs. Essentially all of the available data on thyroid effects of lower brominated PBDEs have been obtained from oral studies in rats. It is speculated that the extent that PBDEs affect circulating levels of thyroid T_4 or T_3 might vary with species, and rats are often regarded as more sensitive than humans. As indicated in the Comparative Toxicokinetics section below, specific evidence is needed to determine whether PBDEs are likely to affect thyroid function in humans, or if humans are less sensitive to these effects than rats. Studies designed to elucidate the mechanism(s) of action for thyroid and other effects of lower brominated 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.

A commercial decaBDPE product (97.34% DBDPO, 2.66% nonaBDE and octaBDE) was administered to groups of 25 mated female Sprague-Dawley rats by gavage in corn oil in daily doses of 0, 100, 300, or 1,000 mg/kg/day on gestation days 0 through 19 in a GLP-compliant study (Hardy et al. 2002). Each female was sacrificed on gestation day 20 and necropsied. End points included maternal clinical observations, maternal body weight/weight gain and food consumption, maternal gravid uterine and liver weights, maternal gross lesions, total number of corpora lutea, uterine implantations, early and late resorptions, viable and nonviable fetuses, and fetal weight and sex. Fetuses were examined grossly (all fetuses), evaluated for skeletal/cartilaginous malformations and ossification variations (approximately

half of each litter), and evaluated for visceral malformations (remaining fetuses). No treatment-related effects on any maternal or fetal endpoints were observed, indicating that 1,000 mg/kg/day was the NOAEL for maternal and developmental toxicity.

One intermediate-duration oral toxicity study has been conducted for high purity decaBDE. In this study, multiple dose levels of a commercial decaBDE product (94–97% pure) was fed to rats and mice for 13 weeks (NTP 1986). Comprehensive histological examinations were performed, but were limited to the control and high-dose groups, and no hematology, clinical chemistry, or urine indices, or thyroid hormone levels were evaluated. There were no compound-related clinical signs, deaths, body weight or food consumption changes, gross pathology, or histopathology, indicating that the highest tested doses in rats and mice (8,000 and 9,500 mg/kg/day, respectively) were intermediate-duration NOAELs for systemic toxicity. A developmental toxicity study in rats identified a NOAEL of 1,000 mg/kg/day (Hardy et al. 2002). Because doses of decaBDE higher than 1,000 mg/kg/day have not been tested for developmental toxicity, and the NTP (1986) study indicates that this dose is also a NOAEL for systemic toxicity, the 1,000 mg/kg/day developmental toxicity NOAEL was used to derive the MRL. Additional systemic and developmental toxicity studies could provide an indication of NOAEL/LOAEL thresholds and possibly provide a better basis for an intermediate-duration oral MRL for decaBDE.

The inhalation database for intermediate-duration exposure to PBDEs consists of one well-conducted 13-week unpublished industry study of octaBDE in rats (Great Lakes Chemical Corporation 2001). Hepatic, nasal, lung, thyroid, and ovarian effects were observed, and a NOAEL for changes in thyroid hormone levels was used as the basis for estimation of an intermediate-duration inhalation MRL.

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. One chronic study of high purity decaBDE has been conducted. In this study, a commercial decaBDE product (94–97% pure) was fed to rats and mice for 103 weeks (NTP 1986). Comprehensive gross and histological examinations were performed on all animals, but no hematology, clinical chemistry, or urine indices, or thyroid hormone levels, were evaluated. The lowest tested dose in the study, 1,120 mg/kg/day in male rats, was a LOAEL for a liver lesion (neoplastic nodules) that is precancerous and associated with thrombosis in the same tissue, precluding estimation of an MRL. Additional chronic dose-response information is needed to provide information on the NOAEL/LOAEL threshold and an appropriate basis for derivation of a chronic MRL for decaBDE. Neoplastic effects in this study 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.

Information on the chronic oral toxicity data of lower brominated PBDEs is available from a study in which rats were fed a 77.4% pure commercial decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for approximately 2 years (Kociba et al. 1975; Norris et al. 1975b). Evaluations that included clinical signs, body weight, food consumption, hematology, clinical chemistry, urine indices, and comprehensive histological examinations showed no exposure-related effects. The highest tested dose (1 mg/kg/day) was a NOAEL, but this effect level is not an appropriate basis for MRL estimation due to insufficient sensitivity of the study. In particular, a chronic oral MRL based on this study would be higher than the intermediate MRL. No exposure-related neoplastic changes were found, but the power of this study to detect carcinogenic effects is limited by the low dose levels. Considering the limitations of the available data, well-designed chronic toxicity studies of pentaBDE and/or octaBDE are needed to provide adequate bases for MRL derivation and cancer assessment for lower brominated PBDEs. Evaluations that include the thyroid and neurobehavioral end points would be particularly informative

because acute and intermediate-duration oral studies indicate that the thyroid and developing central nervous system are particularly sensitive targets for lower brominated 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 (BDE 47), 3,4-diBDE (BDE 12), and 2-monoBDE (BDE 1) 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). Evaluation for histologic effects on reproductive organs in the available studies of PBDEs has generally reported no detectable effects. 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 with lower brominated mixtures (Argus Research Laboratories 1985b; Breslin et al. 1989; Dow Chemical Co. 1975, 1985; Hardy et al. 2002; Life Science Research Israel Ltd. 1987; Norris et al. 1975a, 1975b; WIL Research Laboratories

1986). Effects of gestational exposure to lower brominated 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, respectively (Argus Research Laboratories 1985b; Breslin et al. 1989; Life Science Research Israel Ltd. 1987). Exposure to decaBDE at level as high as 1,000 mg/kg/day (highest tested dose) caused no fetal or maternal effects in rats (Hardy et al. 2002). The available evidence appears to adequately show that teratogenicity and fetal toxicity is not a critical effect of concern for either lower brominated PBDEs or decaBDE. However, there is increasing evidence that the developing nervous system is a sensitive target of particular PBDE congeners, including decaBDE, as shown by impairments in tests of spontaneous motor behavior and learning and memory in adult mice exposed early in life (Branchi et al. 2001, 2002; Eriksson et al. 1999, 2001a, 2002a; Viberg et al. 2001a, 2001b, 2002a, 2002b, 2003a) (see neurotoxicity data needs section).

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 1978; 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 (BDE 47) caused significantly reduced numbers of total lymphocytes and CD4+, CD8+, and CD45R+ subtypes in the spleen (Darnerud and Thuvander 1998). In a 2-year study, NTP (1986) reported that exposure to 2,240 mg/kg/day of decaBDE in the diet resulted in a significant increase in splenic fibrosis; while not a measure of effects on immune function, it does indicate a treatment-related effect on an immune tissue. 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 neuro-psychological 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. A limited amount of information is available on neurological effects of commercial PBDE mixtures. No clinical signs of neurotoxicity or neurohistopathology were observed in rats or mice exposed to commercial decaBDE in dietary doses as high as 16,000–19,000 mg/kg/day for 14 days, 8,000–9,000 mg/kg/day for 13 weeks, or 2,550–7,780 mg/kg/day for 103 weeks (NTP 1986). Although the high doses and extended exposure durations provided opportunities for the induction and/or development of clinical signs, the study is limited by lack of testing for subtle behavioral changes and neurodevelopmental effects. A commercial pentaBDE mixture was evaluated for several behavioral end points in offspring of rats that were perinatally exposed to 1–100 mg/kg/day by gavage on GD 6 through PND 21 (MacPhail et al. 2003; Taylor et al. 2002, 2003). Evaluation of the offspring as adults showed no alterations in motor or sensory development as assessed by motor activity, habituation, and auditory startle response, although suggestive decreases in fear conditioning were observed.

Neurobehavioral effects of individual PBDE congeners were evaluated in mice that were exposed during perinatal and/or early postnatal periods to 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',5,5'-hexaBDE (BDE 153), or 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209) (Branchi et al. 2001, 2002; Eriksson et al. 1999, 2001a, 2002a; Viberg et al. 2001a, 2001b, 2002a, 2002b, 2003a). Most of these studies used similar single oral dose experimental designs and evaluated spontaneous motor behavior and swim maze performance at 2–6 months of age. The findings collectively indicate that the nervous system is a target of particular PBDE congeners during a defined critical phase of neonatal brain development, as shown by mild impairments in spontaneous motor behavior and learning and memory in older mice. One study used a different experimental design in which mice were exposed to BDE 99 from GD 6 to PND 21, and were evaluated using a variety of somatic (body weight gain, hair growth, day of eyelid and ear opening, day of incisor eruption) and neurobehavioral (righting reflex, forelimb stick grasping reflex, forelimb placing reflexes, negative geotaxis, screen grasping and climbing, pole grasping, ultrasonic vocalizations, homing test) end points during PNDs 2–22, as well as spontaneous activity endpoints on PNDs 22–120 (Branchi et al. 2001, 2002). Findings were suggestive of delayed sensorimotor development and altered spontaneous behavior.

Additional oral studies using comprehensive neurobehavioral test batteries are needed to better characterize the potential for PBDEs to cause neurotoxic effects in humans. Based on the limited available information (predominantly study abstracts), studies evaluating effects of exposure to lower-brominated PBDEs and decaBDE commercial mixtures during critical postnatal periods of brain development would be particularly useful.,

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

(BDE 47) and plasma TSH after age adjustment, but BDE 47 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. No epidemiological data on PBDEs are available for non-oral exposure routes.

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, both the lower PBDEs and decaBDE, to induce these and other kinds of effects as well as the relationship between PDBE body burden and the observed 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 (Blanck et al. 2000b; Brilliant et al. 1978; Humphrey and Hayner 1975; Lambert et al. 1990; Landrigan et al. 1979; 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. It should be noted, however, that solubilities in adipose and breast milk are likely to vary with the congener; for example, decaBDE is much less soluble in adipose than pentaBDE. These differences must be kept carefully in mind when designing studies evaluating PBDE 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). However, using thyroid changes as a biomarker may not be reliable, as thyroid changes are not specific to exposure to PBDEs and the effects associated with the thyroid in non-clinical studies are likely specific to the rodent and may or may not be directly relevant to the human. 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 monobromo-biphenyls 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 commercial 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. There are still data gaps in the toxicokinetics of decaBDE, including an incomplete understanding of 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 (BB 153), 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 (Blanck et al. 2000b; Lambert et al. 1990; Rosen et al. 1995); one possible reason for this difference is differences in body fat between humans and laboratory rodents resulting in a different distribution of the administered compound. 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.

The extent that PBDEs affect circulating levels of thyroid T_4 or T_3 might vary with species and rats are often regarded as more sensitive than humans. The main basis for this opinion seems to be studies showing that PBDEs affect binding of thyroid hormones to transthyretin (TTR), the primary transport protein in rats. Because TTR is not the major transport protein in humans, the findings have been interpreted as evidence that humans will be less sensitive than rats to thryoid effects of PBDEs. As discussed in Section 5.5.3, the greater sensitivity of rats is thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid, and to a more rapid clearance of secreted hormone in the rat; the latter being, in part, related to the absence of thyroid binding globulin (TBG) in rats. Whereas TTR is the major thyroid hormone binding protein in rats, TBG is the main binding protein in humans and most other mammals. Specific evidence is needed to determine whether PBDEs are likely to affect thyroid function in humans, or if humans are less sensitive to these effects than rats.

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 AhR 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 AhR-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 (BDE 47) and 2,2',4,4',5-pentaBDE (BDE 99) (Eriksson et al. 1998, 1999, 2001a, 2002a). Effects were observed in adult 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, 2002a). 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 Section 8.8.1 Identification of Data Needs: Exposures of Children.

5.12.3 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 U.S. government agencies, are listed in Table 5-9.

The Great Lakes Chemical Corporation is collaboratively working with Health Canada to assess potential effects of pentaBDE using a three-tier study approach (Biesemeier 2004). The first tier study, a 28-day repeated oral (gavage) toxicity study in rats, has been completed, but the draft report was not available as of June 2004. The basis of this study was mainly to serve in selecting gavage dose levels for the second

Table 5-9. Ongoing Studies on the Health Effects of PBBs and PBDEs

Investigator	Affiliation	Research description	Sponsor	Source
Anderson HA	Wisconsin Department of Health and Family Services, Madison, Wisconsin	To characterize human exposures to PCBs, PBDEs, and DDT from Great Lakes fish consumption and to determine mechanisms by which PBDEs in Great Lakes fish may act separately or synergistically with PCB exposure to impair human thyroid function	EPA	EPA 2004d
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[a]	FEDRIP 2002
Hites RA and Bigsby M	Indiana University, Bloomington, Indiana	Compare the concentration of PBDEs in infants and analyze sediments and fish in the Great Lakes	EPA	EPA 2004d
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	FEDRIP 2003
Karmaus W et al.	Michigan State University, East Lansing, Michigan	An effort to determine if exposure to halogenated organic compounds (including PBBs and PBDEs) via breastfeeding creates a risk to the immune system of the child	EPA	EPA 2004d
Ludewig G	University of Kentucky, Lexington, Kentucky	A multispecies approach to analyze the toxic effects of PBDEs on organs and development	EPA	FEDRIP 2002
Marcus M	Emory University, Atlanta, Georgia	Investigation of the effect PBBs have on pubertal development, reproductive health, and ovarian function	NIEHS	FEDRIP 2003
Omann GM	Department of Veterans Affairs, Washington, DC	The immunotoxicological potential of PBDEs found in the environment will be assessed using fish immune cells in an *in vitro* model	Department of Veteran Affairs	FEDRIP 2003
Palmer BD	University of Kentucky Medical Center, Lexington, Kentucky	Multidisciplinary/multispecies investigation of end points and mechanisms of action for PBDEs and PCDEs, including structure-activity relationships for endocrine disruption	NIEHS/EPA[a]	FEDRIP 2002
Raymer JH et al.	Research Triangle Institute, Research Triangle Park, North Carolina	Development of a PBPK animal model for PBDEs to estimate fetal exposure in humans and to determine the validity of the model by creating/using new analytical methods using cord blood and meconium	EPA	EPA 2004d

Table 5-9. Ongoing Studies on the Health Effects of PBBs and PBDEs

Investigator	Affiliation	Research description	Sponsor	Source
Robertson L	University of Kentucky Medical Center, Lexington, Kentucky	Laboratory synthesis of pure PBDE and PCDE congeners and their metabolites	NIEHS/EPA[a]	FEDRIP 2002
Sikka HC	State University of New York College at Buffalo, Buffalo, New York	Disposition and metabolism of PBDEs in fish	NOAA[b]	FEDRIP 2002
Trosko JE	Michigan State University, East Lansing, Michigan	Epigenic effects of PBBs and other environmental toxicants on cellular communication pathways	NIEHS/EPA[a]	FEDRIP 2002
Vos J	Bilthoven, Netherlands	Risk assessment of brominated flame retardants for human health and wildlife	EU	EU 2004
Willett LB	Ohio State Universities, Wooster, Ohio	Develop methods to monitor the occurrence of PBBs and other xenobiotics in the environment of cattle; create methods that will reduce or eliminate exposure of cattle and the food products they produce to these xenobiotics; determine mechanisms by which xenobiotics are transported, bound, and mobilized *in vivo*; describe the pharmacokinetics; and to study target organ modifications in cattle caused by xenobiotic chemicals that result in cellular or metabolic alterations	Department of Agriculture	FEDRIP 2003

[a]NIEHS/EPA Superfund Basic Research Program
[b]National Sea Grant College Program

DDT = dichlorodiphenyltrichloroethane; EPA = U.S. Environmental Protection Agency; EU = European Union; NIEHS = National Institute of Environmental Health Sciences; NOAA = National Oceanic and Atmospheric Administration; PCB = polychlorinated biphenyls; PBPK = physiologically based pharmacokinetic; USDA = U.S. Department of Agriculture

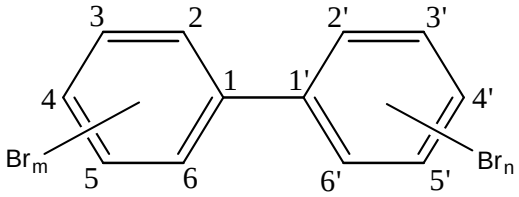
tier study, a one-generation reproductive study in rats, of which the draft protocol is currently being written (as of June 2004). This protocol is being drafted with a pharmacokinetic segment, but it has not yet been confirmed whether it will be retained in the final study design. The results of the one-generation study will be used to select gavage dose levels for the third tier study, a two-generation reproductive study in rats with endocrine, developmental neurobehavioral, and other end point segments. The entire program is not expected to be completed until near the end of 2005.

NTP is in the process of designing a study to assess the toxicity of tetraBDE (NTP 2004).

6. CHEMICAL AND PHYSICAL INFORMATION

6.1 CHEMICAL IDENTITY

Polybrominated Biphenyls. PBBs are a class of structurally similar brominated hydrocarbons in which 2–10 bromine atoms are attached to the biphenyl molecule. Monobrominated structures (i.e., one bromine atom attached to the molecule) are often included when describing PBBs. The general chemical structure of PBBs is shown below:



where m + n = 1–10

It can be seen from the structure that a large number of brominated compounds are possible. The 209 possible compounds for PBBs are called "congeners". However, the number of PBB congeners that actually exist in commercial PBB mixtures is much less compared to polychlorinated biphenyls (PCBs). Typically, only a subset of the 209 possible congeners is observed for PBBs. PBBs can be categorized by degree of bromination. The term "homolog" is used to refer to all PBBs with the same number of bromines (e.g., tribromobiphenyls). Based on the number of bromine substituents, there are 10 homologous groups of PBBs (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 group of dibromobiphenyl homologs contains 12 isomers. The numbering system for PBBs is also shown above. Positions 2, 2', 6, and 6' are called *ortho* positions, positions 3, 3', 5, and 5' are called *meta* positions, and positions 4 and 4' are called *para* positions. 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=0°) and nonplanar (the two benzene rings are in perpendicular planes to each other; dihedral angle=90°). 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 a configuration with a larger dihedral angle or a 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 >0°) or "near" planar configuration. These

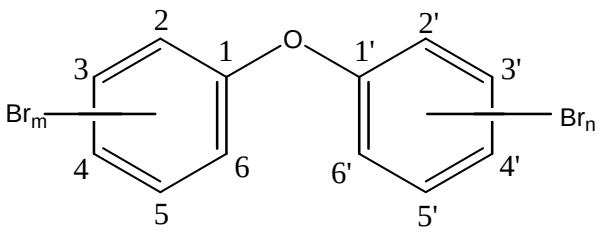
molecules are referred to as planar or coplanar congeners. The benzene rings of other congeners cannot assume a planar or coplanar configuration and are referred to as nonplanar congeners (Hardy 2002).

Like PCBs, the 209 congeners for PBBs are arranged in ascending numerical order using a numbering system developed by Ballschmiter and Zell (1980) that follows the IUPAC rules of substituent characterization of biphenyls. The resulting numbers assigned by Ballschmiter and Zell (which are also referred to as congener, IUPAC, or BZ numbers) are widely used for identifying individual congeners of PBBs. For example, the PBB congener, 2,2',4,4',5,5'-hexabromobiphenyl, may be referred to as BB 153 in this document. The identities of several PBB congeners are shown in Table 6-1 (WHO 1994a, 1994b).

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). However, the FireMaster trade name has also been used for other brominated flame retardants using different numerical designations. Other former 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).

The chemical identities of hexabromobiphenyl, octabromobiphenyl, decabromobiphenyl (BB 209), and BB 153, the most abundant congener in commercial FireMaster FF-1 and FireMaster BP-6, are listed in Table 6-2.

Polybrominated Diphenyl Ethers. PBDEs are a class of structurally similar brominated hydrocarbons, 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 PBDEs. The general chemical structure of PBDEs is shown below:



where m + n = 1–10

Table 6-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners

IUPAC No.[a]	Compound/ substituents	CAS No.[b]	
		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	2,2’	13029-09-9	
5	2,3	115245-06-2	
6	2,3’	49602-90-6	
7	2,4	53592-10-2	
8	2,4’	49602-91-7	
9	2,5	57422-77-2	
10	2,6	59080-32-9	
11	3,3’	16400-51-4	
12	3,4	60108-72-7	
13	3,4’	57186-90-0	
14	3,5	16372-96-6	
15	4,4’	92-86-4	
	Tribromobiphenyl	51202-79-0	49690-94-0
16	2,2’,3		
17	2,2’,4		
18	2,2’,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	2,3’,5	59080-35-2	
27	2,3’,6		
28	2,4,4’	6430-90-6	
29	2,4,5	115245-07-3	
30	2,4,6	59080-33-0	
31	2,4’,5	59080-36-3	
32	2,4’,6	64258-03-3	
33	2’,3,4		
34	2’,3,5		
35	3,3’,4		

Table 6-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners

IUPAC No.[a]	Compound/ substituents	CAS No.[b]	
		Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
36	3,3',5		
37	3,4,4'	6683-35-8	
38	3,4,5	115245-08-4	
39	3,4',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	2,2',4,4'	66115-57-9	
48	2,2',4,5		
49	2,2',4,5'	60044-24-8	
50	2,2',4,6		
51	2,2',4,6'	97038-95-4	
52	2,2',5,5'	59080-37-4	
53	2,2',5,6'	60044-25-9	
54	2,2',6,6'	97038-96-5	
55	2,3,3',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		
66	2,3',4,4'	84303-45-7	
67	2,3',4,5		
68	2,3',4,5'		
69	2,3',4,6		
70	2,3',4',5	59080-38-5	
71	2,3',4',6		
72	2,3',5,5'		
73	2,3',5',6		
74	2,4,4',5		

Table 6-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners

IUPAC No.[a]	Compound/ substituents	CAS No.[b]	
		Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
75	2,4,4',6	64258-02-2	
76	2',3,4,5		
77	3,3',4,4'	77102-82-0	
78	3,3',4,5		
79	3,3',4,5'	97038-98-7	
80	3,3',5,5'	16400-50-3	
81	3,4,4',5	59589-92-3	
	Pentabromobiphenyl	56307-79-0	32534-81-9
82	2,2',3,3',4		
83	2,2',3,3',5		
84	2,2',3,3',6		
85	2,2',3,4,4'		
86	2,2',3,4,5		
87	2,2',3,4,5'		
88	2,2',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	2,2',3,5',6	88700-05-4	
96	2,2',3,6,6'		
97	2,2',3',4,5		
98	2,2',3',4,6		
99	2,2',4,4',5	81397-99-1	
100	2,2',4,4',6	97038-97-6	
101	2,2',4,5,5'	67888-96-4	
102	2,2',4,5,6'	80274-92-6	
103	2,2',4,5',6	59080-39-6	
104	2,2',4,6,6'	97063-75-7	
105	2,3,3',4,4'		
106	2,3,3',4,5		
107	2,3,3',4',5		
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		

Table 6-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners

IUPAC No.[a]	Compound/ substituents	CAS No.[b]	
		Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
114	2,3,4,4',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	2,3',4,4',5	6788-97-5	
119	2,3',4,4',6	86029-64-3	
120	2,3',4,5,5'	80407-70-1	
121	2,3',4,5',6		
122	2',3,3',4,5		
123	2',3,4,4',5	74114-77-5	
124	2',3,4,5,5'		
125	2',3,4,5,6'		
126	3,3',4,4',5	84303-46-8	
127	3,3',4,5,5'	81902-33-2	
	Hexabromobiphenyl	36355-01-8	36483-60-0
128	2,2',3,3',4,4'	82865-89-2	
129	2,2'3,3',4,5		
130	2,2',3,3',4,5'	82865-90-5	
131	2,2',3,3',4,6		
132	2,2',3,3',4,6'	119264-50-5	
133	2,2',3,3',5,5'	55066-76-7	
134	2,2',3,3',5,6		
135	2,2',3,3',5,6'	119264-51-6	
136	2,2',3,3',6,6'		
137	2,2',3,4,4',5	81381-52-4	
138	2,2',3,4,4',5'	67888-98-6	
139	2,2',3,4,4',6		
140	2,2',3,4,4',6'		
141	2,2',3,4,5,5'	120991-47-1	
142	2,2',3,4,5,6		
143	2,2',3,4,5,6'		
144	2,2',3,4,5',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	2,2',3,4',5',6	69278-59-7	
150	2,2',3,4',5,6'	93261-83-7	
151	2,2',3,5,5',6	119264-53-8	
152	2,2',3,5,6,6'		

Table 6-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners

IUPAC No.[a]	Compound/ substituents	CAS No.[b]	
		Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
153	2,2',4,4',5,5'	59080-40-9	
154	2,2',4,4',5,6'	36402-15-0	
155	2,2',4,4',6,6'	59261-08-4	
156	2,3,3',4,4',5	77607-09-1	
157	2,3,3',4,4',5'	84303-47-9	
158	2,3,3',4,4',6		
159	2,3,3',4,5,5'	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	2,3,3',4',5',6	82865-91-5	
165	2,3,3',5,5',6		
166	2,3,4,4',5,6		
167	2,3',4,4',5,5'	67888-99-7	
168	2,3',4,4',5',6	84303-48-0	
169	3,3',4,4',5,5'	60044-26-0	
	Heptabromobiphenyl	35194-78-6	68928-80-3
170	2,2',3,3',4,4',5	69278-60-0	
171	2,2',3,3',4,4',6		
172	2,2',3,3',4,5,5'	82865-92-7	
173	2,2',3,3',4,5,6		
174	2,2',3,3',4,5,6'	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	2,2',3,3',5,5',6	119264-54-9	
179	2,2',3,3',5,6,6'		
180	2,2',3,4,4',5,5'	67733-52-2	
181	2,2',3,4,4',5,6		
182	2,2',3,4,4',5,6'	119264-55-0	
183	2,2',3,4,4',5',6		
184	2,2',3,4,4',6,6'	119264-56-1	
185	2,2',3,4,5,5',6		
186	2,2',3,4,5,6,6'	119264-57-2	
187	2,2',3,4',5,5',6	84303-49-1	
188	2,2',3,4',5,6,6'	119264-58-3	
189	2,3,3',4,4',5,5'	88700-06-5	
190	2,3,3',4,4',5,6	79682-25-0	
191	2,3,3',4,4',5',6		

Table 6-1. Chemical Identity of Polybrominated Biphenyl (PBB) and Polybrominated Diphenyl Ether (PBDE) Congeners

IUPAC No.[a]	Compound/ substituents	CAS No.[b]	
		Brominated biphenyls (BB)[c]	Brominated diphenyl ethers (BDE)[d]
192	2,3,3',4,5,5',6		
193	2,3,3',4',5,5',6		
	Octabromobiphenyl	27858-07-7	32536-52-0
194	2,2',3,3',4,4',5,5'	67889-00-3	
195	2,2',3,3',4,4',5,6		
196	2,2',3,3',4,4',5',6		
197	2,2',3,3',4,4',6,6'	119264-59-4	
198	2,2',3,3',4,5,5',6		
199	2,2',3,3',4,5,6,6'		
200	2,2',3,3',4,5,6,6'	119264-60-7	
201	2,2',3,3',4,5',6,6'	69887-11-2	
202	2,2',3,3',5,5',6,6'	59080-41-0	
203	2,2',3,4,4',5,5',6		
204	2,2',3,4,4',5,6,6'	119264-61-8	
205	2,3,3',4,4',5,5',6		
	Nonabromobiphenyl	27753-52-2	63936-56-1
206	2,2',3,3',4,4',5,5',6	69278-62-2	
207	2,2',3,3',4,4',5,6,6'	119264-62-9	
208	2,2',3,3',4,5,5',6,6'	119264-63-0	
	Decabromobiphenyl	13654-09-6	1163-19-5
209	2,2',3,3',4,4',5,5',6,6'	13654-09-6	1163-19-5

[a]Ballschmiter and Zell 1980
[b]Not all PBBs have been assigned CAS numbers; with the exception of BDE 209, no CAS numbers were identified for the PBDE class.
[c]WHO 1994b
[d]WHO 1994a

Table 6-2. Chemical Identity of Selected PBBs[a]

Characteristic	Hexabromo-biphenyl	Octabromo-biphenyl	Decabromo-biphenyl	2,2',4,4'5,5'-Hexa-bromobiphenyl
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'hexa-bromo-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				
Identification numbers:				
CAS registry	59536-65-1 (BP-6); 67774-32-7 (FF-1); 36355-01-8 (hexa-bromo mixture)	27858-07-7 (octo-bromo mixture) 61288-13-9 (Bromkal 80)	13654-09-6 (pure and technical)	59080-40-9
NIOSH RTECS	LK 5060000 (BP-6); LK 5065000 (FF-1)	DV 570000 (octa-bromo 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	2913
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.

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

It can be seen from the structure that a large number of brominated compounds are possible. The 209 possible compounds for PBDEs are called “congeners”. However, the number of PBDE congeners that actually exist in commercial PBDE mixtures are much less compared to PCBs. Typically, only a subset of the 209 possible congeners is observed for PBDEs. PBDEs can also be categorized by degree of bromination. The term “homolog” is used to refer to all PBDEs with the same number of bromines (e.g., tribromodiphenyl ether refers to PBDEs containing only three bromine atoms). Based on the number of bromine substituents, there are 10 homologous groups of 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 group of dibromodiphenyl ether homologs contains 12 isomers. The numbering system for PBDEs is also shown above. The structures of representative PBB and PBDE molecules appear similar when drawn in one dimension. However, there are important three-dimensional differences in their structures due to the ether linkage and location/number of halogen atoms. The *ortho* positions of the aromatic rings must be nonhalogen-substituted for a diphenyl ether molecule to assume a planar or near planar configuration. Halogen substitution of the diphenyl ether molecule in the *ortho* position (2,2’,6,6’) will force the aromatic rings orthogonal to one another (e.g., the phenyl rings will be positioned in space with a dihedral angle >0°). This is particularly evident for decabromodiphenyl ether, which is predicted to have a dihedral angle of ca. 90° and a high barrier to rotation around the ether linkage preventing this molecule from assuming a planar configuration. The benzene rings of non-*ortho* substituted PBDEs may assume a small dihedral angle (in which the dihedral angle is small, but >0°) or “near” planar configuration. These molecules are referred to as planar or coplanar congeners (Hardy 2002).

Like PCBs, the 209 congeners for 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 assigned by Ballschmiter and Zell (which are also referred to as congener, IUPAC, or BZ numbers) are widely used for identifying individual congeners of PBDEs. For example, the PBDE congener, 2,2',4,4'-tetrabromodiphenyl ether may be referred to as BDE 47 in this document. The identities of several PBDE congeners are shown in Table 6-1 (WHO 1994a, 1994b).

In the United States, Albemarle Corporation and Great Lakes Chemical Corporation market mixtures of PBDEs under trade names (e.g., DE-60F, DE-61, DE-62, and DE-71 for pentaBDE mixtures; DE-79 for octaBDE mixtures; and DE 83R, Saytex 102E for decaBDE mixtures). There are also several trade

names used by producers from Europe and Japan for the BDE mixtures. The chemical identities of commercial mixtures of penta-, octa-, and decabromodiphenyl ethers are listed in Table 6-3 (WHO 1994a).

Various synonyms and abbreviations for PBDEs exist in the literature and are shown below:

polybrominated biphenyl ethers	=	Polybromobiphenyl ethers	=	PBBE
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

6.2 PHYSICAL AND CHEMICAL PROPERTIES

Polybrominated Biphenyls. Information found in the literature regarding the physical and chemical properties of hexabromobiphenyl, octabromobiphenyl, decabromobiphenyl, and BB 153 is presented in Table 6-4. The data for the properties listed in Table 6-4 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. However, recent physical and chemical property data have been reported for hexabromobiphenyl in Tittlemier et al. (2002).

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

Table 6-3. Chemical Identity of 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=4–6	$C_{12}H_{10-y}Br_yO$ where y=6–9	$C_{12}Br_{10}O$
Chemical structure			
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
OHM/TADS	No data	No data	No data
DOT/UN/IMCO shipping	No data	No data	No data
HSDB	7109	7110	2911
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

Table 6-4. 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 °C	200–250 °C; 367–367 °C[b] (for industrial product)	380–386 °C	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; 3 µg/L[c]	20–30 µg/L	Insoluble	11 µg/L[d]
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[e]	5.53	8.58[f]	9.10 (estimated)[d]
Log K_{oc}	3.33–3.87[g]	No data	No data	5.088[d]
Vapor pressure	5.2×10^{-8} mmHg at 25 °C[h]; 5.6×10^{-6} mm Hg (liquid sub-cooled)[c]	7×10^{-11} mmHg at 28 °C[i]	No data	7.6×10^{-5} mm Hg at 90 °C[d]
Henry's law constant	3.9×10^{-6} atm-m^3/mol[j]; 1.38×10^{-6} atm-m^3/mol[c]	No data	No data	5.7×10^{-3} atm-m^3/mol[d]
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
Conversion factors	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.			
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]Tittlemier et al. 2002
[d]Hardy (2002)
[e]Doucette and Andren 1988
[f]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.
[g]Estimated from the Freundlich adsorption constants given by Jacobs et al. (1978).
[h]Jacobs et al. 1976
[i]Waritz et al. 1977
[j]Estimated from the ratio of vapor pressure and water solubility.

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 6-5 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 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 decabromobiphenyl 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).

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 °C 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 °C 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 °C 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

Table 6-5. Identified PBB Congeners in FireMaster® BP-6 and FireMaster® FF-1

IUPAC No.[a]	Structure	Percent composition of FireMaster BP-6	Percent 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
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

Table 6-5. Identified PBB Congeners in FireMaster® BP-6 and FireMaster® FF-1

IUPAC No.[a]	Structure	Percent composition of		References
		FireMaster BP-6	FireMaster FF-1	
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

of PBB hydrolysis under much milder environmental conditions remains unknown (Pomerantz et al. 1978).

Hexabromonapthalene has been identified as a toxic contaminant of Firemaster BP-6 or FF-1 at concentration levels of approximately 150 ppm (Birnbaum et al. 1983). Previously reported to be a single compound, hexabromonapthalene was shown to be a 60:40 mixture of 1,2,3,4,6,7-hexabromonaphthalene and 2,3,4,5,6,7-hexabromonaphthalene.

Polybrominated Diphenyl Ethers. Information found in the literature regarding the physical and chemical properties of selected technical PBDE mixtures is presented in Table 6-6. Recent information regarding the vapor pressure, water solubility, Henry's Law constant, and log K_{ow} of some PBDE congeners is presented in Table 6-7.

Commercially available product mixtures of PBDEs (see Table 6-3) 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 tetrabromodiphenyl ether (24–38%) and pentabromodiphenyl ether (50–62%) homologs with small amounts of hexabromodiphenyl ether (4–8%) and trace amounts of tribromodiphenyl ether (0–1%) homologs. In this document, the commercial mixture of pentaBDE may be called "the commercial pentaBDE mixture," "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 6.1). 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 may be called "the commercial octaBDE mixture," "technical octaBDE," or "technical OBDE" to distinguish this mixture of different homologs from the octaBDE homolog, which refers to polybrominated diphenyl ethers with only eight bromine atoms (see Section 6.1). 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 may be called "the commercial decaBDE mixture," "technical decaBDE," or "technical DeBDE" which represents 97% BDE 209 congener with 3% nona- and octaBDE homolog impurities. The composition of commercial octaBDE (e.g., DE-79) is <10% of nonaBDE, <33% of octaBDE, <45% of heptaBDE, and <12% of hexaBDE (i.e., 2% of BDE 154 and 14% of BDE 153)

Table 6-6. 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 °C (commercial)[b]	85–89 °C (commercial)[c]; 200 °C (range, 167–257)[a]; 79–87 °C[a]; 170–220 °C[a]	290–306 °C[a]
Boiling point	>300 °C (decomposition starts above 200 °C)[a,b]	Decomposes at >330 °C (commercial)[c]	Decomposes at >320, >400, and 425 °C[a]
Density (g/mL)	2.28 at 25 °C[a]; 2.25–2.28[b]	2.76[a]; 2.8 (commercial)[c]	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 (commercial)[b,d]; 2.4 µg/L (pentabromodiphenyl ether component)[b]; 10.9 µg/L (tetrabromodiphenyl ether component)[b]	<1 ppb at 25 °C (commercial)[c]; 1.98 µg/L (heptabromodiphenyl ether component)[c]	<0.1 µg/L[g]
Organic solvent(s)	10 g/kg methanol; miscible in toluene[d]	acetone (20 g/L); benzene (200 g/L); methanol (2 g/L) all at 25 °C[a]	acetone (0.05%), benzene (0.48%), methylene bromide (0.42%), xylene (0.87%), and toluene (0.2%)[e]
Partition coefficients:			
Log K_{ow}	6.64–6.97[d]; 6.57 (commercial)[b]	6.29 (commercial)[c]	6.265[e]
Log K_{oc}	4.89-5.10[f]	5.92-6.22[f]	6.80[f]
Vapor pressure	$2.2x10^{-7}$–$5.5x10^{-7}$ mm Hg at 25 °C[d]; $3.5x10^{-7}$ mm Hg (commercial)[b]	$9.0x10^{-10}$–$1.7x10^{-9}$ mm Hg at 25 °C[d]; $4.9x10^{-8}$ mm Hg at 21 °C (commercial)[c]	$3.2x10^{-8}$ mm Hg[g]; $3.47x10^{-8}$ mm Hg[e]
Henry's Law constant (atm-m^3/mole)	$1.2x10^{-5h}$; $1.2x10^{-6f}$; $3.5x10^{-6f}$	$7.5x10^{-8f}$; $2.6x10^{-7f}$	$1.62x10^{-6h}$; $1.93x10^{-8d}$; $1.2x10^{-8f}$; $4.4x10^{-8f}$
Autoignition temperature	Decomposes above 200 °C[b,d]	Decomposes above 330 °C (commercial)[c]	Not applicable[a]
Flashpoint	No data	No data	None
Flammability limits	Not applicable (flame retardant)[b,d]	Not applicable (flame retardant)[c]	Non-flammable[a]

Table 6-6. Physical and Chemical Properties of Technical PBDE Mixtures

Property	Pentabromodiphenyl ether	Octabromodiphenyl ether	Decabromodiphenyl ether
Conversion factors	1 ppm=23.48 mg/m^3 at 20 °C[d]	No data	No data
Explosive limits	None[b,g]	None[c]	No data

[a] WHO 1994a
[b] ENVIRON 2003a
[c] ENVIRON 2003b
[d] EU 2001
[e] American Chemistry Council 2002
[f] Estimated values were calculated using EPIWIN v3.10 (EPA 2001).
[g] Hardy 2002
[h] Estimate value was calculated using vapor pressure and water solubility values in table.

Table 6-7. Physical and Chemical Properties of Some PBDE Congeners[a,b]

Congener	Vapor pressure (mm Hg)[a,c]	Water solubility (µg/L)[a]	Henry's Law constant (atm m^3/mol)[a]	Log K_{ow}[b]
BDE-3	$1.94x10^{-3}$	–	–	–
BDE-15	$1.30x10^{-4}$	130	$2.07254x10^{-4}$	–
BDE-17	–	–	–	5.74
BDE-28	$1.64x10^{-5}$	70	$5.03331x10^{-5}$	5.94
BDE-47	$1.40x10^{-6}$	15	$1.48038x10^{-5}$	6.81
BDE-66	$9.15x10^{-7}$	18	$4.93461x10^{-6}$	–
BDE-77	$5.09x10^{-7}$	6	$1.18431x10^{-5}$	–
BDE-85	$7.40x10^{-8}$	6	$1.08562x10^{-6}$	–
BDE-99	$1.32x10^{-7}$	9	$2.26992x10^{-6}$	7.32
BDE-100	$2.15x10^{-7}$	40	$6.80977x10^{-7}$	7.24
BDE-138	$1.19x10^{-8}$	–	–	–
BDE-153	$1.57x10^{-8}$	1	$6.61238x10^{-7}$	7.90
BDE-154	$2.85x10^{-8}$	1	$2.36862x10^{-6}$	7.82
BDE-183	$3.51x10^{-9}$	2	$7.30323x10^{-8}$	8.27
BDE-190	$2.12x10^{-9}$	–	–	–

[a]Tittlemier et al. 2002
[b]Braekvelt et al. 2003
[c]liquid sub-cooled vapor pressures

– = No data reported; BDE = brominated diphenyl ether

(ENVIRON 2003b). The composition of commercial pentaBDE (e.g., DE-71) is 4–12% of hexaBDE (i.e., 4% BDE 154 and 6% BDE 153), 50–62% of pentaBDE (i.e., 8% of BDE 100, 43% of BDE 99), 24–38% of tetraBDE (i.e., <1% of BDE 66, <1% of BDE 49, 28% of BDE 47), and 0–1% of triBDE (i.e., >1% of BDE 28/33) (ENVIRON 2003b). The compositions of commercial product mixtures of PBDEs (e.g., technical penta-, octa-, and decaBDE) are given in Table 6-8. The chemical composition of commercial pentaBDE product has been shown to vary over the past 10–20 years and between different commercial products (ENVIRON 2003a).

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). The commercial decaBDE product has been analyzed for trace quantities of 15 2,3,7,8-substituted polybrominated-*p*-dibenzodioxins (PBDDs) and polybrominated dibenzofurans (PBDFs). None of the analytes were present at or above the quantization limits established under an EPA test rule (BFRIP 2002). While in today's commercial PBDE samples, there are not measurable quantities of PBDDs/PBDFs, there are some materials that have reported quantifiable levels of these contaminants. For example, hexabromodibenzofurans have been detected in commercial decaBDE mixtures at concentrations as high as 200 µg/kg. In other PBDE mixtures (e.g., tetra- to hexaBDEs), the sum of tetra-, penta-, and hexabromodibenzofurans were reported at a concentrations of 8,000 µg/kg. In addition, tetra- and pentabromo- *p*-dibenzodioxins have been measured in commercial decaBDE at concentrations of 0.05 and 0.35 µg/kg, respectively (WHO 1998).

When pyrolyzed up to 900 °C, PBDEs may produce PBDFs and 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 (decaBDE) in the temperature range of 400–700 °C (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. 1989a, 1990; Lenoir et al. 1994). However, studies performed in the late 1980's may have suffered from analytical methods that could not differentiate between PBDD/Fs formed (e.g., 2,3,7,8-substituted congeners) and decaBDE which might have artificially elevate levels of PBDFs detected (Ranken et al. 1994).

Table 6-8. Composition of Commercial Brominated Diphenyl Ethers

		Great Lakes				
		Commercial pentaBDE product		Commercial octaBDE product		Commercial decaBDE product
BDE homologue group	BDE congener[a]	2002	Late 1970s – early 1980s	2002	Late 1970s – early 1980s	2002
		DE-71b	Product	DE-79b	Product	DE-83R and DE-83b
DecaBDE (1 congener)	BDE-209	–	0.8	<0.70%	1.6%	>98%
NonaBDE (3 congeners)	–	–	0.2	<10%	13.0%	–
OctaBDE (12 congeners)	–	–	0.3	<33%	30.7%	–
HeptaBDE (24 congeners)	–	–	2.6	<45%	45.1%	–
HexaBDE (42 congeners)		4–12%	13.3	<12%	8.5%	–
	BDE-154	(4%)		(2%)		
	BDE-153	(6%)		(14%)		
PentaBDE (46 congeners)		50–62%	58.1	<0.50%	1.1%	–
	BDE-100	(8%)		(ND)		
	BDE-99	(43%)		(<1%)		
	BDE-85	(–)		(–)		
TetraBDE (42 congeners)		24–38%	24.6	–	–	–
	BDE-66	(<1%)		(ND)		
	BDE-49	(<1%)		(ND)		
	BDE-47	(28%)		(<1%)		
TriBDE (24 congeners)		0–1%	–	–	–	–
	BDE-28/33	(>1%)		(ND)		

Source: ENVIRON 2003b

aIUPAC numbering system
bAs currently produced

– = Data not reported; ( ) = % concentration of congener; BDE = bromodiphenyl ether; ND = Not detected

7. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

7.1 PRODUCTION

Polybrominated Biphenyls. The commercial production of polybrominated biphenyls (PBBs) generally involves bromination of biphenyl, a process involving a much more specific reaction and that 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 2002b). 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 5.2), 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 of PBBs 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 atmospheric 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). As of 2003, in the United States, penta- and octabromodiphenyl ethers (pentaBDE and octaBDE) are produced by the Great Lakes Chemical Corporation in El Dorado, Arkansas (SRI 2002). According to SRI (2002), as of 2003, technical decabromodiphenyl ether (decaBDE) is produced by Albemarle Corporation in Magnolia, Arkansas. Technical PentaBDE is produced commercially in the United States as Great Lakes DE-60F, DE-61, DE-62, and DE-71. Technical octaBDE is produced commercially in the United States as DE-79. Technical decaBDE (BDE 209) is produced commercially in the United States as DE-83R and Saytex 102E. Dead Sea Bromines/Eurobrome and Tosoh are currently producing PBDEs in the Netherlands and Japan, respectively (WHO 1994a). No current estimates of PBDE production quantities were located (SRI 2002).

In 2001, the total market demand for PBDEs in the Americas was 33,100 metric tons (see Table 7-1). Technical decaBDE constituted about 24,500 metric tons (74%), while technical mixtures of octaBDEs and pentaBDEs were 1,500 and 7,100 metric tons (4 and 22 %) of this total, respectively (BSEF 2003). In 2001, the total market demand for PBDEs in the world was 67,390 metric tons. Technical decaBDE constituted about 56,100 metric tons (83%), while technical mixtures of octaBDEs and pentaBDEs were 3,790 and 7,500 metric tons (6 and 11%) of this total, respectively (BSEF 2003). About 98% of the global demand for the technical pentaBDE mixture resides in North America (Hale et al. 2003). The Great Lakes Chemical Corporation recently announced that it is voluntarily phasing out production of

Table 7-1. Total Market Demand of PBDEs by Regions of the World in 2001[a]

	Americas	Europe	Asia	Rest of world	Total
PentaBDE	7,100	150	150	100	7,500
OctaBDE	1,500	610	1,500	180	3,790
DecaBDE	24,500	7,600	23,000	1,050	56,100

Source: BSEF 2003

[a]Data in metric tons

decaBDE = commercial decabrominated diphenyl ether mixture; octaBDE = commercial octabrominated diphenyl ether mixture; pentaBDE = commercial pentabrominated diphenyl ether mixture

pentaDBEs and octaDBEs by the end of 2004. Since there are no other pentaDBE manufacturers in the United States, this decision functionally eliminated U.S. production of this compound (Tullo 2003).

Table 7-2 lists the facilities in each state that manufacture or process technical decaBDE, the intended use, and the range of maximum amounts of technical decaBDE that are stored on-site. There are 141 facilities that produce or process technical decaBDE in the United States (TRI01 2003). The data from the Toxics Release Inventory (TRI) listed in Table 7-2 should be used with caution, however, since only certain types of facilities were required to report. The TRI is not an exhaustive list. Facilities are only required to report to the TRI if they manufacture or process more than 25,000 pounds of a TRI listed chemical during the year, or otherwise use more than 10,000 pounds, and have the equivalent of more than 10 full-time employees. According to the EPA, TRI data have certain limitations. TRI data reflect releases and other waste management of chemicals, and not exposures of the public to those chemicals. TRI data alone are not sufficient to determine exposure or calculate potential adverse effects on human health and the environment.

7.2 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 deca-bromobiphenyl 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 2001, worldwide demands for technical penta-, octa-, and decabromodiphenyl ethers were 7,500, 3,790, and 56,100 metric tons, respectively (see Table 7-1; BSEF 2003).

7.3 USE

Polybrominated Biphenyls. PBBs are no longer used in the United States. In the past, PBBs were used as additive flame retardants 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

Table 7-2. 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	5	1,000	9,999,999	1, 4, 7, 8
CA	5	1,000	999,999	7, 8
CT	3	1,000	99,999	7, 8, 9, 14
FL	2	100	999,999	7
GA	5	100	99,999	2, 3, 5, 7, 8, 11, 12
IL	2	10,000	999,999	7, 8
IN	6	0	99,999	7, 8
KY	2	10,000	99,999	7
LA	1	100,000	999,999	12
MA	12	1,000	99,999	7, 8
MD	1	10,000	99,999	8
MI	5	1,000	9,999,999	7, 8
MN	3	10,000	99,999	7, 8
MO	1	1,000	9,999	7
MS	2	10,000	99,999	7, 8
NC	13	1,000	99,999	7, 8
NE	1	10,000	99,999	8
NH	1	1,000	9,999	7
NJ	4	10,000	999,999	7, 8
NY	3	10,000	99,999	6, 7, 8
OH	10	1,000	999,999	2, 3, 7, 8, 10
PA	7	1,000	9,999,999	7, 8
RI	1	1,000	9,999	7
SC	9	1,000	999,999	7, 8
TN	7	1,000	99,999	7
TX	8	1,000	99,999	1, 2, 3, 7, 8, 12
VA	5	10,000	999,999	7, 8
VT	1	10,000	99,999	2, 5, 7, 12
WA	1	10,000	99,999	8
WI	2	1,000	9,999	7, 8

Source: TRI01 2004

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

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 2002b). 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). As of August 15, 2004, no products containing more than 0.1% penta- or octoBDE by mass can be sold in the European Union (EU 2003b).

The commercial pentaBDE product is used predominantly (95–98%) for flame retardant purposes as an additive in consumer products manufactured by the furniture industry (ENVIRON 2003a). It is used almost exclusively for flame retard flexible polyurethane foam (FPUF), which is used in bed mattresses and cushioning in upholstered products. The commercial pentaBDE is typically used in FPUF as an additive mixture with aromatic phosphate esters (e.g., mixture of 75% pentaBDE and 25% aromatic phosphate esters). Mattress FPUF contains approximately 2–3% flame retardant mixture and cushion FPUF contains 3–5% flame retardant mixture (ENVIRON 2003a). Scrap materials from both industries have been used as padding beneath carpets, and as a result, carpet padding likely contains 3–5% flame retardant mixture. However, not all of the FPUF found in cushion, mattress, and carpet padding products are treated with commercial pentaBDE. Approximately 7.5% of the more than 2.1 billion pounds of FPUF produced annually in the United States uses the commercial pentaBDE product as a flame retardant additive (ENVIRON 2003a). The majority of FPUF products treated with the commercial pentaBDE product are sold in California, the only state requiring by law that upholstered products achieve a prescribed level of ignition resistance (ENVIRON 2003a). A small percentage of pentaBDE is used in commercial adhesive products. Historical uses of commercial pentaBDE included coatings for specialty

textiles, printed circuit board components, hydraulic and oilfield completion fluids, and rubber products. However, all of these uses have been discontinued in recent years. In the past, automotive and airplane seating cushions contained FPUF with commercial pentaBDE. However, this use was discontinued in the early 1990s. Prior to approximately 1990, the commercial pentaBDE product may have been used in small quantities as a flame retardant in specialty fire-resistant clothing using polyurethane treatment and in polyurethane coatings in carpets (ENVIRON 2003a). With the exception of small quantities used in rigid polyurethane elastomers for instrument casings, the commercial pentaBDE product is not used in electronic equipment. However, it is possible that electronic equipment containing pentaBDE produced in other countries (principally Asian) could find its way into the United States (EU 2001). The commercial pentaBDE product is not used in acrylonitrile-butadiene-styrene plastics or electronics equipment (ENVIRON 2003a). Other applications of pentaBDE may include use as an additive flame retardant for flexible polyester polyurethane foam, rigid polyurethane, rigid polyurethane foams, epoxies, laminates, adhesives, coatings, unsaturated polyesters, and flexible polyvinyl chloride (PVC) compounds (Great Lakes Chemical Corporation 2004a).

The commercial octaBDE is used by the plastics industry as an additive flame retardant for manufactured products. It is used almost exclusively to flame retard acrylonitrile-butadiene-styrene (ABS) terpolymers used in computer casings and monitors (ENVIRON 2003b). In the European Union, approximately 95% of the total commercial octaBDE product sold to the electronics and plastics industries is used in ABS (EU 2003a). Although data are not available in the United States, similar volumes are expected (ENVIRON 2003b). The commercial octaBDE product is used in ABS products at 12–18% weight loadings of flame retardant. OctaBDE is always used as a flame retardant in conjunction with antimony trioxide. Other minor uses for octaBDE, accounting for the remaining 5% use, include high impact polystyrene (HIPS), polybutylene terephthalate (PBT), and polyamide polymers (EU 2003a). Other possible applications of octaBDE include use as additive flame retardant in polycarbonate, phenol-formaldehyde resins, unsaturated polyesters (EU 2003a), nylon, thermoplastic elastomers, polyolefins, adhesives, and coatings (Great Lakes Chemical Corporation 2004b).

The commercial decaBDE product is an additive flame retardant used in a variety of polymer applications. Industry information indicates that decaBDE is used at loadings of 10–15% weight in polymers and is always used in conjunction with antimony trioxide (EU 2002). The major application for decaBDE is in high impact polystyrene (HIPS), which is used in the television industry for cabinet backs. It is also used for a large number of other polymers with end-uses in electrical and electronic equipment (e.g., computers, connectors, electrical boxes, wire and cable, etc.). Examples include polypropylene (for

electronics), acetate copolymers (ethylene-vinyl acetate [EVA] and other copolymers for wire and cable), ethyelene-propylene-diene terpolymer (EPDM) and thermoplastic elastomers (for wire and cable), and polyester resins (for electronics). Other minor uses include styrenic rubbers, polycarbonates, polyamides, and terphthalates, and small amounts are reported to be used in hot-melt adhesives (EU 2002). Other possible applications of decaBDE are as an additive flame retardant for low-density polyethylene (LDPE), unsaturated polyester, epoxy, coatings, adhesive systems, and backcoatings for fabrics (Great Lakes Chemical Corporation 2004c). Upholstered furniture in commercial settings in the United States is required to meet federal flammability standards and may utilize upholstery textiles that are flame retarded with a backcoating containing decaBDE at 5 mg/m^2 (BFRIP 2002).

Currently, technical decaBDE is the most widely used PBDE flame retardant worldwide, followed by technical pentaDBE. About 95% of technical pentaBDE is used in the manufacture of flexible polyurethane foam used as cushioning in upholstery. Flexible polyurethane foam is also used in foam-based laminated automotive applications, for domestic furniture, and in foam-based packaging (EU 2001). Technical octaBDE 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 octaBDE is also used in adhesives and coatings applications (WHO 1994a). Technical decaBDE is primarily used in combination with antimony trioxide in high impact polystyrene (HIPS) applications, such as electronic enclosures (e.g., television cabinets). Other minor uses of technical decaBDE are in textile applications to flame retard upholstery fabric (e.g., polyester fiber additives and coatings for automobile fabric, tarpaulins, and tents) (WHO 1994a).

7.4 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).

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 currently used as flame retardants in a wide range of consumer products (see Section 7.3). In the United States, waste disposal of PBDE-containing consumer products is described as transfers to disposal (landfill), recycling, energy recovery (incineration), or publicly owned treatment works (POTWs) (Darnerud et al. 2001). No other information was located on the past or present volumes of PBDE-containing consumer products disposed of by each method of waste transfer.

Landfill disposal of plastic consumables containing pentaBDE (e.g., polyurethane foams), octaBDE (e.g., computer monitors) and decaBDE (e.g., televisions) to landfills is likely to increase in the United States due to their limited useful lifespan. Given that all PBDEs have low water solubilities (see Table 6-6), the potential for leaching of PBDE from landfills appears to be small (EU 2002). Well-designed landfills will include measures to minimize leaching and those measures would also be effective in minimizing the leaching of any PBDE particulates present (EU 2002).

PBDEs in sewage are disposed of in publicly owned treatment works (POTWs), as indicated by analysis of sewage sludge from various countries. Tetra- and penta-BDEs have been detected in sewage sludge from POTWs in the United States with the composition of PBDEs in these biosolids closely resembling the DE-71 (i.e., pentaBDE) commercial formulation (La Guardia et al. 2000). Hale et al. (2001b) reported that the practice of land application of sewage sludges may introduce significant amounts of the pentaBDE commercial mixture into the environment, although levels have not yet been quantified.

Incineration of waste materials containing PBDEs is thought to be a potential source of PBDFs and/or PBDDs. The formation of PBDFs/PBDDs as a result of uncontrolled landfill fires is also a possibility, although 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. Sakai et al. (2001a) measured residues of PBDFs/PBDDs in effluents from a municipal incineration plant burning domestic waste materials. Flue gases, fly ash, and bottom ash reportedly contained PBDFs/PBDDs at concentration ranges of 0.28–3.3 ng/N m^3, 0.082–13 ng/g, and 0.0058–27 ng/g, respectively. However, modern, properly operated municipal waste incineration should not emit significant quantities of PBDFs/PBDDs, regardless of the composition of municipal waste (WHO 1994a).

In the United States, waste disposal of industrial by-products containing PBDEs may also be described as transfers to disposal (landfill), recycling, energy recovery (incineration), industrial treatment works, or POTWs. The types of waste transfer may be different for manufacturing versus processing sectors, and also from within different types of processing. Waste disposal from manufacturing processes is predominantly to secure chemical landfills (e.g., those built with liners and leachate collection). For example, solid wastes (e.g., filter cakes) from the commercial production of technical octaBDE are disposed of in hazardous waste landfills as these wastes may contain toluene from the production process (EPA 1995). Plastic processors typically transfer most waste to disposal (landfill), recycling, energy recovery (incineration), and industrial treatment works, while minimal releases are to POTWs. In contrast, textile processors typically transfer most waste to POTWs. This difference in waste transfers between the plastic and textile sectors is because textile processors use water in their processing operation and other processors (e.g., processors of plastic) do not.

Recycling of plastic materials containing PBDEs is a common practice in industry. It has been demonstrated that decaBDE-containing resins can be successively recycled without generation of PBDDs/PBDFs (Brenner and Knies 1990; Donnelly et al. 1987); McAllister et al. 1990). For example, virgin high impact polystyrene (HIPS) resins (containing antimony trioxide [Sb_2O_3] and decaBDE) and repeatedly ground and injected molded (e.g., “recycled”) HIPS/decaBDE/Sb_2O_3 resins both met the requirements of the German Chemicals Banning Ordinance with respect to 2,3,7,8-substituted PBDD/PCDF congeners. These resins were at least 1 order of magnitude below the regulated limit values

for PBDDs/PCDFs (1 ppb for the sum of four congeners, 5 ppb for the sum of all eight regulated congeners).

8. POTENTIAL FOR HUMAN EXPOSURE

8.1 OVERVIEW

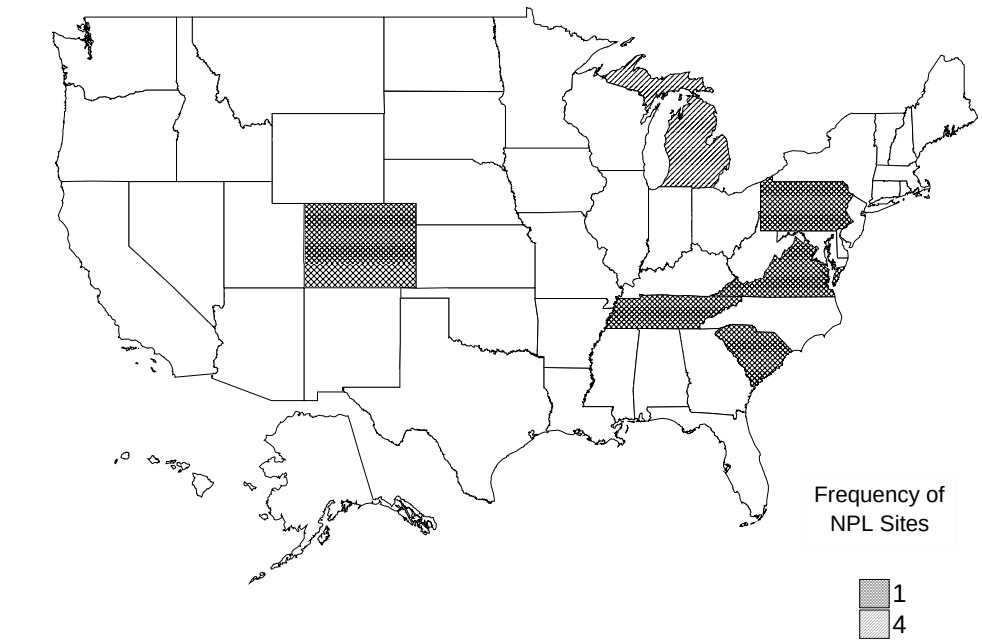
Polybrominated Biphenyls. PBBs have been identified in at least 9 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for PBBs is not known. The frequency of these sites can be seen in Figure 8-1. Of these sites, all are located within the United States and none are located in the Commonwealth of Puerto Rico (not shown).

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 feed in a number of farms in the lower peninsula in Michigan (see Section 5.2 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 as 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 of the PBBs and organic carbon content of 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 after a 19-day period. Leachate quantities in this study were 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;

Figure 8-1. Frequency of NPL Sites with PBB Contamination



Derived from HazDat 2004

Kawasaki 1980; Shelton 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 tops of carrots grown in soil contaminated with PBBs showed no uptake of PBBs, and only minor uptake occurred on 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 coastal 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. Current intake of PBBs for the general population is expected to be zero or very small. 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 the presence of some lower-brominated congeners in the environment (e.g., 2,2’,4,4’-tetrabromodiphenyl ether [BDE 47]). However, highly brominated congeners (e.g., decaBDE) are typically detected only near point sources. 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 incinerated as municipal waste, deposited in landfills, discharged to municipal sewage-treatment plants, or emitted directly to the atmosphere as particulates (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 of PBDEs and organic carbon content of soil and sediment increase. As a result, most PDBEs have little or no mobility in soil and are not expected to leach (e.g., into groundwater). Lower BDE homologs (e.g., tri- and tetraBDE), which may exist partially in the vapor phase, have the potential for long-range transport in the atmosphere. The detection of lower brominated PBDEs (e.g., 2,2',4,4'-tetraBDE [BDE 47]) in remote regions of the world suggests that long-range transport of these congeners is occurring. Higher BDE homologs (e.g., decaBDE) will primarily exist near point sources. Biodegradation will not be significant for PBDEs, but under certain conditions, some PBDEs compounds (e.g., decaBDE) may degrade by direct photolysis to form lower-brominated congeners. However, determining the rate and extent of degradation processes (e.g., biodegradation and photolysis) for PBDEs, such as decaBDE and pentaBDE commercial mixtures, is still an active area of research.

Monitoring studies indicate that lower brominated PBDEs, for example, 2,2',4,4'-tetrabromodiphenyl ether (BDE 47) and 2,2'4,4',5-pentabromodiphenyl ether (BDE 99), are transported globally. Atmospheric, water, and biota levels of PBDEs also tend to be dominated by lower brominated congeners (e.g., BDE 47, BDE 99). Environmental concentrations of lower brominated PBDEs (i.e., tetraBDE and pentaBDE) appear to be leveling off in Europe, but appear to be increasing in certain areas in Canada and the United States, although data are too sparse to make broad statements regarding trends. In the environment, higher brominated commercial mixtures (e.g., decaBDE) are concentrated in soils and sediment near industrial point sources.

Studies of the biota indicate that lower brominated congeners (e.g., 2,2',4,4'-tetraBDE [BDE 47]) are being preferentially bioconcentrated. Lower brominated diphenyl ether (e.g., tetra- and penta-) concentrations increase with respect to trophic level; thus, organisms that reside higher on food chains tend to have higher concentrations of these brominated diphenyl ethers. Body-burden data indicate that the general population is exposed to low levels of lower brominated (e.g., tetra- and penta-) BDEs. In general, decaBDE is not found in body burden data.

Humans are primarily exposed to lower brominated (e.g., tetra- and pentaBDEs) BDEs by inhalation of ambient or contaminated air and ingestion of contaminated food. Levels of PBDEs in body tissues and fluids from individuals living in the United States have recently been determined. Most studies indicate that levels of lower brominated BDEs (e.g., 2,2',4,4'-tetraBDE [BDE 47]) in body fluids and tissues are a factor of 10–100-fold higher for individuals living in the United States compared to individuals living in other regions of the world (e.g., Europe). In general, decaBDE is not detectable in body fluids and tissues. Occupational exposure to PBDEs occurs primarily by inhalation of air containing PBDEs.

PBDEs have not been identified in any of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for PBDEs is not known.

8.2 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 feed in a number of farms in the lower peninsula in Michigan (see Section 5.2 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 the presence of lower brominated diphenyl ether congeners, for example, 2,2',4,4'-tetrabromodiphenyl ether (BDE 47) and 2,2'4,4',5-pentabromodiphenyl ether (BDE 99), in the environment. Higher brominated congeners (e.g., octabromodiphenyl ether and decabromodiphenyl) tend to concentrate near point sources (Wania and Dugani 2002). The commercial production of PBDEs began in late 1970s (WHO 1994a). In 2001, the total market demand for PBDEs in the Americas was 33,100 metric tons (BSEF 2003). Technical decabromodiphenyl ether constituted about 24,500 metric tons (74%), while technical mixtures of octa- and pentabromodiphenyl ethers were 1,500 and 7,100 metric tons (4 and 22% of this total), respectively (BSEF 2003). 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 some PBDEs congeners (e.g., lower brominated congeners) may diffuse out of the treated materials to some extent (EU 2001). Waste from products containing PBDEs may be either incinerated as municipal waste, deposited in landfills, or discharged to municipal sewage-treatment plants (Darnerud et al. 2001). In the future, the disposal of plastic consumables containing PBDEs to landfills is likely to increase in the United States and elsewhere in the world.

The widespread use of pentaBDE over the past 30 years has resulted in the rapid increase in concentrations of lower brominated congeners, for example, 2,2',4,4'-tetrabromodiphenyl ether (BDE 47) and 2,2'4,4',5-pentabromodiphenyl ether (BDE 99), and their presence in the environment. No quantitative information was located on the releases of the commercial pentaBDE product from its production and use in the United States. The commercial pentaBDE product is used predominantly (95–98%) as an additive flame retardant in flexible polyurethane foam (FPUF), which has applications as cushioning in bed mattresses and upholstered products (see Section 7.3). No quantitative information was located on the releases of pentaBDE from the production of flexible polyurethane foams. However, the main source of release for liquid flame retardant additives (e.g., pentaBDE) is associated with the handing of the raw material (e.g., splashes and spills) prior to the foaming process, where releases are to waste water (EU 2001). There is a potential release to air during the curing phase since the polyurethane foam is heated at elevated temperatures (e.g., up to 160 °C) for several hours. Foam scrap will be disposed of to a landfill or possibility incinerated (EU 2001). Since pentaBDE is an additive flame retardant, it may be subject to volatilization or leaching from the polymer matrix during the lifetime of the use of an article. Losses of foam particles containing the substance (e.g., due to abrasion) may also occur. However, pentaBDE has a very low vapor pressure (see Table 6-6) and volatilization losses from polyurethane foam would be expected to be low. Given that the major use of pentaBDE is as a component of polyurethane foam for furniture/seating/automobile use, the potential for leaching of pentaBDE during use will be minimal. This is because, although it is likely that foam coverings may be washed during the lifetime of use, it is very unlikely that the foam cushioning containing pentaBDE will be washed as well (EU 2001). Residual 'waste' pentaBDE in the environment will be particles of polymer (foam) products that contain pentaBDE (e.g., 2,2'4,4'-tetraBDE). Polyurethane foam has an open cell structure, which presents a large surface area to the environment and therefore, the potential for release is likely to be greater than the hard dense plastics where octaBDE and decaBDE are used. In addition, this foam may become friable and crumble with age. Thus, small particles thereby released could move into the environment and disperse its components (i.e., commercial pentaBDE mixture) (BFRIP 2002). These form particles are released to

the urban/industrial soil compartment, but may also end up in sediment or air (EU 2001). Movement of polymer (foam) particles containing pentaBDE within the landfill could provide a transport mechanism leading to entry into leachate water or groundwater. However, well-designed landfills, in general, already include measures to minimize leaching and these measures would also be effective in preventing any leaching of pentaBDE as well (EU 2001).

Commercial octaBDE is used almost exclusively to flame retard acrylonitrile-butadiene-styrene (ABS) terpolymers used in computer casings and monitors (ENVIRON 2003b). No quantitative information was available on emissions of octaBDE from production operations. The major sources of air emissions are thought to be as a result of grinding and bagging operations. The emission to air of octaBDE vapor from production can be considered to be negligible (EU 2003a). The most likely way in which octaBDE may reach water from its production is due to washing out of equipment. The major source of octaBDE waste is from filter waste and reject material (EU 2003a). Much of the loss from polymer applications (e.g., acrylonitrile-butadiene-styrene) is likely to be in the form of dust. It is expected that much of this dust will be collected for reuse or disposed of to landfill/incineration. Some of this may end up in waste water as a result of cleaning floors and equipment (EU 2003a). Given that the major use of plastics containing octaBDE appears to be in electrical applications and that the substance has very low water solubility, the potential for leaching of octaBDE from the products during uses appears to be small. Waste remaining in the environment can be considered to be particles (or dust) of polymer product, or dust generated from polymer products, that contain octaBDE. These particles are primarily released to urban/industrial soil, but may also end up in sediment or air. Plastics containing octaBDE will usually be disposed of either to landfills or by incineration. No experiments have been carried out on the leachability of octaBDE from polymers in landfills. However, octaBDE is not expected to leach to a significant extent from polymers, unless the polymer itself undergoes some form of degradation, thus releasing octaBDE. It is expected that emissions of octaBDE from incineration processes will be near zero (EU 2003a).

Commercial decaBDE product is an additive flame retardant used in a variety of polymer applications (EU 2002). The major application for decaBDE is in high-impact polystyrene (HIPS), which is used in the television industry for cabinet backs. No quantitative information is available on emissions of decaBDE from production operations. Since the major use of plastics containing decaBDE is in electrical/electronic applications and the substance has very low water solubility, the potential for leaching of decaBDE from plastic products during use appears to be small (EU 2003a). A study of the leaching of decaBDE (DOW FR-300-BA; 77.4% deca-, 21.8% nona-, and 0.8% octaBDE) from pellets of acrylonitrile-butadiene-styrene (ABS) polymer and polystyrene (both containing 10% decaBDE) was

undertaken. The lack of increase in bromine concentration with time was observed. In static extractions of ABS containing 4.25% decaBDE (Dow FR-300-BA) with water, acetic acid, and cottonseed oil at elevated temperatures, little or no leaching of the decaBDE was evident. No decaBDE was detected in the water and acetic acid and only 0.03% of the total decaBDE was extracted by cottonseed oil over 7 days at elevated temperatures (EU 2002).

Releases of decaBDEs are required to be reported under the Superfund Amendments and Reauthorization Act (SARA) Section 313; consequently, data are available for this compound in the Toxics Release Inventory (TRI) (EPA 1995). According to the TRI, a total of 649,541 pounds (294,627 kg) of decaBDE were released to the environment in 2001. In addition, an estimated 787,927 pounds (357,398 kg) were transferred off-site, including to publicly-owned treatment works (POTWs) (TRI01 2004). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Facilities are only required to report to the TRI if they manufacture or process more than 25,000 pounds of a TRI listed chemical during the year, or otherwise use more than 10,000 pounds, and have the equivalent of more than 10 full-time employees. According to the EPA, TRI data have certain limitations. TRI data reflect releases and other waste management of chemicals and not exposures of the public to those chemicals. TRI data alone are not sufficient to determine exposure or calculate potential adverse effects on human health and the environment.

On-site land releases dominate decaBDE releases on-site from its manufacture and use, and are predominantly associated with disposal of decaBDE in either a manufacturer's on-site landfill in Arkansas or in a commercial chemical landfill in Louisiana. On-site air and water releases make up only a small fraction of total on-site releases. For example, on-site air emissions in 2000 were ~6.6% of the total; on-site surface water discharges also make up only a small fraction of the total (~0.2% of the 2000 total) and are nearly all associated with operations that apply decaBDE to upholstery textiles. DecaBDE releases off-site for disposal from its manufacture and use are typically larger than those on-site to land; decaBDE-waste transfers for further waste management are dominated by transfers to POTWs from the textile industry, although a significant rise in recycling has occurred in recent years. The plastics industry released minimal amounts to POTWs. The largest releases of decaBDE or decaBDE-waste to water occur in Maryland, North Carolina, and South Carolina and result from its use in textiles (TRI01 2004).

8.2.1 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 1,647 NPL hazardous waste sites, where they were detected in some environmental media (HazDat 2004).

Polybrominated Diphenyl Ethers. The widespread use of pentaBDE technical mixtures over the past 30 years has resulted in the increasing concentrations of lower brominated congeners in air, e.g., 2,2’,4,4’-tetrabromodiphenyl ether (BDE 47) and 2,2’4,4’,5-pentabromodiphenyl ether (BDE 99). No quantitative information was located on the releases of the pentaBPE technical mixtures to the atmosphere from its production and use. However, the release of pentaBDE technical mixtures to air has the potential to occur during the curing phase, since the polyurethane foam is at elevated temperatures (e.g., up to 160 °C) for several hours during this phase. Since pentaBDE technical mixtures are additive flame retardants, they may be subject to volatilization or leaching from the polymer matrix during the lifetime of the use of the foam article. Losses of foam particles containing the substance (e.g., due to abrasion) may also occur. However, most congeners in pentaBDE technical mixtures have very low vapor pressures (see Table 6-6) and therefore, losses from polyurethane foam due to volatilization would be

expected to be low. Migration of pentaBDE technical mixtures from consumer products may be a significant diffuse source of lower brominated congeners of pentaBDE technical mixtures to the atmosphere. Although no studies were found that determined the migration rate of pentaBDE technical mixtures from polymers into the air, estimates have been made. The estimated migration rate for pentaBDE technical mixtures is 0.39% per year (Danish EPA 1999).

In the regions surrounding metal-recycling plants in Taiwan and Japan, a variety of tri-, tetra-, and hexabromodiphenyl ethers (BDEs) 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.

No quantitative information is available on emissions of octaBDE technical mixtures to the atmosphere from production operations. The major sources of air emissions of octaBDE technical mixtures are thought to be a result of grinding and bagging operations. However, the emission to air of vapors from production of octaBDE technical mixtures may be considered to be negligible (EU 2003a). OctaBDE technical mixtures are used almost exclusively to flame retard ABS terpolymers used in computer casings and monitors (ENVIRON 2003b). No quantitative information was available on emissions of octaBDE technical mixtures to the atmosphere from ABS applications. However, much of the loss from polymer applications is likely to be in the form of dust. Losses of octaBDE technical mixture powders (particle sizes >40 μm) have been estimated as 0.21% during handling of raw materials. These losses will initially be to the atmosphere, but it is expected that this dust will rapidly settle and may be disposed of to landfills. OctaBDE technical mixtures in the compounding stage are also susceptible to dust generation. However, losses at this stage are thought to be lower than during the handling of raw materials (EU 2003a). Plastics containing octaBDE technical mixtures will usually be disposed of either to landfill or by incineration. It is expected that emissions of PBDE congeners resulting from incineration of plastics containing octaBDE technical mixtures will be negligible (EU 2003a).

No quantitative information is available on emissions of decaBDE technical mixtures to the atmosphere from production operations. In 1979, decaBDE was found in the atmosphere as particulate matter in the vicinity of plants manufacturing brominated flame retardants (Zweidinger et al. 1979); the concentration of decaBDE ranged from not detected to 72 ng/m^3. The estimated releases of decaBDE vapor to air during production are low, typically 1.1×10^{-5} mg/metric tons of production (EU 2002). The major source of air emissions is thought to be a result of grinding and bagging operations. Losses of powders during the handling of raw materials will initially be to the atmosphere, but it is expected that this dust will rapidly settle within the production facility and therefore, these losses will be mainly to solid waste (EU

2002). The compounding stage is also susceptible to dust generation, but losses are thought to be lower than during handling of raw materials (i.e., an order of magnitude lower). Releases will again be initially to the atmosphere, but the particles would be expected to settle within the compounding facility and will ultimately be to solid waste or waste water. In addition to particulates, emissions to the atmosphere due to the volatility of the flame retardant at the elevated processing temperatures may be possible. However, due to the high vapor pressure of decaBDE (see Table 6-6), volatilization is expected to be negligible.

The commercial decaBDE product is an additive flame retardant used in a variety of polymer applications (EU 2002). The major application for decaBDE is in high-impact polystyrene (HIPS), which is used in the television industry for cabinet backs. Thus, decaBDE made be released during the polymer processing of HIPS. Waste remaining in the environment can be considered to be small particles of polymer product or dust generated from polymer products containing decaBDE (EU 2002). These particles are primarily released to soil, but may also end up in air. End products with outdoor uses are most likely to be atmospheric sources of decaBDE dust. Releases from these products occur over the lifetime of the product due to weathering and wear. Waste of this type may also be generated during disposal of a variety of plastic articles, in particular, where these articles are dismantled or subject to other mechanical processes. Ultimately, plastic articles containing technical decaBDE will be disposed of either to landfill or by incineration. Emissions of decaBDE from controlled incineration processes will be near zero (EU 2002). The concentration of decaBDE was determined in bottom ash from two municipal incinerators in Finland. With a method detection limit of 0.02–0.06 μg/kg, decaBDE was not detected in either ash sample (EU 2002). The low vapor pressure of decaBDE (see Table 6-6) limits its volatility to the atmosphere when disposed of in a landfill (EU 2002).

The estimated release of 97,198 pounds (44,088 kg) of decaBDE to the atmosphere from 54 manufacturing, processing, and waste disposal facilities in 2001 accounted for about 15.0% of the estimated total on-site environmental releases (TRI01 2004). These releases are summarized in Table 8-1. The data from the TRI listed in Table 8-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

DecaBDE was not identified in air samples collected from 1,647 NPL hazardous waste sites (HazDat 2004).

Table 8-1. Releases to the Environment from Facilities that Produce, Process, or Use Decabromodiphenyl Ether[a]

		Reported amounts released in pounds per year[b]						
State[c]	Number of facilities	Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
AL	1	10	5	0	0	15	0	15
AR	5	81,717	0	0	130,000	211,717	9,902	221,619
CA	5	750	0	0	0	750	100,023	100,773
CT	3	1,024	No data	0	0	1,024	24,149	25,173
FL	2	0	No data	0	0	0	19,040	19,040
GA	7	755	0	0	0	755	11,225	11,980
IL	2	32	No data	0	0	32	13,700	13,732
IN	6	20	0	0	0	20	3,987	4,007
KY	2	555	No data	0	0	555	17,478	18,033
LA	1	0	No data	0	270,000	270,000	0	270,000
MA	13	292	8	0	0	300	30,658	30,958
MD	1	0	No data	0	0	0	0	0
MI	6	3,741	0	0	23,600	27,341	26,503	53,844
MN	3	0	No data	0	0	0	8,507	8,507
MO	1	500	No data	0	0	500	1,189	1,689
MS	2	106	No data	0	0	106	30,933	31,039
NC	14	2,818	4,237	0	99,090	106,145	73,151	179,296
NE	2	0	No data	0	0	0	0	0
NH	1	2	5	0	0	7	285	292
NJ	5	97	No data	0	0	97	84,846	84,943
NV	1	No data	No data	No data	No data	No data	No data	0
NY	4	0	5	0	990	995	36,837	37,832
OH	9	322	0	0	750	1,072	77,277	78,349
PA	7	1,996	109	0	0	2,105	156,439	158,544
RI	1	13	No data	0	0	13	1,766	1,779
SC	12	0	2,055	0	40	2,095	20,758	22,853
TN	7	786	42	0	18,137	18,965	13,644	32,609
TX	8	1,390	5	0	3,265	4,660	5,712	10,372
VA	5	270	No data	0	0	270	15,087	15,357
VT	1	0	No data	0	0	0	0	0

Table 8-1. Releases to the Environment from Facilities that Produce, Process, or Use Decabromodiphenyl Ether[a]

		Reported amounts released in pounds per year[b]						
State[c]	Number of facilities	Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
WA	1	0	No data	0	0	0	0	0
WI	3	2	No data	0	0	2	4,831	4,833
Total	141	97,198	6,471	0	545,872	649,541	787,927	1,437,468

Source: TRI01 2004

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]The sum of fugitive and stack releases are included in releases to air by a given facility.
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[f]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

8.2.2 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 (0.1–0.2 ppb), but those in water from a drainage ditch and catch basin were much higher (0.35–1.2 ppm) (Di Carlo et al. 1978).

PBBs have been identified in 2 and 5 surface water and groundwater samples, respectively, collected from 1,647 NPL hazardous waste sites (HazDat 2004).

Polybrominated Diphenyl Ethers. Industrial and urban effluents are significant sources of PBDEs to surface waters and sediments. Limited data on industrial and urban effluents were located for the United States. Hale et al. (2002) measured the concentration of soil and stream sediments collected near a polyurethane manufacturing plant (near the Dan River, Virginia). Summed concentrations of 2,2’,4,4’-tetraBDE (BDE 47), 2,2’,4,4’,5-pentaBDE (BDE 99), and 2,2’,4,4’,6-pentaBDE (BDE 100), the dominant congeners in these samples, ranged from <1 to 132 μg/kg (ng/g) dry weight. 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. 1998a). Samples were analyzed for tetraBDEs (50 ng/g dry weight) and pentaBDEs (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, BDE 99, BDE 100, and BDE 209 in sediments increased as samples were collected further downstream where additional industries were located (Sellström et al. 1998a). The lowest levels of PBDEs were found upstream of the textile industries. The combined concentration of BDE 47, BDE 99, and BDE 100 ranged from not detected to 120 ng/g (μg/kg) dry weight; the concentration of BDE 209 ranged from not detected to 16,000 ng/g (μg/kg) 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 pentaBDE and octaBDE, including a manufacturer, several industries, landfills, and a reference site. The highest concentrations of BDE 47, BDE 99, pentaBDE (as 2,3',4',6-tetrabromodiphenyl ether or BDE 71), and octaBDE (as 3,3',4,5'-tetrabromodiphenyl ether or BDE 79) were in sediments near or downstream from a manufacturing site at Newton Aycliffe in River Skerne. The highest concentrations of decaBDE (as 2,2',3,3',5-pentabromodiphenyl ether or 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 pentaBDE congeners (BDE 47, BDE 99, BDE 100, BDE 153 [i.e., 2,2',4,4',5,5'-hexabromodiphenyl ether], and BDE 209) ranged from 0.07 to 10.6 ng/g (µg/kg) dry weight in freshwater sediments from Denmark (Christensen and Platz 2001). The highest concentrations were found in sediment close to populated areas.

Although the available information indicates that leaching of PBDEs from landfills is minimal, movement of polymer particles containing pentaBDE, octaBDE, and decaBDE commercial mixtures within the landfill could lead to entry into leachate water of groundwater. However, it is not currently possible to assess the significance of this type of process. Well designed landfills already include measures to minimize leaching in general, and these measures would also be effective in minimizing leaching of any PBDEs present (EU 2002, 2003).

The estimated release of 6,471 pounds (2,935 kg) of decaBDE to water from nine domestic manufacturing and processing facilities in 2001 accounted for about 0.45% of the estimated total environmental releases (TRI01 2004). An additional 787,927 pounds (357,398 kg) were transferred off-site, including to POTWs (TRI01 2004). These releases are summarized in Table 8-1. The data from the TRI listed in Table 8-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

PBDEs were not identified in water samples collected from 1,647 NPL hazardous waste sites (HazDat 2004).

8.2.3 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 (5,350,000 kg) of hexabromobiphenyl was 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 was 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 5 soil and 3 sediment samples collected from 1,647 NPL hazardous waste sites (HazDat 2004).

Polybrominated Diphenyl Ethers. PBDEs are released to land (i.e., landfills) as waste from their manufacture (both raw material and polymer) and as municipal wastes with the disposal of consumer products. Solid waste from commercial production of octaBDE is typically disposed in landfills (EPA 1995). 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 (14 kg), an estimated 350 million pounds (160,000,000 kg) 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.

PBDEs are released to farmland with their disposal as biosolids (i.e., sewage sludge). PBDEs were detected in biosolids destined for land applications in four different regions of the United States (Pardini et al. 2001). The total concentrations of pentaBDE in biosolids ranged from 1,100 to 2,290 µg/kg dry weight; the levels of pentaBDE were high and consistent, regardless of the region of origin. The concentration of decaBDE (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.

In 2001, 545,872 pounds (247,603 kg) of decaBDE was released to land from 8 domestic manufacturing, processing, and waste-disposal facilities reporting releases of the compound to the environment (TRI01 2004). No releases (0 pounds) of decaBDE occurred via underground injection (TRI01 2004). Releases to the environment from facilities that produce, process, or use decaBDE are summarized in Table 8-1. The data from the TRI should be used with caution since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

PBDEs were not identified in soil and sediment samples collected from 1,647 NPL hazardous waste sites (HazDat 2004).

8.3 ENVIRONMENTAL FATE

8.3.1 Transport and Partitioning

Polybrominated Biphenyls. PBBs exist 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} mm Hg 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 5.2x10^{-8} mm Hg at 25 °C (Jacobs et al. 1976). The vapor pressure of octabromobiphenyl is 7.0x10^{-11} mm Hg at 28 °C (Waritz et al. 1977). Although no data are available, the vapor pressures of decabromobiphenyl at ambient temperatures should be lower than octabromobiphenyl. Thus, PBBs produced in the 1970s should exist 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 be transported 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 3.9x10^{-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 in which losses of octabromobiphenyl and decabromobiphenyl from water to air were found to be 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, sorption of water-bound PBBs to particulate matter and sediment 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 in which bioconcentration may take place. Data from different laboratories on the bioconcentration of PBBs in fish show wide variation. The experimentally determined bioconcentration factor (BCF; the BCF is the concentration of the chemical in fish tissues over concentration of chemical 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 269,000; 115,000; 1,440,000; and 708,000; respectively (Gobas et al. 1989). BCF values for mono- to tetra- bromobiphenyl congeners tend to increase with higher degrees of bromination while BCF values for tetra- and higher congeners tend to decrease with higher degrees of bromination. A similar trend in BCF

values for various PBBs was also observed in juvenile Atlantic salmon (*Salmo salar*). For example, the whole body BCF values determined 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 BCF values determined 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 solids by adsorption. The presence of certain types of 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 as would happen at some contaminated sites (Griffin and Chou 1981b). This phenomenon is commonly called “co-solvency.” The transport of PBBs from soil to the atmosphere by volatilization is not important due to the low volatility and strong adsoprtion 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 tops of carrots 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, PBDE commercial mixtures, which have low vapor pressures and exist in the particulate phase, will be removed from the atmosphere by wet and dry deposition. Thus, in general, PBDEs are not expected to travel long distances in the environment. However, some congeners in pentaBDE commercial mixtures, 2,2’,4,4’-tetrabromodiphenyl ether (BDE 47) and 2,2’,4,4’,5-pentabromodiphenyl ether (BDE 99), have been found in Arctic regions. It has not been definitively explained how these lower brominated congeners have been transported such long distances

from areas of emission. However, it is likely that they have been transported to remote regions as dust particles rather than in the vapor phase. 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 hexa- bromodiphenyl ether) should exist in both the vapor and particulate phase in the atmosphere, while PBDEs with vapor pressures $<10^{-8}$ mm Hg (hexa- to decaBDE) 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 °C): 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 PBDE mixtures, such as pentaBDE ($2.2x10^{-7}$–$5.5x10^{-7}$ mm Hg) and decaBDE ($3.2x10^{-8}$ mm Hg at 25 °C) (EU 2001; NRC 2000). Since particulate phase PBDEs will precipitate out by wet and dry deposition, these PBDEs would not be expected to be transported 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., pentaBDEs and hexaBDEs) may have the potential to be transported and would likely be found at higher concentration close to PBDE point sources. Lower BDE homologs (e.g., tetraBDE), which exist partially in the vapor phase, have the potential for long-range transport in the atmosphere (Dodder et al. 2000a). For example, 2,2',4,4'-tetrabromodiphenyl ether (BDE47), 2,2',4,4',5-pentabromodiphenyl ether (BDE 99), and 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE 153) were detected in air samples from urban, rural, and remote areas of the Great Lakes region 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 pentaBDE and decaBDE are 13.3 and <0.1 µg/L, respectively (EU 2001; Hardy 2002b). As consequence of their low water solubility, they have not detected PBDEs in environmental waters (see Section 8.4.2).

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 pentaBDEs (Watanabe 1988). K_p values for tetra-, penta-, and hexaBDEs are 28,300, 49,200, and 62,700 L/kg, respectively, which suggest strong partitioning to sediment. High log K_{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).

DecaBDE and octaBDE commercial products do not bioconcentrate in fish. The reported BCFs for these commercial mixtures are typically less than 50 (Hardy 2002b). A single study on a mixed range of PBDEs, between hexaBDE and decaBDE, indicated little bioconcentration in carp (e.g., *Cyprinus carpio*) with a bioconcentration factor of <4 after 8 weeks of exposure (WHO 1994a). A bioconcentration study was carried out with rainbow trout under static conditions. The concentration in the water was 20 µg ^{14}C-decaBDE per liter. Fish were exposed to decaBDE for 0, 0.5, 1, 2, 4, 6, 12, 24, or 48 hours. For each of the exposure periods, there was no measurable accumulation of decaBDE in flesh, skin, or viscera (WHO 1994a).

An abundance of monitoring data illustrates the uptake of lower brominated diphenyl ethers by aquatic organisms, which results in bioconcentration (see Section 8.4.4). The commercial pentaBDE product undergoes bioconcentration with a BCF of approximately 14,000 (Hardy 2002b). Congener components of the pentaBDE commercial product bioconcentrate to different extents. For example, approximately 50–70% of PBDEs detected in fish is a single isomer (2,2’,4,4’-tetrabromodiphenyl ether [BDE 47]). The next most prominent isomer is typically 2,2’,4,4’,5-pentabromodiphenyl ether (BDE 99) followed by 2,2’,4,4’,6-pentabromodiphenyl ether (BDE 100). In a laboratory study of Baltic blue mussels (*Mytilus edulis* L), 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 2,2’,4,4’,5,5’-hexabromodiphenyl ether (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 $1x10^9$ for BDE 99 and BDE 100, and $\approx 2.5x10^7$ for BDE 28, $\approx 2.5x10^8$ for BDE 47, and $\approx 1.6x10^8$ for BDE 153.

Bioaccumulation of PBDEs in the aquatic food web is inversely related to the degree of bromination (Burreau et al. 2000; Jansson et al. 1993). Higher brominated congeners (e.g., decaBDE) are rarely detected in biota. This is a result of their low solubility, high log K_{ow} values, and sorption to soil and sediment (Hardy 2000). In contrast, tetraBDE to hexaBDE homologs are more frequently detected in biota (Burreau et al. 1997; Hale et al. 2003), which would be expected due to their greater water solubility and relatively high K_{ow} values.

Concentrations of lower brominated diphenyl ethers in biota are related to the trophic level of the species. For example, Haglund et al. (1997) examined the concentrations of tetra- to hexa- bromodiphenyl ethers in herring, salmon muscle, and gray and ringed seals collected along the Swedish coast of the Baltic Sea between 1981 and 1988. The concentrations of tetrabromodiphenyl ethers (e.g., 2,2',4,4'-tetrabromo-diphenyl ether, BDE 47) were found to increase with trophic level. Concentrations of PBDEs in herring and their predators, grey seal and guillemot, all collected at the same location of the Baltic Sea, have been compared to estimate potential biomagnification (de Wit 2002). The herring were caught in the autumn of the same year as guillemot egg collection (1987). Biomagnification factors for guillemot egg versus herring were 19, 17, and 7.1 for BDE 47, 2,2'4,4',5-pentabromodiphenyl ether (BDE 99), and 2,2',4,4',6-pentabromodiphenyl ether (BDE 100), respectively. Burreau et al. (2000) analyzed small herring and salmon from the Atlantic Ocean (near Iceland) for several PBDEs. The calculated biomagnification factors for Atlantic salmon versus small herring were 3.5, 3.8, and 6.0 for BDE 47, BDE 99, and BDE 100, respectively. These authors concluded that biomagnification was occurring for the lower brominated congeners.

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 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 6-6).

8.3.2 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.

8.3.2.1 Air

Polybrominated Biphenyls. In air, the two processes that may result in significant degradation or transformation of PBBs are photooxidation by hydroxyl (OH) 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 are probably not 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 deca- bromodiphenyl ether 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 will not be important.

In water, some PBDEs have been reported to undergo direct photolysis (Hua et al. 2003). Likewise, PBDEs present in the vapor phase (e.g., tetraBDE) or as particulates (e.g., decabromodiphenyl ether) may also undergo photolysis in the atmosphere. However, the rate and extent of the photolysis of PBDEs in air cannot be evaluated due the lack of information.

8.3.2.2 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'-hexachlorobiphenyl (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).

PBBs are not expected to undergo abiotic hydrolysis under environmental conditions due to the lack of hydrolysable functional groups (Boethling and Mackay 2000).

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 8.3.2.3). 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 in river sediments obtained from populated areas 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 with certain inoculations (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 absorb light in the environmental spectrum. Hua et al. (2003) found that decaBDE and the commercial octaBDE absorbed light up to 325 nm, which indicates that these compounds may be susceptible to photodegradation at environmental wavelengths (Hua et al. 2003). Di- and tetrabromodiphenyl ethers were reported to absorb minimal light at wavelengths >300 nm. This trend suggests that the lower brominated diphenyl ethers (e.g., pentaBDE commercial mixtures) will be less susceptible to photolysis compared to octaBDE and decaBDE commercial mixtures.

PBDEs undergo debromination by direct photolysis in organic solvents and organic solvent:water mixtures. Laboratory studies of the photolytic breakdown of decaBDE in toluene have shown that it is

successively debrominated by UV light to hexaBDE and that photolysis occurs very rapidly (Sellström et al. 1998b). The photolysis half-life in toluene was <15 minutes. However, the amounts of lower brominated congeners appear to be small (EU 2002). The photolysis of decaBDE (and tetra-, penta-, hexa-, hepta-, and octabromodiphenyl ethers) was recently reported in a 80:20 mixture of methanol:water at wavelengths >290 nm (EU 2002). The rate of photodegradation was found to increase with increasing degree of bromination. DecaBDE was found to degrade with a half-life of around 30 minutes while half-lives for tetra-, penta-, hexa-, hepta-, and octabromodiphenyl ethers were 12–16 days, 2.4 days, 1.2 days, 1.2 days, and 5 hours, respectively. The decomposition products of decaBDE were identified to be PBDEs (with >6 bromine atoms per molecule) and polybrominated furans (with <6 bromine atoms per molecule). Results of this study indicate that the photochemical stability of PBDEs increases with decreasing bromination (EU 2002). Rayne et al. (2003b) recently reported that 4,4'-dibromodiphenyl (BDE 15) photodegraded in organic (acetonitrile-methanol) and aqueous (H_2O:acetonitrile; 1:1 v/v) solvent systems at a wavelength of 300 nm. Reductive bromination was reported to be much slower in the aqueous system (e.g., 73% remained after 300 minutes) compared to the organic system (where 51% and 41% remained after 30 minutes). However, these studies were conducted in the presence of organic solvents, which are not representative of conditions found in the environment. Organic solvents can act as hydrogen donors in photolysis reactions, which will potentially affect the distribution of products formed.

In a recent study, the photolysis of PBDEs was examined under environmentally relevant conditions. Hua et al. (2003) studied the degradation of decaBDE in several different experiments: (1) on humic acid-coated silica particles, (2) on glass surfaces in contact with aqueous humic acid solutions, and (3) on glass surfaces in contact with water. DecaBDE dissolved in toluene was deposited on the solid substrate under a stream of nitrogen (to evaporate the solvent) and then desiccated to remove any residual toluene. The adsorbed decaBDE on the solid substrate was then inundated with the aqueous test solution, followed by irradiation for the duration of the test period. In all experiments, natural sunlight (location, 40° 26' N, 86° 55' W) was used. The extent of degradation was determined using high-performance liquid chromatography (HPLC) with ultraviolet detection (UV) detection or by gas chromatography-mass spectrometry (GC-MS). In the first experiment, solar irradiation of decaBDE adsorbed onto humic acid-sand indicated that the photolysis of decaBDE was slow. After 96 hours of exposure to sunlight, 88% of initial decaBDE remained on the coated sand. There is some evidence that lower brominated congeners (e.g., 2,2',4,4',6,6'-hexabromodiphenyl ether [BDE 155]) were formed in the experiment (EU 2002). In the second experiment, decaBDE was adsorbed on glass tubes containing a humic acid. In this study, the concentration of decaBDE decreased relatively quickly over the first 24 hours of exposure, after which,

the concentration remained stable. Bromide ion accumulated at an almost linear rate from start to end of the 72-hour exposure period. Approximately 70% of the initial decaBDE remained after the 72-hour exposure. The difference in kinetics (for the disappearance of decaBDE vs. the appearance of bromide ion) suggests that after the initial degradation of decaBDE, bromide ion was generated by the degradation of lower brominated diphenyl ether congener products (possibly octa- and nonabromodiphenyl ethers). Bromide ion mass balance for the system indicated that 70% of the total bromine present was accounted for by decaBDE or bromide, with the remaining 30% present as unidentified compounds. In the third experiment, Hua et al. (2003) investigated the photodegradation of decaBDE adsorbed on glass tubes, which were filled with aqueous solutions (without humic acid). The result of this test showed a much more rapid loss of decaBDE than found in the analogous test using humic acid solutions. Approximately 29% of the initial decaBDE present remained after 72 hours. The rate of decaBDE loss and bromide ion accumulation was relatively constant over the entire 72-hour test period. Mass balance indicated that approximately 50% of the total bromine was present as either decaBDE or bromide ion, while the remaining 50% was possibly unidentified nona- and octabromodiphenyl ether congeners. The difference between the tests using glass tubes with and without humic acid solution is possibly due to the absorption of light by humic acids, which may attenuate the degradation process. These studies indicate that adsorbed decaBDE may undergo photolysis forming octa- and nonabromodiphenyl ethers under somewhat environmentally relevant conditions. Lower brominated diphenyl ether congeners are also formed although only to a minor extent. These tests do not provide evidence that lower brominated diphenyl ethers (e.g., tetra- and pentabromodiphenyl ethers) are a major degradation product of decaBDE (EU 2002). There is also insufficient information from these studies to estimate the rate of photolysis or if intermediate degradation products build up after long-term exposures (EU 2002).

Söderström et al. (2004) examined the time course of photolysis of decaBDE (BDE 209) in toluene, on silica gel, sand, sediment, and soil using artificial sunlight and on the natural matrices (e.g., sediment, soil, and sand) using natural sunlight. On natural samples, BDE 209 was first dissolved in toluene and then deposited on the natural matrix. The toluene was allowed to evaporate, and then the sample was reconstituted with water to resemble natural conditions. BDE 209 was photolytically labile and formed debromination products in all matrixes studied. Nona- to tetra- BDEs were formed as well as some PBDFs. The half-lives in toluene and on silica gel were less than 15 minutes, and half-lives on other matrices ranged from 40 to 200 hours. No differences were observed in the debromination patterns under different matrices or light conditions. These experiments show that photolytic debromination of BDE 209 is a possible pathway for the formation of more bioavailable, lower brominated PBDEs. However, the mostt commonly found BDEs in environmental samples (e.g., 2,2’,4,4’-tetrabromodiphenyl ether

[BDE 47], 2,2'4,4',5-pentabromodiphenyl ether [BDE 99], and 2,2',4,4',6-pentabromodiphenyl ether [BDE 100]) were only formed to a minor degree (Söderström et al. 2004).

Following the methodology described for decaBDE, photolysis experiments were conducted on 2,2',4,4'-tetraBDE (BDE 47) (EU 2002). BDE 47 was adsorbed on glass tubes filled with an aqueous solution and exposed to natural sunlight. After 72-hours of exposure, 30% of the initial BDE 47 remained. The rate of disappearance of BDE 47 was comparable to that found for decaBDE under similar test conditions. Accumulation of bromide was initially slow with the rate increasing after 24 hours while the disappearance of BDE 47 was initial rapid over the first 24 hours. Using GC-MS, the authors concluded that 2,4,4'-tribromodiphenyl ether was being formed during this reaction and that removal of bromine atoms *ortho* to the ether functionality may be a significant reaction pathway for removal of bromine atoms under the conditions of this study. This study suggests that adsorbed pentabromodiphenyl ether congeners, like decaBDE, may undergo photolysis under somewhat environmentally relevant conditions (EU 2002).

PBDEs are not expected to undergo abiotic hydrolysis under environmental conditions due to the lack of hydrolysable functional groups (Boethling and Mackay 2000).

PBDEs are unlikely to biodegrade rapidly in the environment under aerobic conditions. PentaBDE did not undergo biodegradation (determined by CO_2 evolution) 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% tetraBDE, 54.6% pentaBDE, and 11.7% hexaBDE. The test was extended to 93 days to allow sufficient opportunity for adaptation to occur. At the end of 93 days, 2.4% of the theoretical amount of CO_2 had been evolved. Thus, pentaBDE was determined to be not readily biodegradable. No degradation (as oxygen uptake) was seen for octaBDE after 28 days in an OECD 301D ready biodegradation test (EU 2003a). Thus, octaBDE was determined to be not readily biodegradable. The biodegradability of decaBDE has been studied under aerobic conditions using an activated sludge inoculum (EU 2002). DecaBDE at 100 mg/L was incubated with activated sludge (at 30 mg/L) over a 2-week period using a method similar to an OCED 301C MITI test. No degradation (as measured by biochemical oxygen demand) was observed. Thus, decaBDE was determined to be not readily biodegradable.

No data on biodegradation of pentaBDE and octaBDE commercial mixtures under anaerobic conditions are available. An anaerobic degradation study was carried out with 2,2',4,4'-tetrabromodiphenyl ether

(BDE 47) using a mixture of ^{14}C labeled and unlabeled compound (EU 2003a). The test was carried out using a sediment-water (Schuykill River, PA) inoculum. After 32 weeks, it appeared that no significant degradation of BDE 47 had occurred. However, the analytical method (i.e., HPLC using radiometric detection) used in this test indicated that some unidentified products had been formed in samples taken after 32 weeks. From these results, it is clear that BDE 47 has the potential to degrade slowly under anaerobic conditions (EU 2003a). Rayne et al. (2003b) recently reported that 4,4'-dibromodiphenyl undergoes reductive debromination under anaerobic conditions. Debromination proceeds with replacement of a bromine (Br) atom by a hydrogen (H) atom. The authors suggest that anaerobic debromination may sequentially debrominate BDE 15 to the parent diphenyl ether.

The anaerobic biodegradability of ^{14}C-labeled decaBDE was studied over a period of 32 weeks (EU 2002). The test chambers consisted of 500 mL bottles containing 300 mL of sediment (Schuykill River, Pennsylvania) prepared under anaerobic conditions. The test chambers were incubated at 25 °C and in the dark during the test. After the 32-week period, <1% of the total radioactivity added was found as $^{14}CO_2$ and $^{14}CH_4$ indicating that essentially no mineralization had occurred. GC-MS results showed no evidence for the formation of lower brominated congeners from deceBDE under the conditions of this test (EU 2002).

8.3.2.3 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 during 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 8.3.2.2, 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 and light does not penetrate far into 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, in which 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. The extent to which PBDEs undergo direct photolysis in soils and sediment is unknown. However, sunlight would only penetrate the uppermost few millimeters of soil and will not impact sediment. Photolysis of PBDEs is possibily important for land-applied sewage sludge contaminated with PBDEs. However, no information was available on this possibility. Based on studies in water, most PBDEs are unlikely to biodegrade in soils or sediment under aerobic or anaerobic conditions. Lower brominated diphenyl ether congeners (e.g., 2,2’4,4’-tetrabromodiphenyl ether [BDE 47]) may slowly biodegrade under anaerobic conditions in sediment (EU 2003a). However, information on the rate or extent of anaerobic biodegradation of BDE 47 has not been found. No other information was found in the literature about the transformation and degradation processes for PBDEs in soils and sediment.

8.3.2.4 Other Media

No other information was found in the literature about the transformation and degradation processes for PBBs or PBDEs in other media.

8.4 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 9. 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 8.1). 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.

8.4.1 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 8.2.1) (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. In general, limited information is available in the literature reporting the levels of PBDEs in ambient air. The concentrations of PBDEs in air samples are summarized in Table 8-2. Atmospheric concentrations of PBDEs tend to be dominated by lower brominated congeners (e.g., 2,2',4,4'-tetrabromodiphenyl ether [BDE 47], 2,2',4,4',5-pentabromodiphenyl ether [BDE 99], 2,2',4,4',6-pentabromodiphenyl ether [BDE 100], 2,2',4,4',5,5'-hexabromodiphenyl ether [BDE 153], and 2,2',4,4',5,6'-hexabromodiphenyl ether [BDE 154]). DecaBDE (BDE 209) has only been detected in the particulate phase in air near point sources. 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, BDE 99, BDE 100, BDE 153, and BDE 154 (Dodder et al. 2000a; Strandberg et al. 2001). The most significant congeners were BDE 47 and BDE 99. Air measurements were averaged over a 3-year period between 1997 and 1999. The concentration of total PBDEs ranged from 5.5 pg/m^3 in rural environments to 52 pg/m^3 in urban air from Chicago, Illinois. The concentration of BDE 47 was 48 pg/m^3 observed near Chicago, Illinois. The average concentration of decaBDE at the remote and rural locations was <0.10 pg/m^3 for each of the years investigated. The average concentration of decaBDE in the particulate phase at the urban location ranged from 0.20 to 0.35 pg/m^3 (Strandberg et al. 2001).

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 heptabromodiphenyl ethers were detected; the combined concentrations of 2,2',4,4'-tetrabromodiphenyl ether (BDE 47), 2,2',4,4',5-pentabromodiphenyl ether (BDE 99), and 2,2',4,4',6-pentabromodiphenyl ether (BDE 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, Northwest Territories, Canada; Dunai Island, eastern Siberia, Russia) between January 1994 and January 1995 (de Wit 2002). The total concentration of several di- to hexabromodiphenyl ethers ranged from 1 to 4 pg/m^3 at Alert for 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, BDE 99, and BDE 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 decaBDE was found, although the limit of detection limit for decaBDE is much higher than for the lower brominated diphenyl ethers.

Table 8-2. Concentrations (pg/m^3) of Several PBDEs in Air Samples

Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	Reference
Urban, United States	48	25	3.0	77*	Dodder et al. 2000
Rural, United States	6.2–9.2	4.3–5.0	0.6–0.9	2–4.8*	Dodder et al. 2000
Remote, United States	3.7	2.6	0.33	6.9*	Dodder et al. 2000
Alert, Northwest Territories Canada	No data	No data	No data	1–28	Alaee et al. 1999
Eagle Harbor, Wisconsin	2.9	2.1	0.28	5.5*	Strandberg et al. 2001
Sturgeon Point, New York	3.8	2.8	0.39	7.2*	Strandberg et al. 2001
Sleeping Bear Dunes, Michigan	8.4	5.3	0.80	15*	Strandberg et al. 2001
Chicago, Illinois	33	16	2.0	52*	Strandberg et al. 2001
Ammarnäs, Sweden	6.3	1.6	0.4	8.3	de Wit 2000, 2002
Hoburgen, Sweden	0.7	0.35	0.07	1.1	de Wit 2000, 2002
Stoke Ferry, United Kingdom	4.7–50	5.5–13	1.1–3.9	6.7–58	Peters et al. 1999
Hazelrigg, United Kingdom	3.2–61	3.1–22	0.62–5.4	4.1–69	Peters et al. 1999
Dunai Island, Russia	No data	No data	No data	1–8*	Alaee et al. 1999

[a]ΣPBDEs is the sum of BDE 47, BDE 99, and BDE 100, but if more congeners are included, this is marked with an asterisk (*).

Sources: de Wit 2002; Lee et al. 2002; Strandberg et al. 2001

8.4.2 Water

Polybrominated Biphenyls. Recent information on the concentrations of PBBs is not available. 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'-Tetrabromobiphenyl 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. Due to the hydrophobic nature of PBDEs, this class of compounds has not been detected in water to any significant extent. 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). 2,2’,4,4’-Tetrabromodiphenyl ether (BDE 47) and 2,2’,4,4’,5-pentabromodiphenyl ether (BDE 99) were the most abundant congeners, together making up >70% of the total PBDEs. In Japan, nondetectable levels of PBDEs were reported in 75–200 water samples (ENVIRON 2003a). No other information was located about the concentrations of PBDEs in water.

8.4.3 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 to 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. ***N***o information was located on the ambient environmental concentrations of PBDEs in soils in the United States or other parts of the world. Hale et al. (2002) reported the concentration of PBDEs in soil samples collected in the vicinity of a polyurethane foam-manufacturing facility. Levels in these soils are likely to be higher than to be expected in rural and potentially urban areas of the United States. Total PBDE levels in these samples ranged from not detected to 76 µg/kg dry weight. 2,2',4,4',5-Pentabromodiphenyl ether (BDE 99) was the predominant congener in soil followed by 2,2',4,4'-tetrabromodiphenyl ether (BDE 47), and 2,2',4,4',6-pentabromo-diphenyl ether (BDE 100).

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. Burdens of PBDEs in sediment appear to be a function of distance from the source and their organic carbon content (Hale et al. 2003). The concentrations of PBDEs in sediment samples are summarized in Table 8-3.

In the United States, Dodder et al. (2002) analyzed four surficial sediments from Hadley Lake (Indiana). This lake is in the vicinity of a production point source. DecaBDE (BDE 209) was the major congener detected at concentration ranging from 19 to 36 µg/kg (ng/g) dry weight. Other congeners detected (in

Table 8-3. Concentrations (ng/g) of Several PBDEs in Sediment and Suspended Particulate Samples

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs	BDE 209	Reference
Sediment	Hadley Lake, Indiana	16±2 (dw)	37±8 (dw)	7.1±1.5 (dw)	584 (dw)[a]	480±170 (dw)	Dodder et al. 2002
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, Sweden	3.7	8.8	1.6	14.1	No data	Sellström and Jansson 1995
Sediment	Downstream plastics plant, Sweden	780	1,200	270	2,250	No data	Sellström and Jansson 1995
Sediment	River Viskan (Sweden), up-stream and down-stream 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

[a]includes sum of BDE 47, BDE 99, BDE 100, BDE 209, and other congeners (not specified)

dw = dry weight; ND = not detected

Sources: de Wit 2002; Hale et al. 2003

decreasing order: 2,2',4,4',5-tetrabromodiphenyl ether [BDE 99]; 2,2',4,4',5,5'-hexabromodiphenyl ether [BDE 153]; 2,2',4,4',5,6'-hexabromodiphenyl ether [BDE 154]; 2,2',4,4'-tetrabromodiphenyl ether [BDE 47]; and 2,2',4,4',6-pentabromodiphenyl ether [BDE 100]) were less than 5 µg/kg (ng/g) dry weight. PBDEs were above the detection limit (i.e., 0.5 µg/kg [ng/g] dry weight) in 22% of surficial sediment samples (from 133 sites) in freshwater tributaries of Virginia (Hale et al. 2001b). BDE 47 was the predominant congener followed by BDE 99 and BDE 100. The maximum concentration detected in sediment was 52.3 µg/kg (ng/g) dry weight. Hale et al. (2002) reported that stream sediment adjacent to a former polyurethane foam production facility in North Carolina contained up to 132 µg/kg (ng/g) dry weight of pentaBDE.

In Japan, tetra-, penta-, hexa-, and decabromodiphenyl ethers have been observed in river sediments (Watanabe et al. 1986, 1987, 1995). The combined concentrations of tetra- and pentabromodiphenyl ethers ranged from 21–59 ng/g (µg/kg) dry weight. The concentration of decaBDE (BDE 209) ranged from <25 to 11,600 ng/g (µg/kg) dry weight (deWit 2002). In 1999, sediment samples from several locations in the Netherlands contained BDE 47, BDE 99, and BDE 209 (de Boer et al. 2000). Concentrations ranged from 0.3 to 7.1 ng/g (µg/kg) dry weight for BDE 47, not detected to 5.5 ng/g (µg/kg) dry weight for BDE 99, and not detected to 510 ng/g (µg/kg) dry weight for BDE 209. The concentration of PBDEs in suspended particulate matter ranged from not detected to 9 ng/g (µg/kg) dry weight for BDE 47, not detected to 23 ng/g (µg/kg) dry weight for BDE 99, and not detected to 4,600 ng/g (µg/kg) 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 (µg/kg) 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 BDE 153 ranged from 0.013 to 0.056 ng/g (µg/kg) dry weight in these sediments. The concentrations of decaBDE were highest in sediment from the Seine, ranging from 2.4 to 3.9 ng/g (µg/kg) dry weight. The concentrations of decaBDE in River Mersey (Great Britain), Schelde and River Liffey (Ireland) ranged from 34 to 1,800 ng/g (µg/kg) dry weight. In the southern Baltic Sea (Bornholm Deep), the upper layer of sediment was analyzed for BDE 47, BDE 99, and BDE 100; the combined concentration of these three congeners was 0.52 ng/g (µg/kg) 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 retrospective temporal

trend from 1939 to 1987 showed that the PBDE levels (i.e., sum of BDE 47, BDE 99, and BDE 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, BDE 47, BDE 66, BDE 99, and BDE 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). It is important to note that this study identified the presence of PBDEs compounds in sediments from the late 1950s and early 1960s. This is nearly a decade prior to any significant commercial production of these substances. The existence of PBDEs at these early dates lends some credibility to the likelihood that either the substances identified in the environment as PBDEs are not necessarily PBDEs or that there are yet unknown sources of PBDEs produced in nature.

8.4.4 Other Environmental Media

Polybrominated Biphenyls.

Food. 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).

Fish. 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. Recently, Luross et al. (2002) determined the concentrations of several PBB congeners in lake trout from Lakes Huron, Superior, Erie, and Ontario. 2,2’,4,4’,5,5’-Hexabromobiphenyl (BB-153) and 2,2’,4,5,5’-pentabromobiphenyl (BB-101) were found at the highest levels at concentrations ranging from 189 to 2,083 pg/g wet weight and from 42 to 633 pg/g wet weight, respectively. Several other congeners were also detected in these lake trout samples (see Table 8-4).

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. 3,3’,4,4’,5,5’-Hexabromobiphenyl (BB-169) was found at a maximum concentration of 36 mg/kg (µg/g) 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 2,2’,4,4’,5,5’-hexabromobiphenyl (BB-153) ranged from 0.2 to 4.2 mg/kg (µg/g) lipid (de Boer et al. 2000a).

Animals. 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 (µg/g) and not detected to 1.8 mg/kg (µg/g), respectively (Hesse and Powers 1978). Three bottlenose dolphins

Table 8-4. Mean Concentrations of Nine PBB Congeners in Lake Trout from the Great Lakes (pg/g Wet Weight)

Congener	Lake Superior	Lake Huron	Lake Erie	Lake Ontario
BB-26/29	<1.3	5.2±2.3	<1.3	<1.3
BB-31	<1.8	5.2±1.8	<1.8	<1.8
BB-49	6.8±1.7	125±43	20±7.6	14±4.9
BB-52	8.4±3.6	191±77	24±9.5	11±4.5
BB-80	<3.8	<3.8	<3.8	<3.8
BB-101	42±18	633±359	71±20	109±50
BB-103	<1.5	4.4±1.9	<1.5	<1.5
BB-153	189±105	2,083±1,282	220±47	1,008±513
BB-155	1.0±0.78	5.8±3.4	<0.98	1.1±0.43

Source: Luross et al. 2002

(*Tursiops truncatus*) collected during 1987–1988 from the U.S. mid-Atlantic contained PBBs at concentrations of 14–20 µg/kg (ng/g) 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 (*Haliaeetus leucocephalus*) collected from 29 states in 1977 were 0.07 and 0.05 mg/kg (µg/g), respectively (Kaiser et al. 1980). Twenty-two other specimens did not contain detectable levels (<0.03 mg/kg [µg/g]) 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 (µg/g) 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 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 (ng/g) wet weight from harbor seals collected from the North Sea (decaBB <1 µg/kg [ng/g] 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 (ng/g) wet weight, respectively. Tetra-, penta-, and deca-BBs concentration ranges were 1.1–1.9, 0.4–0.9, and <0.5 µg/kg (ng/g) wet weight, respectively, in sperm whales from the Atlantic Ocean (de Boer et al. 1999).

Human Tissues and Body Fluids. 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 5.5.1).

Hexabromobiphenyl was detected (detection limit 6.6 µg/kg [ng/g]) 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 (ng/g) (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 (µg/g) (Humphrey and Hayner 1975).

In the fall of 1993, the serum levels of BB-167 (2,2’,4,4’,5,5’-hexabromobiphenyl) 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 [ng/g]) and Lake Erie fish consumers had the lowest (0.2 ppb [ng/g]). When the data were then stratified by state of residence, on average, Great Lakes sport fish consumers who live in Michigan had the highest PBB level (0.7 ppb [ng/g]) and residents of Wisconsin had the lowest level (0.05 ppb [ng/g]).

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 [ng/g]), respectively, compared to corresponding median concentrations of 0.003 and 0.006 mg/kg (3 and 6 ppb [ng/g]) 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 (ng/g); serum, 1.7 µg/L) and were lowest in the upper peninsula (median: adipose tissue, 15 µg/kg (ng/g); 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 [ng/g]; 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). Serum PBBs were determined 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 were followed up annually from 1978 through 1993. Median serum PBB concentrations were 2 ppb (n=290; range=0.5–419 ppb [µg/L]).

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 8-5. Recent levels of PBBs in human breast milk (i.e., 1990 to present) were not located (WHO 1994b).

Cow's Milk. 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).

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 8-5. 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 non-quarantined 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 from 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
	Non-pregnant women from exposed farms	3.1 µg/L	No data	Eyster et al. 1983
	Exposed women enrolled in the Michigan Department of Public Health registry	2 µg/L	1993	Henderson et al. 1995
Cord serum	Exposed mothers from lower peninsula	3.2 µg/L	1976–1977	Landrigan et al. 1979
	Mothers from 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 non-quarantined farms	3 µg/L	1974	Humphrey and Hayner 1975
	Children from non-quarantined farms	6 µg/L	1974	Humphrey and Hayner 1975
Placenta	Exposed mothers	<1 µg/L	No data	Eyster et al. 1983
Breast milk	Exposed mothers	370 µg/kg (fat basis)	No data	Eyster et al. 1983
	Exposed mothers from 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

Table 8-5. Tissue Levels of PBBs in Michigan Residents

Tissue	Subject(s)	Mean/median concentration[a]	Year	Reference
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 from lower peninsula	3,940 µg/kg	No data	Brown et al. 1981
	Farm residents from 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 from 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.

Food. Information about the concentrations of PBDEs in food-stuff is very limited. Huwe et al. (2002a) reported total PBDE levels in farm chickens raised in two different regions of the United States. The total PBDE level of discrete samples of chickens raised in Arkansas was 39.4 ng/g whole weight, while one composite sample of chickens raised in North Dakota was 1.7 ng/g whole weight. In the United States, chickens fed ball clay and chickens bought in the grocery store were analyzed for total PBDEs (Environ 2003b). 2,2',4,4',5-Pentabromodiphenyl ether (BDE 99) was the dominant congener in all samples. Total PBDEs ranged between 4 and 35 ng/g lipid weight in chickens fed ball clay and 0.5 ng/g lipid weight in store-bought chicken. Recently, Ohta et al. (2002a) 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 2,2',4,4'-tetrabromodiphenyl ether (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 2,2',4,4',5,5'-hexabromodiphenyl ether (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. 2002a). Bocio et al. (2003) determined the concentrations of PBDEs in food samples from Catalonia, Spain during 2000. The highest concentration of total PBDEs was found in oils and fats (587.7–569.3 pg/g), followed by fish and shellfish (333.9–325.3 pg/g), meat and meat products (109.2–102.4 pg/g), and eggs (64.5–58.3 pg/g). In all these food groups, a predominance of the tetra- and pentaBDE homologs, followed by hexaBDE, was observed in the sum total PBDEs. By contrast, PBDEs were not detected in the groups of fruits, cereals, and tubers. 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 seafoods from the Inland Sea of Japan were determined for samples collected in 1998 (Hori et al. 2000). The congeners, 2,4,4'-tribromodiphenyl ether (BDE 28); BDE 47; 2,3',4,4'-tetrabromodiphenyl ether (BDE 66); BDE 99; 2,2',4,4',6-pentabromodiphenyl ether (BDE 100); BDE 153; and 2,2',4,4',5,6'-hexabromodiphenyl ether (BDE 154) were detected in all analyzed seafood samples. BDE 47 was detected as the predominant congener with concentrations ranging from 58 to 2,100 pg/g wet weight. Harrad et al. (2004) determined the concentrations of several PBDE concengers in omnivorous and vegetarian diet samples from the United Kingdom. Median concentrations of BDE 47

(2,2',4,4'-tetraBDE), 99 (2,2',4,4',5-pentaBDE), 100 (2,2',4,4',6-pentaBDE), 153 (2,2',4,4',5,5'-hexa-BDE), and 154 (2,2',4,4',5,6'-hexaBDE) in omnivorous diet samples were 66.8, 63.8, 10, 20, and 20 pg/g dry weight, respectively. In vegetarian samples, median concentrations of BDE 47 (2,2',4,4'-tetraBDE), 99 (2,2',4,4',5-pentaBDE), 100 (2,2',4,4',6-pentaBDE), 153 (2,2',4,4',5,5'-hexaBDE), and 154 (2,2',4,4',5,6'-hexaBDE) were 47.2, 56.7, 10.0, 20, and 20 pg/g dry weight, respectively. Concentrations of BDE 47, 99, and total PBDE were found to be statistically higher in omnivorous diet samples compared to vegitarian diet samples.

Biosolids and Effluents. The concentrations of PBDEs in biosolids (sewage sludge) and effluents are summarized in Table 8-6. PBDEs were detected in biosolids from four different regions of the United States (Pardini et al. 2001). The total concentrations of pentaBDE in biosolids ranged from 1,100 to 2,290 ng/g dry weight; the levels of pantaBDE were high and consistent, regardless of the region of origin. The concentration of decaBDE (BDE 209) varied widely among biosolids from different regions; the concentration of BDE 209 ranged from 84.8 to 4,890 ng/g dry weight in the biosolid samples. Sewage sludges in the vicinity of the Dan River (Virginia) were collected and analyzed for PBDEs (Hale et al. 2002). Congener patterns suggestive of both penta- and decaBDE commercial products were present at concentrations of 1,370 ng/g dry weight (sum of BDE 47 to BDE 154) and from 1,470 ng/g dry weight, respectively. While no known industrial source of pentaBDE discharged to this plant, the distribution pattern for lower brominated congeners matched the pentaBDE commercial product.

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. de Boer et al. (2000b) determined the concentration of PBDEs in sewage treatment-plant effluents (STP) from the Netherlands. The concentration of total PBDEs ranged from 11 to 35 ng/g dry weight, while the concentrations of 2,2',4,4'-tetrabromodiphenyl ether (BDE 47) and BDE 209 were 11–35 and 310–920 ng/g dry weight, respectively. Kohler et al. (2003) determined the levels of decaBDE in sewage sludge from Switzerland between 1993 and 2002. These authors reported that the average concentration of decaBDE increased with time from 220 to 1,100 ng/g dry weight, corresponding to an average increase of 560%.

World Trade Center Site. In 2001, PBDEs were detected in dust and smoke samples taken near the World Trade Center (WTC) disaster site (Lioy et al. 2002). The highest concentration was for decaBDE (i.e., BDE 209), which was present in thermoplastics (e.g., computers). Concentrations of PBDE

Table 8-6. Concentrations (ng/g Dry Weight) of Several PBDEs in Biosolids (Sewage Sludge) and Effluents

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Sewage sludge	Dan River, Virginia	No data	No data	No data	2,840*	1,470	Hale et al. 2002
Sewage sludge	Gothenburg, Sweden	15	19	3.5	38	No data	Nylund et al. 1992
Sewage sludge	Klippan, Sweden	22	18	5.4	45.4	No data	Sellström 1999; Sellström and Jansson 1995
Sewage Sludge	Rimbo, Sweden	53	53	13	119	No data	Sellström 1999; Sellström and Jansson 1995
Sewage sludge	Three plants, Stockholm, Sweden	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 effluents	Netherlands, several sites	11–35	<1	No data	11–35	310–920	de Boer et al. 2000b

[a]ΣPBDEs 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; Hale et al. 2002

congeners were 107–174 µg/kg dry weight basis for 2,2',4,4'-tetrabromodiphenyl ether (BDE 47), 51.1–74.1 µg/kg dry weight basis for 2,2',4,4',6-pentabromodiphenyl ether (BDE 100), 155–293 µg/kg dry weight basis for 2,2',4,4',5-pentabromodiphenyl ether (BDE 99), 42.0–53.5 µg/kg dry weight basis for 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE 153), 219–305 µg/kg dry wt basis for 2,2',4,4',5,6'-hexabromodiphenyl ether (BDE 154)/PBB-153, and 1,330–2,660 µg/kg dry wt basis for decaBDE (BDE 209). Levels of PBDEs were found to be similar to levels found in sewage sludge (Lioy et al. 2002). No further information on levels of PBDEs in environmental was located for the WTC site.

Freshwater Fish. Monitoring data indicated that the levels of PBDEs are increasing in freshwater organisms with higher concentrations near point sources. The congener profiles show the highest levels for 2,2',4,4'-tetrabromodiphenyl ether (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 in the United States are summarized in Table 8-7. 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, 2,2',4,4',5-pentabromodiphenyl ether [BDE 99], 2,2',4,4',6-pentabromodiphenyl ether [BDE 100], 2,2',4,4',5,5'-hexabromodiphenyl ether [BDE 153], and 2,2',4,4',5,6'-hexabromodiphenyl ether [BDE 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, BDE 99, BDE 153, and BDE 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 BDE 99. An analysis of fish tissue samples from selected locations in Washington State showed that total PBDE concentrations ranged from 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. TetraBDE 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). TetraBDEs dominated the congener pattern with 94–96% of total PBDEs. TetraBDE and pentaBDE 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, BDE 99, BDE 100, BDE 153, and BDE 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

Table 8-7. Concentrations (ng/g Lipid Weight, Except as Noted) of Several PBDEs in Freshwater Fish Samples from the United States

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Alewife	Grand Traverse Bay, Lake Michigan	16	No data	No data	36	No data	Stapleton and Baker 2003
Bloater chub	Grand Traverse Bay, Lake Michigan	11 (fw)	No data	No data	23 (fw)	No data	Stapleton and Baker 2003
Bluegill	Hadley Lake, Indiana	420	320	240	1,900	No data	Dodder et al. 2000
Bluegill	Lake of the Ozarks, Missouri	200	91	59	390	No data	Dodder et al. 2000
Burbot	Grand Traverse Bay, Lake Michigan	43 (fw)	No data	No data	86 (fw)	No data	Stapleton and Baker 2003
Carp	United States	No data	No data	No data	13–22* (fw)	No data	Loganathan et al. 1995
Carp	Detroit River, Grosse Isle, Michigan	3.0 (fw)	0.50 (fw)	0.48 (fw)	40.7*	No data	Rice et al. 2002
Carp	Des Plaines River, Joliet, Illinois	2.54 (fw)	0.5 (fw)	0.44 (fw)	281*	No data	Rice et al. 2002
Carp	Des Plaines River, Joliet, Illinois	1.34 (fw)	0.50 (fw)	0.49 (fw)	78.3*	No data	Rice et al. 2002
Carp (fillet)	Yakima River, Washington	No data	No data	No data	22 (fw)	No data	Johnson and Olson 2001
Crappie	Hadley Lake, Indiana	250	430	150	1,500*	No data	Dodder et al. 2000
Crappie	Lake of the Ozarks, Missouri	190	78	59	340*	No data	Dodder et al. 2000
Deepwater sculpin	Grand Traverse Bay, Lake Michigan	2.8 (fw)	No data	No data	3 (fw)	No data	Stapleton and Baker 2003
Lake trout	Grand Traverse Bay, Lake Michigan	75 (fw)	No data	No data	126 (fw)	No data	Stapleton and Baker 2003
Lake trout	Lake Ontario, United States	No data	No data	No data	540*	No data	Alaee et al. 1999
Lake trout	Lake Ontario, United States	58 (fw)	14 (fw)	5.7 (fw)	No data	No data	Luross et al. 2002
Lake trout	Lake Huron, United States	No data	No data	No data	240*	No data	Alaee et al. 1999
Lake trout	Lake Huron, United States	27 (fw)	7.7 (fw)	3.8 (fw)	No data	No data	Luross et al. 2002
Lake trout	Lake Superior, United States	No data	No data	No data	140*	No data	Alaee et al. 1999
Lake trout	Lake Superior, United States	29 (fw)	12 (fw)	4.1 (fw)	No data	No data	Luross et al. 2002
Lake trout	Lake Erie, United States	No data	No data	No data	117*	No data	Alaee et al. 1999

Table 8-7. Concentrations (ng/g Lipid Weight, Except as Noted) of Several PBDEs in Freshwater Fish Samples from the United States

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Lake trout	Lake Erie, United States	16 (fw)	2.0 (fw)	2.5 (fw)	No data	No data	Luross et al. 2002
Largescale sucker (whole)	Yakima River, Washington	No data	No data	No data	64 (fw)	No data	Johnson and Olson 2001
Largescale sucker (whole)	Spokane River, Washington	No data	No data	No data	105 (fw)	No data	Johnson and Olson 2001
Mountain whitefish (whole)	Spokane River, Washington	No data	No data	No data	1,250 (fw)	No data	Johnson and Olson 2001
Rainbow trout (whole)	Douglas Creek, Washington	No data	No data	No data	1.5 (fw)	No data	Johnson and Olson 2001
Rainbow trout	Spokane River, Washington	No data	No data	No data	20-174 (fw) (fillet) 297 (fw) (whole)	No data	Johnson and Olson 2001
Salmon	Grand Traverse Bay, Lake Michigan	34 (fw)	No data	No data	95 (fw)	No data	Stapleton and Baker 2003
Salmon	Lake Michigan, United States	52.1 (fw)	9.3 (fw)	9.7 (fw)	2,440	No data	Manchester-Neesvig et al. 2001
Smelt	Lake Superior, United States	5.7 (fw)	1.8 (fw)	0.98 (fw)	150	<1.5 (fw)	Dodder et al. 2002
Smelt	Lake Ontario, United States	10 (fw)	5.3 (fw)	1.6 (fw)	240	<1.6 (fw)	Dodder et al. 2002
Starry flounder (whole)	Columbia River, Washington	No data	No data	No data	30 (fw)	No data	Johnson and Olson 2001
Steelhead trout	Lake Michigan, United States	1,700	600	360	3,000*	No data	Asplund et al. 1999b
Whitefish	Columbia River, United States	No data	No data	No data	72 (fw)	No data	Rayne et al. 2003a
Whitefish	Grand Traverse Bay, Lake Michigan	9.8 (fw)	No data	No data	18 (fw)	No data	Stapleton and Baker 2003

[a]ΣPBDEs is the sum of BDE 47, BDE 99, and BDE 100, but if more congeners are included, this is marked with an asterisk (*).

Sources: Luross et al. 2002; Manchester-Neesvig et al. 2001; Rayne et al. 2003; Stapleton and Baker 2003

dw = dry weight; fw = fresh weight

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, 2001b). 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 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) concentrations in 58% of the samples analyzed. PBDEs were identified in fish collected from the Detroit River (Michigan) and Des Plaines Rivers (Illinois). In Detroit River fish (carp and large mouth bass), the congener patterns were dominated by BDE 47; however, in the Des Plaines River carp, the dominant congeners were heptaBDE congeners (2,2',3,4,4',5,6-heptBDE [BDE 181] and 2,2',3,4,4',5',6-heptaBDE [BDE 183]), lesser amounts of 2,3,3',4,4',5,6-heptaBDE (BDE 190), and two hexaBDEs (BDE 154 and BDE 153). Possible sources for the heptaBDE congeners were not obvious since none of the commercial mixtures are known to contain these congeners. Three possible explanations were proposed to explain the presence of the heptaBDE congeners found in Des Plaines River carp: waste discharge from an industrial facility; publicly-owned treatment works (POTW) effluents; or formation *in situ* by decaBDE deposits.

The concentrations of PBDEs in freshwater fish samples from Europe are summarized in Table 8-8. Between 1986 and 1988, levels of 2,2'4,4'-tetrabromodiphenyl ether (BDE 47), 2,2',4,4',5-pentabromodiphenyl ether (BDE 99), and 2,2',4,4',6-pentabromodiphenyl ether (BDE 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

Table 8-8. Concentrations (ng/g Lipid Weight Except as Noted) of Several PBDEs in Freshwater Fish Samples from Europe

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Arctic char	Lake Vättern, Sweden	400	64	51	520	No data	Sellström et al. 1993
Bream	Netherlands (several sites)	0.2–130 (dw)	Not detected	No data	No data	No data	de Boer et al. 2000b
Eels	Netherlands	<20–1,400	No data	No data	<50–1,700	No data	de Boer 1990
Osprey	Sweden	1,800	140	200	2,140	No data	Sellström et al. 1993
Pike	Lake Bolmen, Sweden	65	42	19	130	No data	Kierkegaard et al. 1993
Pike	Dalslands canal, Sweden	94–98	60–79	25–36	180–210	No data	Sellström et al. 1993
Pike	River Viskan, Sweden, upstream and downstream	<46–2,000	<37–1,600	<14–1,000	<130–4,600	Trace	Sellström et al. 1998a
Several fish species	Germany	No data	No data	No data	19–983*	No data	Krüger 1988
Trout	Dalslands canal, Sweden	120–460	130–590	33–150	280–1,200	No data	Sellström et al. 1993
Whitefish	Lake Storvindeln, Sweden	15	7.2	3.9	26	No data	Sellström et al. 1993
Whitefish	Lake Geneva, Switzerland	26	13	2.5	44*	No data	Zennegg et al. 2003
Whitefish	Lake Greifen, Switzerland	96	52	9.1	165*	No data	Zennegg et al. 2003
Whitefish	Lake Biel, Switzerland	75.9	39	7.1	128*	No data	Zennegg et al. 2003
Whitefish	Lake Lucerne, Switzerland	56	46	10	121*	No data	Zennegg et al. 2003
Whitefish	Lake Zürich, Switzerland	56	25	4.5	89*	No data	Zennegg et al. 2003
Whitefish	Lake Nauchatel Switzerland	41	20	4.0	68*	No data	Zennegg et al. 2003
Whitefish	Lake Constance, Switzerland	32	15	2.9	52*	No data	Zennegg et al. 2003
Whitefish	Lake Thun, Switzerland	19	12	2.5	36*	No data	Zennegg et al. 2003

[a]ΣPBDEs is the sum of BDE 47, BDE 99, and BDE 100, but if more congeners are included, this is marked with an asterisk (*).

Sources: de Wit 2002; Zennegg et al. 2003

dw = dry weight; fw = fresh weight

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, BDE 99, and BDE 100 were later confirmed in a follow-up study in which 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, BDE 99, and BDE 100 ranged from not detected to 4,600 ng/g lipid weight, with BDE 47 being the predominant congener (50–90% of total). DecaBDE (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. 1998a). 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 pentaBDE and octaBDE, several industries using pentaBDE, and several landfills receiving wastes suspected to contain PBDEs. Levels of BDE 47, BDE 99, pentaBDE (as technical mixture DE-71), and octaBDE (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, BDE 99, BDE 153, and BDE 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, BDE 99, and BDE 153, respectively; BDE 209 was below the detection limit.

Saltwater Fish. No identifiable temporal trends were found for PDBE levels in marine aquatic species. Spatial trends show higher levels of lower brominated BDE congeners found near human populated areas. The congener profiles show the highest levels for 2,2',4,4'-tetrabromodiphenyl ether (BDE 47). The levels of several PBDEs in marine aquatic species are summarized in Table 8-9. In the year 2000, sole liver collected from five sites along the Canadian west coast (Crofton, Bamfield, Kitimat, Trincomali, and Vancouver) were analyzed for 14 BDE congeners (Ikonomou et al. 2002b); the total PBDE concentrations were 64–340 ng/g lipid while the three highest congener concentrations were 27–160 ng/g lipid (BDE 47), 8.5–54 ng/g lipid (2,2',4,4',6-pentabromodiphenyl ether [BDE 100]), and 9.5–46 ng/g lipid (2,2',4,4',5-pentabromodiphenyl ether [BDE 99]), respectively. The highest levels were found in sole samples collected near Vancouver, Canada. DecaBDE was not detected in these samples at the level of procedural blank. Farmed salmon collected at two locations in Canada were analyzed for PBDE congeners (Easton et al. 2002). Forty-one congeners were detected with BDE 47 at the highest level (690 and 2,600 ng/g wet weight) followed by BDE 99 and BDE 100; total BDE congener levels were 1,188 and 4,147 ng/g wet weight for the two samples. Likewise, wild salmon from four locations in Canada were analyzed for BDE congeners. Levels were a factor of 10 lower for these samples compared to farmed salmon samples. The total PBDE concentration for the 41 detected congeners ranged from 38.7 to 485.2 ng/g wet weight. The concentration of the highest congener, BDE 47, ranged from 29 to 280 ng/g wet weight (Easton et al. 2002). PBDE concentrations in skipjack tuna from Asian offshore waters, off-Seychelles, off-Brazil, and open seas were determined for samples collected during 1996–2001 (Ueno et al. 2003). The concentration of total BDEs in muscles tissues ranged from not detected (<0.05 ng/g lipid) to 53 ng/g lipid. The concentration of the highest congener in muscle tissues, BDE 47, ranged from <0.1 to 15 ng/g lipid. BDE 99, BDE 100, BDE 153, and BDE 154 also were detected; BDE 209 was below the detection limit (<5.0 ng/g lipid) for these samples. Samples collected off the coast of the Seychelles (relatively pristine area) did not have detectable levels of any PBDEs, while samples collected in industrial areas of southeast Asia had the highest. Fall-caught herring (*Clupea harengus*) muscle from five sites along the Swedish coast was analyzed for BDE 47, BDE 99, and BDE 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, BDE 99, and BDE 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, BDE 99, and BDE 153 in Baltic sprat (*Sprattus sprattus*, age 3–13 years). However, this trend was not evident for herring. BDE 47 was the

Table 8-9. Concentrations (ng/g Lipid Weight) of Several PBDEs in Marine Aquatic Species

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Farmed Salmon	Canada	690; 2,600 (ww)	140; 390 (ww)	130; 470 (ww)	1,187; 4,147 (ww)	No data	Easton et al. 2002
Salmon (wild)	Canada	29–280 (ww)	ND–97 (ww)	4.2–43 (ww)	38.7–485.2 (ww)	No data	Easton et al. 2002
Sole liver	West coast, Canada	27–160	9.5–46	8.5–54	64–340*	ND	Ikonomou et al. 2002
Skipjack tuna	Seychelles, Indian Ocean	<0.1	<0.05	<0.05	ND	<5.0	Ueno et al. 2003
Skipjack tuna	East China Sea	9.0–15	2.4–4.7	3.4–4.4	23–34	<5.0	Ueno et al. 2003
Skipjack tuna	Pacific Ocean	2.9–7.9	0.18–3.0	0.56–2.1	5.8–21	<5.0	Ueno et al. 2003
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, Sweden	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
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

Table 8-9. Concentrations (ng/g Lipid Weight) of Several PBDEs in Marine Aquatic Species

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
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]ΣPBDEs is the sum of BDE 47, BDE 99, and BDE 100, but if more congeners are included, this is marked with an asterisk (*).

Source: Easton et al. 2002; de Wit 2002; Ikonomou et al. 2002; Ueno et al. 2003

primary congener with levels ranging from 7.6 to 24 ng/g lipid weight for 1–3-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, BDE 99, and BDE 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, BDE 99, and BDE 153 concentrations in Baltic salmon (*Salmo salar*) muscle were 167, 52, and 4.2 ng/g lipid, respectively (Haglund et al. 1997). BDE 47, BDE 99, and BDE 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, BDE 99, and BDE 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). 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 from several sites in the Netherlands (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 the Amsterdam and Rotterdam harbors, and off the Dutch coast; BDE 47 and BDE 99 ranged from 15 to 280 and from <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. TetraBDE and pentaBDE levels ranged from 0.1 and 17 ng/g fresh weight, with tetraBDE being the major congener. decaBDE 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 (2,4,4'-triBDE [BDE 28], 2,2',4,4'-tetraBDE [BDE 47], 2,3',4,4'-tetraBDE [BDE 66], 2,2',4,4',5-pentaBDE [BDE 99], 2,2',4,4',6-pentaBDE [BDE 100], 2,2',4,4',5,5'-hexaBDE [BDE 153], and 2,2',4,4',5,6'-hexaBDE [BDE 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 near Seto, Japan (Akutsu et al. 2001). Seven PBDEs (BDE 28, BDE 47, 2,3',4,4'-tetraBDE [BDE 66], BDE 99, BDE 100, BDE 153, and BDE 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 Aquatic Organisms. Marine mussels (*Mytilus edulis*) collected at several locations in the Netherlands and analyzed for 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',5,5'-hexaBDE (BDE 153), and decaBDE (BDE 209) (de Boer et al. 2000). Concentrations of BDE 47 and BDE 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.

Marine Animals. In marine animals, temporal trends show increasing levels of lower brominated BDE congeners 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 8-10. PBDEs have been detected in several species of seal from several different sites. In San Francisco Bay, California, the concentrations of PBDEs in harbor seals have increased dramatically over the past decade, with current levels among the highest reported for this species (She et al. 2002). The concentration of total PBDEs (sum of BDE 47, 2,2',4,4',5-pentaBDE [BDE 99], 2,2',4,4',6-pentaBDE [BDE 100], 2,2',4,4',5,5'-hexaBDE [BDE 153], and 2,2',4,4',5,6'-hexaBDE [BDE 154]) in harbor seal blubber increased by over a factor of 50 from a concentration of 88 ng/g lipid for species samples collected in 1988 to a concentration of 2,985–8,325 ng/g lipid for species samples collected in 1998. The highest concentrations reported were for BDE 47, which increased from 45.6 ng/g lipid for blubber samples in 1989 to 2,343–6,682 ng/g lipid for blubber samples collected in 1998. The dominance of the tetraBDE congeners over other congeners may indicate that tetraBDEs bioaccumulate more than the higher brominated congners (She et al. 2002). 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, BDE 99, and BDE 100) (Jansson et al. 1993); male grey seals had 280 ng PBDE/g lipid 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

Table 8-10. Concentrations (ng/g Lipid Weight) of Several PBDEs in Marine Animals

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Bottlenose dolphin	Gulf of Mexico	No data	No data	No data	8,000	No data	Kuehl and Haebler 1995
Harbor seal	San Francisco Bay, California	46–6,682	17–303	No data	No data	No data	She et al. 2000
Harbor seal (blubber)	San Francisco Bay, California	1,304	112	87.1	1,730*	No data	She et al. 2002
Herring Gull Eggs	Lake Superior, United States	253–323 (fw)	202–284 (fw)	83.6–113 (fw)	664–887 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Lake Michigan, United States	522–602 (fw)	323–459 (fw)	167–203 (fw)	1,366–1,400 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Lake Huron, United States and Canada	146–291 (fw)	74.6–161 (fw)	37.3–89.5 (fw)	308–652 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Detroit River, United States	322 (fw)	130 (fw)	92.6 (fw)	639 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Lake Erie, United States	70–163 (fw)	52–55.9 (fw)	24.6–51.8 (fw)	192–340 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Niagara River, United States	168 (fw)	111 (fw)	53 (fw)	432 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Lake Ontario, Canada	220–401 (fw)	113–322 (fw)	66.5–102 (fw)	530–1,003 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	St Lawrence River, United States	220 (fw)	89.8 (fw)	56.6 (fw)	453 (fw)*	No data	Norstrom et al. 2002
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
Bottlenose dolphin	South Atlantic Ocean	No data	No data	No data	180–220	No data	Kuehl et al. 1991
Brunnich's guillemot	Svalbard, Sweden	No data	No data	No data	130	No data	Jansson et al. 1987
Cormorant	England, United Kingdom	170–3,500	50–250	50–1,500	300–6,400*	No data	Allchin et al. 2000
Cormorant liver	Rhine delta, Germany	No data	No data	No data	28,000 (fw)	No data	de Boer 1990
Galaucous gull	Bear Island, Norway (Arctic)	290–634	160	No data	No data	No data	de Wit 2002
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

Table 8-10. Concentrations (ng/g Lipid Weight) of Several PBDEs in Marine Animals

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Harbor porpoise	Britsh Columbia, Canada	50–1,200	No data	No data	350–2,300*	No data	Ikononmou et al. 2000b
Harbor porpoise	England and Wales, United Kingdom	227–6,790	No data	No data	440–7,670	No data	Law et al. 2000
Harbor seal	Baltic Sea	No data	No data	No data	90	No data	Jansson et al. 1987
Harbor seal	Skagerrak, Norway and Sweden	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
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
Minke whale	Netherlands	630	160	79	870	No data	de Boer et al. 1998
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, Sweden	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
Sperm whale	Netherlands	130–250	32–64	21–35	187–349	No data	de Boer et al. 1998
Whitebeaked dolphin	Netherlands	5,500	1,000	1,200	7,700	No data	de Boer et al. 1998

[a]ΣPBDEs is the sum of BDE 47, BDE 99, and BDE 100, but if more congeners are included, this is marked with an asterisk (*).

Sources: de Wit 2002; Norstrom et al. 2002; She et al. 2002

fw = fresh weight

blubber sampled between 1981 and 1988 contained 419 and 350 ng PBDEs/g lipid (total of BDE 47, BDE 99, and BDE 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 evident 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, BDE 99, and BDE 153 in harbor seal from the San Francisco Bay area (She et al. 2000). Mean concentrations for BDE 47, BDE 99, and BDE 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 suggest that PBDEs are transferred to young through breast milk. On Holman Island, Northwest 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 temporal trend study, archived samples of blubber from ringed seals from Holman Island, Northwest 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; 2,2’,4,4’-tetrabromodiphenyl ether (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 2,2’4,4’-tetraBDE (BDE 47), 2,2’,4,4’,5-pentaBDE (BDE 99), and 2,2’,4,4’,6-pentaBDE (BDE 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 2,2',4,4',5-pentaBDE (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, BDE 99, 2,2',4,4',6-pentaBDE (BDE 100), and 2,2',4,4',5,6'-hexaBDE (BDE 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 (decaBDE) was below detection limits in all samples.

Marine Birds. Increasing levels of PBDEs have been found in marine birds and eggs, with 2,2'4,4'-tetra-BDE (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). In 2000, herring gull eggs collected from 15 locations around the Great Lakes (United States and Canada) were pooled and analyzed for PBDEs (Norstrom et al. 2002). A total of 25 di- to hepta-BDE congeners were identified in herring gull throught the Great Lakes system. No mono-, octa-, nona-, or decaBDEs were found at the detection limit of the analysis (0.01–0.05 ng/g wet weight). Seven congeners, 2,4,4'-triBDE (BDE 28), BDE 47, 2,2',4,4',5-pentaBDE (BDE 99), 2,2',4,4',6-pentaBDE (BDE 100), 2,2',4,4',5,5'-hexaBDE (BDE 153), 2,2',4,4',5,6'-hexaBDE (BDE 154), and 2,2',3,4,4',6,6'-heptaBDE (BDE 184) constituted 97.5% of total PBDEs (192–1,400 ng/g wet weight). BDE 47 was the dominant congener (70–602 ng/g wet weight) followed by BDE 99 (52–459 ng/g wet weight). The highest concentrations (1,003–1,400 ng/g wet weight) were found in two Lake Michigan colonies and in Toronto Harbor, Lake Ontario

(Norstrom et al. 2002). Muscle tissues from ospreys (*Pandion haliaetus*), found dead at various locations around Sweden, were pooled and analyzed for PBDEs (Jansson et al. 1993; Sellström et al. 1993). The ospreys' diet was freshwater fish. The combined concentration of BDE 47, BDE 99, and BDE 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, BDE 99, and BDE 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, BDE 99, and BDE 100) was 190 ng/g lipid, with BDE 47 as the predominant congener.

Human Body Tissues and Fluids. 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 lower brominated 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 8-11, 8-12, and 8-13 summarize the concentrations of PBDEs found in blood (serum), adipose tissue, breast milk, and other body tissues or fluids, respectively. Levels of PBDEs in body tissues and fluids from individuals living in the United States have recently been determined. These studies indicate that levels of lower brominated BDEs in body fluids are a factor of 10–100-fold higher for individuals living in the United States compared to individuals living in other regions of the world (e.g., Europe). Serum samples collected from 12 U.S. blood donors in 1988 were analyzed for PBDEs, and BDE 47, BDE 153, BDE 183, and BDE 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, 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). DecaBDE was found at levels above the limit of quantification (1 pmol/g lipid) in 5 of 12 serum samples (Patterson et al. 2000). Serum samples were

Table 8-11. Concentrations (ng/g Lipid Weight) of Several PBDEs in Human Blood Samples

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Human blood	San Francisco, California	ND	No data	No data	No data	No data	Petreas et al. 2002
Human blood	San Francisco, California	95	No data	No data	No data	No data	Petreas et al. 2002
Human blood	San Francisco, California	16.5	No data	No data	No data	No data	Petreas et al. 2003
Human blood	United States (in 1988)	0.63 (median)	0.32 (median)	0.17 (median)	No data	<0.1	Sjödin et al. 2001
Maternal serum	Indiana	28 (9.2–310)	5.7 (2.4–68)	4.2 (1.9–110)	37 (15–580)	No data	Mazdai et al. 2003
Fetal serum	Indiana	25 (8.4–210)	7.1 (2.2–54)	4.1 (1.8–91)	39 (14–460)	No data	Mazdai et al. 2003
Human blood	Sweden	No data	No data	No data	2.1*	No data	Klasson Wehler et al. 1997
Human blood	Sweden, computer dis-assembly 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
Maternal blood	Sweden	0.83 (0.3–5.1)	0.19 (<0.01–1.43)	0.17 (<0.01–0.52)	2.07 (0.71–8.39)	No data	Meironyte Guvenius et al. 2003
Cord blood	Sweden	0.98 (0.33–3.28)	0.07	0.07	0.46–4.28	No data	Meironyte Guvenius et al. 2003
Human blood	Germany	3.9	No data	No data	5.6*	No data	Schröter-Kermani et al. 2000

[a]ΣPBDEs 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; Sjödin et al. 2001

Table 8-12. Concentrations (ng/g Lipid Weight) of Several PBDEs in Human Adipose Tissue Samples

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Human adipose tissue	Northern California	7.0–28	3.1–7.3	No data	No data	No data	She et al. 2000
Human adipose tissue	San Francisco, California	16.5 (5.2–196)	No data	No data	No data	No data	Petreas et al. 2003
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	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	Finland	7.3	2.3	No data	6.2–22*	No data	Strandman et al. 1999
Human adipose tissue	Finland	1.20	0.26	0.09	No data	No data	Smeds and Saukko 2003
Human adipose tissue	Spain	1.36	0.42	No data	No data	No data	Meneses et al. 1999
Human adipose tissue	Japan	459	118	250	1,288	No data	Choi et al. 2003

[a]ΣPBDEs 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; Petreas et al. 2003

ND = not detected

Table 8-13. Concentrations (ng/g Lipid Weight) of Several PBDEs in Human Breast Milk Samples

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Human breast milk	Texas	18.4	5.7	2.9	34.0	8.24 (max)	Schecter et al. 2003b
Human breast milk	Germany	No data	No data	No data	0.6–11*	No data	Krüger 1988
Human breast milk	Uppsala County, Sweden	2.35	0.62	0.38	4.01	No data	
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	Maritimes, 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 area)	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]ΣPBDEs is the sum of BDE 47, BDE 99, and BDE 100, but if more congeners are included, this is marked with an asterisk (*).

collected from a group of 50 Laotian immigrants (aged 19–40) participating in a reproductive outcome study in the San Francisco Bay area (Petreas et al. 2002). Participants were recruited and sampled in the late 1990s. The mean level of BDE 47 in serum was approximately 95 ng/g lipid. The contemporary samples were compared to serum samples taken from a group of over 400 women from the San Francisco Bay in the 1960s. Levels of BDE 47 in all archived samples were below the limit of detection. Recently, Petreas et al. (2003) expanded their investigation to include a diverse group of local women from the San Francisco Bay area sampled in the late 1990s. Their results confirmed earlier findings reported in Petreas et al. (2002). Mean concentrations of BDE 47 in serum samples taken from California women ranged from 5 to 510 ng/g lipid, with a median (16.5 ng/g lipid) 3–10 times higher than those reported from Europe (Petreas et al. 2003). In 2001, Mazdai et al. (2003) determined the concentration of six PBDE congeners (BDE 47, 2,2',4,4',5-pentaBDE [BDE 99], 2,2',4,4',6-pentaBDE [BDE 100], BDE 153, 2,2',4,4',5,6'-hexaBDE [BDE 154], and BDE 183) and total PBDEs in maternal and fetal blood samples taken from subjects in Indianapolis, Indiana. Median levels of total PBDE (sum of six congeners) were 39 and 37 ng/g lipid for fetal and maternal serum, respectively. BDE 47 was the predominant congener reported at median concentrations of 25 and 28 ng/g lipid for fetal and maternal serum samples, respectively. When compared with serum PBDE levels for a similar population of Swedish mothers and newborns, the levels for the Indiana population were 20- to 69-fold higher for maternal blood and 30- to 106-fold higher for fetal blood. In fact, the median blood levels for this study were comparable to Swedish workers considered to have direct work-related exposures. These observations indicated that women in some areas of North America are exposed to much higher levels of lower brominated BDEs (i.e., BDE 47) than are European women. In general, the PBDE congener profile found in human serum was similar to that detected in environmental samples, except that there was an apparent decrease in the proportion of BDE 99. BDE 183 was detected in <17% of the samples even though it is the primary congener in octaBDE commercial mixtures (Mazdai et al. 2003).

Six PBDE congeners (2,4,4'-triBDE [BDE 28], 2,2',4,4'-tetraBDE [BDE 47], 2,3',4,4'-tetraBDE [BDE 66], 2,2',4,4',5-pentaBDE [BDE 99], 2,2',4,4',6-pentaBDE [BDE 100], and 2,2',4,4',5,5'-hexa-BDE [BDE 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, BDE 47, BDE 66, 2,2',3,4,4'-hexa-BDE (BDE 85), BDE 99, BDE 100, BDE 153, and 2,2',4,4',5,6'-hexaBDE (BDE 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). 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).

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 decaBDE (BDE 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, BDE 153, BDE 154, BDE 47, and BDE 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, BDE 183, and BDE 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 of BDE 153. Two octaBDE congeners and one nonaBDE congener were also detected. Connections were observed between fish consumption and serum concentrations for congeners BDE 47, BDE 153, and BDE 183, and between worktime at the computer and congeners BDE 153 and BDE 183.

DecaBDE, as well as hexa- through nonaBDE, 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 octaBDE. NonaBDE concentrations were estimated to be >1 ng/g fat; decaBDE 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 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) (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. Average total PBDEs levels (86 ng/g lipid) were the highest human levels reported to date. Recently, Petreas et al. (2003) expanded their investigation to include a diverse group of local women from the San Francisco Bay area sampled in the late 1990s. Their results confirmed earlier findings reported in She et al. (2000). Mean concentrations of BDE 47 in adipose tissues samples taken from California women were 28.9 ng/g lipid. 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 (2,4,4'-triBDE [BDE 28], 2,2',4,4'-tetraBDE [BDE 47], 2,2',3,4,4'-pentaBDE [BDE 85], 2,2',4,4',5-pentaBDE [BDE 99], 2,2',4,4',6-pentaBDE [BDE 100], 2,2',4,4',5,5'-hexaBDE [BDE 153], and 2,2',4,4',5,6'-hexa-BDE [BDE 154]) (Meironyté Guvenius and Norén 1999). The distribution of congener concentrations in the adipose and liver tissues for each individual were similar. BDE 47, BDE 99, and BDE 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 for 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, BDE 28, BDE 47, BDE 66, BDE 100, BDE 99, BDE 85, BDE 154, and BDE 153) were 5–18 and 4–8 ng/g lipids in liver and adipose tissue, respectively. The PBDE congeners BDE 47, BDE 99, and BDE 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, BDE 99, and BDE 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, BDE 99, and BDE 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).

Human Milk. Recently, Schecter et al. (2003b) reported the first findings on levels of PBDEs congeners in human milk from individuals in the United States. Forty-seven individual milk samples were analyzed from nursing mothers, 20–41 years age, from a milk bank in Austin, Texas, and a community health clinic

in Dallas, Texas, both in the year 2001. The median concentration of the sum of PBDE congeners was 34.0 ng/g lipid. The predominant congener was BDE 47 (18.4 ng/g lipid); other congeners detected were 2,2',4-triBDE (BDE 17), 2,4,4'-triBDE (BDE 28), 2,3',4,4'-tetraBDE (BDE 66), 2,2',3,4,4'-pentaBDE (BDE 85), 2,2',3,4,4'-pentaBDE (BDE 99), 2,2',4,4',6-pentaBDE (BDE 100), 2,2',3,4,4',5'-hexaBDE (BDE 138), 2,2',4,4',5,5'-hexaBDE (BDE 153), 2,2',4,4',5,6'-hexaBDE (BDE 154), and 2,2',3,4,4',5',6-heptaBDE (BDE 183) at median concentrations of 0.01, 1.2, 0.14, 0.41, 5.7, 2.9, 0.09, 2.0, 0.22, and 0.07 ng/g lipd, respectively. DecaBDE was detected in 7 out of 47 samples with a maximum concentration of 8.24 ng/g lipid. PBDE levels in breast milk from this study were similar to levels found in U.S. blood and adipose tissue lipid from California and Indiana and are 10–100 times greater than human tissue levels in Europe (Schecter et al. 2003b).

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 and 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, contains ca. 55% of the total PBDEs. Recently, Lind et al. (2003) reported levels of PBDEs in human breast milk sampled from Uppsala County, Sweden. Total PBDEs, 2,2',4,4'-tetraBDE (BDE 47), 2,2',4,4',5-pentaBDE (BDE 99), and 2,2',4,4',6-pentaBDE (BDE 100) levels were 4.01, 2.35, 0.62, and 0.38 ng/g lipid, respectively. 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 2,4,4-triBDE [BDE 28], -47, -99, -100, 2,2',4,4',5,5'-hexaBDE [BDE 153], and 2,2',3,4,4',5',6-hepta-BDE [BDE 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, BDE 47, BDE 99, and BDE 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, BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154) ranging from 0.66 to 2.8 ng/g lipid weight (Ohta et

al. 2002a). 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. 2002a).

Hydroxy- and Methoxy- Derivatives in Biota. Hydroxy- and methoxy- derivatives of PBDEs have been identified in biota. However, their orgin in the environment has not yet been explained. Anthropogenic sources of these compounds have not been found. Tetra- and pentabrominated methoxy (MeO) BDEs were found in herring, salmon, grey seal, ringed seal, and white-tailed sea eagle from the Baltic region (Asplund et al. 1999a; Haglund et al. 1997; Olsson et al. 2000) as well as beluga whale from Svalbard and pilot whale from the Faroe Islands (van Bavel et al. 2001). The concentrations of hydroxy- and methoxy-derivatives were of the same order of magnitude as PBDEs present in the samples. Biogenic production via metabolism of PBDEs or natural production via biobromination have been suggested as the origin for these compounds. Naturally produced methoxy-tetrabrominated diphenyl ethers have been reported in tropical marine sponges (*sp. Dysidea*) as well as in green algae (*sp. Cladophora*) collected in Japan (Kierkegaard et al. 2004). Kierkegaard et al. (2004) found that the concentrations of 6-methoxy-2,2',4,4'-tetrabromodiphenyl etherin herring from five locations along the Swedish coast increased from south to north in the Baltic Sea. No correlation between the concentrations of BDE congeners and methoxy-brominated diphenyl ethers was observed, indicating sources other than PBDEs for these compounds.

8.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Polybrominated Biphenyls. PBBs 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 8.1), 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 8.4 and Table 8-5). 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 8.4 and Table 8-5). 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 8-5) (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. Body burden data indicate that there are low-level exposures to PBDEs for the general population. However, the current understanding of exactly how low levels of certain PBDE isomers/congeners (e.g., 2,2’,4,4’-tetraBDE [BDE 47]; 2,2’,4,4’,5-pentaBDE [BDE 99]; 2,2’,4,4’,6-pentaBDE [BDE 100]) came to be present in human tissues is insufficient to reach definitive conclusions. Humans appear to be exposed to lower brominated BDEs by ingestion of contaminated foods (e.g., fish) and possibly inhalation of ambient or contaminated air. Dermal exposure to PBDEs could occur by contact with products containing PBDEs such as textiles or polymers. Inhalation exposure could occur from outgassing of PBDEs from electrical appliances and furniture into indoor atmospheres. However, little information is known about the potential exposure from these routes.

In the United States, exposure is evident by the levels of lower brominated PBDEs found in tissues from individuals (see Section 8.4.4). For example, breast adipose samples collected in northern California in the late 1990s contained quantifiable amounts of 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) (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 studies of the general populations of other countries, it has also been shown that exposure to lower brominated PBDE congeners by the general population is widespread (see Section 8.4.4; Haglund et al. 1997; Meneses et al. 1999). In general, levels of decaBDE in human tissues and body fluids are negligible which indicates that direct exposure to decaBDE congener appears to be low. However, the level current information is insufficient to draw conclusions on whether decaBDE degrades in the environment and if possible degradation products of decaBDE may be important sources of human exposure.

The concentration of total PBDEs in outdoor air ranges from 2 (rural) to 77 (urban) pg/m^3 in the United States (Dodder et al. 2000a). Typically, lower brominated congeners (e.g., 2,2',4,4'-tetraBDE [BDE 47]) are predominant which indicates low levels of exposure to these congeners by the general population. Levels of higher brominated congeners (e.g., decaBDE) tend to be below the limit of quantitation. 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, octaBDE 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).

Harrad et al. (2004) found a significant possitive correlation between PBDE concentrations in indoor air and both the number of electrical appliances and the number of chairs containing polyurethane foam. Concentrations of tetra- and pentabrominated concengers (BDE 47, 99, and 100) in indoor air were always higher than those detected in outdoor air. On average, indoor air concentrations were 150, 120, and 140 times higher than outdoor air for BDE 47 (1,700 pg/m^3), 99 (852 pg/m^3), and 100 (217 pg/m^3), respectively. In this study, the median lower bound estimates of inhalation exposure (i.e., where a congener is below the detection limit, the concentration is assumed to be zero) for BDE 47 (2,2',4,4'-tetraBDE), 99 (2,2',4,4',5-pentaBDE), 100 (2,2',4,4',6-pentaBDE), 153 (2,2',4,4',5,5'-hexa-

BDE), 154 (2,2',4,4',5,6'-hexaBDE), and total PBDEs were 4.5, 1.2, 0.41, 0.016, 0.040, and 6.9 ng/day, respectively (Harrad et al. 2004).

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 pentaBDE 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. Harrad et al. (2004) estimated the daily dietary intakes of PBDEs in omnivorous and vegetarian diet samples from the United Kingdom. In this study, the median lower bound estimates of dietary exposure (i.e., where a congener is below the detection limit, the concentration is assumed to be zero) for BDE 47 (2,2',4,4'-tetraBDE), 99 (2,2',4,4',5-pentaBDE), 100 (2,2',4,4',6-pentaBDE), 153 (2,2',4,4',5,5'-hexa-BDE), 154 (2,2',4,4',5,6'-hexaBDE), and total PBDEs were 46.4, 42.6, 0, 0, 0, and 90.5 ng/day, respectively (Harrad et al. 2004). Like PCBs, there may be a higher risk of exposure to PBDEs in Native Americans who reside in the Arctic region and 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 6-6); however, the inhalation of particulate phase PBDEs is possible during plastic reprocessing where grinding or shredding of polymers with PBDEs occurs. Occupational exposure may also likely involve oral exposure to particulate PBDEs as a result of hand-to-mouth activity.

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 (1.25 ng/m^3) for 2,2',4,4'-tetraBDE (BDE 47), 4.6 pmol/m^3 (2.6 ng/m^3) for 2,2',4,4',5-pentaBDE (BDE 99), 6.1 pmol/m^3 (3.93 ng/m^3) for 2,2',4,4',5,5'-hexaBDE (BDE 153), 26 pmol/m^3 (18.8 ng/m^3) for 2,2',3,4,4',5',6-heptaBDE (BDE 183), and 38 pmol/m^3 (36.5 ng/m^3) for decaBDE (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).

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 decaBDE (BDE 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, BDE 153, BDE 154, BDE 47, and BDE 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, BDE 183, and BDE 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 for BDE 153. Two octaBDE congeners and one nonaBDE congener were also detected.

8.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 5.7 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 8.4.4). 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 lower brominated BDEs than children who drink formula milk (see Section 8.4.4). Exposure of neonates is evident due to the presence of lower brominated BDEs (e.g., 2,2',4,4'-tetraBDE [BDE 47]) in breast milk and 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. Schecter et al. (2003b) reported the first findings on levels of PBDEs congeners in human milk from individuals in the United States. The median concentration of the sum of PBDE congeners was 34.0 ng/g lipid with BDE 47 (18.4 ng/g lipid) as the predominant congener. DecaBDE was detected in 7 out of 47 samples with a maximum concentration of 8.24 ng/g lipid. The levels of PBDEs in breast milk from this study were 10–100 times greater than human tissue levels in Europe (Schecter et al. 2003b). Levels of lower brominated BDEs in the breast milk of Swedish women shows an exponentially increasing trend in exposure since the 1970s, with concentrations of lower brominated BDEs in breast milk doubling every fifth year (Lindström 1999). The concentrations of lower brominated BDEs 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 (2,4,4'-triBDE [BDE 28], BDE 47, 2,2',4,4',5-pentaBDE [BDE 99], and decaBDE [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 total PBDEs were found in nulliparous women. In 2001, Mazdai et al. (2003) determined the concentration of six PBDE congeners (BDE 47, BDE 99, 2,2',4,4',6-pentaBDE [BDE 100], BDE 153, 2,2',4,4',5,6'-hexaBDE [BDE 154], and 2,2',3,4,4',5',6-heptaBDE [BDE 183]) and total PBDEs in maternal and fetal blood samples taken from subjects in the United States. Median levels of total PBDE (sum of six congeners) were 39 and 37 ng/g lipid for fetal and maternal serum, respectively. BDE 47 was the predominant congener reported at median concentrations of 25 and 28 ng/g lipid for fetal and maternal serum samples, respectively. Concentrations of PBDEs in fetal and maternal serum were comparable. Thus, the authors concluded that measurement of maternal serum PBDE levels could be used to determine fetal exposure to PBDEs. Concentrations of PBDEs were determined in children from Norway (Thomsen et al. 2002b). Samples were collected between the period of 1975–2002. Children ages 0–4 years had congener levels of BDE 28, BDE 47, BDE 100, BDE 99, 2,2',4,4',5,5'-hexaBDE (BDE 153), and BDE 154 at 0.26, 6.2,

1.7, 1.6, 1.5, and 0.45 ng/g lipid, respectively; while children 4–14 years old had levels of BDE 28, BDE 47, BDE 100, BDE 99, BDE 153, and BDE 154 at 0.20, 2.0, 0.66, 0.37, 0.86, and 0.39 ng/g lipid, respectively. No additional information was found in the literature about the exposure of children to PBDEs (WHO 1994a).

8.7 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 above-average 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 fishermen who consume PBDE-contaminated fish and Native Americans who reside in the Arctic region and consume whale and seal blubber may have a higher risk of exposure to lower brominated PBDEs (WHO 1994a). Other populations with high exposure levels to PBDEs involve occupational exposures (see Section 8.6). No other information was located that identified specific populations with higher exposure levels to PBDEs.

8.8 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 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.

8.8.1 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 6-3). 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 is 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 available (see Table 6-4). Very limited data are available on the physical and chemical properties for the individual congeners (Braekvelt et al. 2003; Tittlemier et al. 2002). 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 for PBDE commercial mixtures (BSEF 2003). PBDEs are used as additive flame retardants in thermoplastics at levels ranging from 5 to 30% by weight (EU 2001). The commercial pentaBDE product is used predominantly (95–98%) for flame-retardant purposes as an additive in consumer products manufactured by the furniture industry (ENVIRON 2003a). The commercial octaBDE is used by the plastics industry as an additive flame retardant for manufactured products. It is used almost exclusively as a flame retardant for acrylonitrile-butadiene-styrene (ABS) terpolymers used in computer casings and monitors (ENVIRON 2003b). The commercial decaBDE product is an additive flame retardant used in a variety of polymer applications. Industry information indicates that decaBDE is used at loadings of 10–15% weight in polymers and is always used in conjunction with antimony trioxide (EU 2002). The Great Lakes Chemical Corporation recently announced that it is voluntarily phasing out production of pentaDBEs and octaDBEs by the end of 2004 (Tullo 2003). In the United States, waste disposal of PBDE-containing consumer products is described as transfers to disposal (landfill), recycling, energy recovery (incineration), or publicly owned treatment works (POTWs) (Darnerud et al. 2001). More information for PBDEs is needed on import/export, release, and disposal. In particular, the mechanism by which PBDEs are leaving the products in which they are used and entering the environment is not understood. Possibilities include

disinigradtion of plastic products in particulates contaminated with PBDEs or volatilization of PBDEs from the plastic itself (Hites 2004). In the United States, waste disposal of PBDE-containing consumer products is described as transfers to disposal (landfills), recycling, energy recovery (incineration), or POTWs (Darnerud et al. 2001). Soil should be a medium of significant contamination due to disposal of PBDE-containing plastics in landfills. The commercial decaBDE and octaBDE products are used in hard dense plastics from which migration would be very difficult (BFRIP 2002). Although it is known that PBDE-containing plastics are disposed in landfills, information on the recycling of PBDE-containing plastics and the amounts of PBDE-containing plastics that are incinerated is not known. Additional information of levels of PBDEs and PBDD/PBDF from incineration of PBDE-containing plastics would be useful in determining exposure to the general population.

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 the 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. Based on limited data, photolysis appears to be the dominant transformation process for some PBDEs (e.g., decaBDE) (Hua et al. 2003). PBDEs absorb light in the environmental spectrum. Hua et al. (2003) found that decaBDE and the commercial octaBDE absorbed

light up to 325 nm, which indicates that these compounds may be susceptible to photodegradation at environmental wavelengths. However, the importance of photochemical transformation reactions in the environment cannot be determined due to lack of quantitative rate information (EU 2002, 2003). Based on a very limited number of studies, biodegradation does not appear to be significant for PBDEs commercial mixtures (EU 2002, 2003). Limited studies have been done on biodegradation of PBDEs in the environment under both aerobic and anaerobic conditions, especially studies investigating de-halogenation mechanisms (EU 2002, 2003). More studies are needed to determine conclusively if commercial PBDE mixtures, such as decaBDE, are degraded to lower brominated congeners (e.g., 2,2'4,4'-BDE [BDE 47]), which appear to bioaccumulate in fish, animals, and humans (see Sections 8.4). 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 5.4). 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 is 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). Also, studies on many persistent halogenated aromatic compounds clearly show that they become progessively less bioavailable with time (Alexander 2000). Often, three-fourths or more of the concentration of such compounds is not bioavailable. Information on the possibility of the very low bioavailability of PBBs is needed.

Polybrominated Diphenyl Ethers. The absorption and distribution of PBDEs as a result of inhalation, ingestion, and dermal exposure are discussed in Sections 5.3.1, 5.3.2, and 5.3.3. Studies that describe the bioavailability of PBDEs commercial mixtures and congeners from ambient air, surface water, and groundwater, or soil do not exist. Essentially no good data exist on the adsorption of PBDEs commercial mixtures and congeners with the exception of decaBDE (BFRIP 2002). Studies on many persistent halogenated aromatic compounds clearly show that they become progessively less bioavailable with time (Alexander 2000). Often, three-fourths or more of the concentration of such compounds is not

bioavailable. Information on the possibility of the very low bioavailability of PBDEs is needed. 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. An abundance of monitoring data illustrate the uptake of lower brominated diphenyl ethers by aquatic organisms, which results in bioconcentration (see Section 8.4.4; Hardy 2002b). Congener components of the pentaBDE commercial product tend to bioconcentrate to different extents. DecaBDE and octaBDE commercial products appear to not bioconcentrate, bioaccumulate, or biomagnify (Hardy 2002b). The limited existing data indicate that lower brominated BDE congeners (e.g., pentaBDE commercial mixtures) bioaccumulate in aquatic and terrestrial food chains and biomagnify in predators due to consumption of contaminated prey. Bioaccumulation of PBDEs in the aquatic food web is inversely related to the degree of bromination (Burreau et al. 2000; Jansson et al. 1993). 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 especially in the United States. Atmospheric concentrations of PBDEs tend to be dominated by lower brominated congeners, e.g., 2,2',4,4'-pentaBDE (BDE 47) (Dodder et al. 2000a; Strandberg et al. 2001). More monitoring data on the concentrations of total PBDEs and PBDE congeners in air in remote, rural, and urban areas, as well as areas near hazardous waste sites and incinerators are needed. Due to the hydrophobic nature of PBDEs, this class of compounds has not been detected in water to any significant extent. BDE 47 was detected at low concentrations in Lake Ontario surface waters (Luckey et al. 2001). Although levels are predicted to be low, monitoring data on PBDE concentrations in finished drinking water nationwide would be helpful. No information was located on the ambient environmental concentrations of PBDEs in soils in the United States or other parts of the world. Hale et al. (2002) reported the concentrations of PBDEs in soil samples collected in the vicinity of a polyurethane foam manufacturing facility, which are higher than expected in rural and potentially urban areas. Sediment concentrations of PBDEs tend to be dominated by higher brominated congeners (e.g., decaBDE or BDE 209) (deWit 2002; Dodder et al. 2002; Hale et al. 2001b, 2002); temporal trends suggest that concentrations of PBDEs in sediments are increasing. Information about the concentrations of PBDEs in food stuffs is very limited (Bocio et al. 2003; Huwe et al. 2002a; Ohta et al. 2002a), especially in the United States. 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. Monitoring data indicated that the levels of PBDEs are increasing in aquatic organisms with higher concentrations near point sources (Alaee et al. 1999; Dodder et al. 2000a; Johnson and Olson 2001; Loganathan et al. 1995; Luross et al. 2000). Additional monitoring data on environmental levels of PBDEs would to useful to determine the extent of contamination in environmental media, and also the mechanisms of human exposure to this class of chemicals.

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 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 lower brominated PBDEs for the general population. The absence of decaBDE (BDE 209) in the ambient population is likely the result of analytical bias since most studies of the ambient population did not include BDE 209 as one of the analytes of interest. Thus, future studies that include the analysis of BDE 209 in body tissues and fluids would be useful (Hites 2004). 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). Limited information on the levels of PBDEs in body tissues and fluids from individuals living in the United States have been located (Mazdai et al. 2003; Patterson et al. 2000; Petreas et al. 2002, 2003; Schecter et al. 2003b; Sjödin et al. 2001). These studies indicate that levels of lower brominated BDEs in body fluids are a factor of 10–100 higher for individuals living in the United States compared to individuals living in other regions of the world (e.g., Europe). Limited 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. Monitoring data indicate 2,2’,4,4’-tetraBDE (BDE 47) and 2,2’,4,4’,5,5’-hexaBDE (BDE 153) are relatively higher in human samples than in the commercial pentaBDE product and that 2,2’,4,4’,5-pentaBDE (BDE 99) is relatively lower. The cause of this difference is not known. It may be due to its relatively higher vapor pressure of BDE 99, or it may be due to the selective environmental elimination of BDE 99, a process that has been observed in some biota (Hites 2004). Additional studies

that examine these trends would be 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 8.4.4). 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; Schecter et al. 2003b; Strandman et al. 2000; WHO 1994a). More data are needed on the levels of PBDEs exposure in nursing women, from occupational situations, 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. 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 is 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 Section 5.12.2 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.

8.8.2 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 of FEDRIP (2003) did not identify ongoing research studies for PBDEs. However, EPA has funded work in the Science To Achieve Results (STAR) Research Grants program, as well as regional and intramural efforts (EPA 2004). In addition, the National Toxicology Program (NTP) has committed to performing studies on the commercial pentaBDE and octaBDE products and their congener components (NTP 2004).

9. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring polybrominated biphenyls (PBBs) and polybromintaed diphenyl ethers (PBDEs), its metabolites, and other biomarkers of exposure and effect to PBBs and PBDEs. 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.

PBBs and 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 analytical methods for PBBs were developed primarily in the 1970s, whereas analytical methods for PBDEs were developed very recently. In the 30 years between analytical efforts directed at PBBs and PBDEs, there have been many advances in the technology and costs of analytical instruments. Thus, while gas chromatography-electron capture detection (GC-ECD) with packed columns (i.e., noncongener specific) was the primary analytical technique used in the 1970s for PBBs, gas chromatography-mass spectrometry (GC-MS) with capillary columns (i.e., congener specific) is the primary analytical technique now used for PBDEs. These points should be considered when comparing the differences and quality of analysis for these two classes of compounds.

Covaci et al. (2003) recently reviewed the determination of brominated flame retardants, with emphasis on PDBEs in environmental and human samples. The analysis methodology for PBBs and PBDEs includes several steps: sample collection and storage, sample pretreatment, extraction, cleanup and fractionation, and analytical determination. Care must be taken to assure that the sample collection follows quality-assurance protocols and that equipment and containers are free from contamination. It is important that laboratories utilize blanks when reporting trace levels of PBBs and PBDEs. This practice will minimize the influence of trace contamination samples that can originate from a variety of sources.

Most sample collections are by grab sampling; however, PBBs and PBDEs may be concentrated from water onto sorbents. Desiccation of solid samples (e.g., soil, sediment, and sewage sludge) is largely done for convenience. Dry samples are more efficiently homogenized, allowing for parallel determination of other analytes (e.g., lipid content) (Covaci et al. 2003).

PBBs and PBDEs are typically separated from the biological and environmental media by extraction with organic solvents. Liquid-solid extraction (e.g., Soxhlet apparatus) remains a widely used technique for solid samples despite recent advances in other extraction techniques. Typical solvents are hexane, toluene, hexane/acetone mixtures, or dichloromethane. New extractions techniques, such as accelerated solvent extraction (ASE) or microwave-assisted extraction (MAE), are also currently used by a number of laboratories. The advantage of these techniques is lower solvent consumption and reduced extraction time. Supercritical fluid extraction (SFE) with solid-phase trapping has been used for the extraction brominated flame retardants from sediment with CO_2 as the supercritical fluid. Extraction with pressurized hot water (PHWE) has been used for the analysis of brominated analytes from sediment. Liquid-liquid extraction has been applied for river and seawater samples, using hexane/acetone mixtures. Solid-phase extraction (SPE) has been used for the analysis of acidic and neutral brominated flame retardants from human plasma (Covaci et al. 2003).

Cleanup steps are necessary to remove compounds that may interfere with the determination (e.g., humic acids, lipids) of PBBs and PBDEs. Lipids (e.g., oils and fats) may be destroyed with concentrated sulfuric acid treatment either directly to the extract or using impregnated silica columns. Chromatography (e.g., gel permeation, silica gel, Florisil) is used to remove other matrix interferences and to fractionate samples (Covaci et al. 2003).

The identification and quantitation of PBBs and PBDEs are most often accomplished by 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 highly brominated compounds. The mass-spectrometer 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 co-elute on a particular HRGC column. The use of MS is indispensable in the definitive identification of PBB and PBDE congeners. 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. However, ECNI, although generally more sensitive and less costly than other ionization methods for PBDE analysis, does not provide information on the molecular ion cluster (as required for qualitative identification). It is also more subject to brominated interferences and does not allow the used of ^{13}C-labeled standards for quantification (Ikonomou and Rayne 2002). Conversely, electron ionization (EI) methods suffer from fragmentation of the molecular ions, creating difficulties in both identification and quantitation of congeners in full-scan and single ion monitoring (SIM) modes, respectively. For example, loss of Br atoms from PBDE congeners during EI may lead to incorrect identification of the parent ion as a lower brominated congener. In addition, the relatively unpredictable fragmentation during EI or ECD restricts the utility of applying relative response factors (RRFs) of one congener for which an analytical standard is available (e.g., 2,2,4,4'-tetrabromodiphenyl ether or BDE 47) for other members of its homolog group (e.g., tetrabromodiphenyl ether [tetraBDEs]). This can result in either under- or overestimating concentrations of congeners for which analytical standards are not available (Ikonomou and Rayne 2002b). In general, hepta- through deca-BDE congeners are difficult to determine accurately by GC analysis, especially in biological samples (Ikonomou and Rayne 2002b).

The analysis of decaBDE (i.e., BDE 209) and 2,2',4,4',5,6'-hexabromodiphenyl ether (i.e., BDE 154) has some analytical difficulties. For example, BDE 209 (1) is not stable at high temperatures in the GC injector and GC column; (2) is sensitive to degradation by UV light (i.e., both sunlight and fluorescent light); (3) behaves differently in the MS source from those of chlorinated and lower brominated compounds (de Boer and Cofino 2002); and (4) may easily adsorb to small dust particles in the laboratory, which may result in sample contamination (Covaci et al. 2003). Thermal decomposition of BDE 209 can be avoided using a short GC column and a thermally inert GC injection port. In contrast, BDE 154 usually coelutes from most gas chromatographic columns with 2,2',4,4',5,5'-hexabromo-biphenyl (PBB-153). In order to ensure the separation of BDE 154 and PBB 153, analysts need to use a sufficiently long GC column. Thus, in order to accurately determine the levels of BDE 209 and BDE 154 in analytical samples, analysts are required perform two separate GC measurements under different operating conditions.

9.1 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; cleanup 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 9-1 and 9-2, 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 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-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; Meironyté Guvenius et al. 2001; Ohta et al. 2002a; Sellström et al. 1993; Sjödin et al. 1999; Thomsen et al. 2001b). Samples are cleaned up to remove interferences using Florisil, silica gel, alumina or activated-charcoal column chromatography, gel-permeation chromatography (GPC),

Table 9-1. 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 ng/g	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 chromato-graphy	GC-ECD	0.7 ng/g	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 ng/g (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 ng/g (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 ng/g	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 ng/g	98	Wolff et al. 1979
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 = hexa-brominated biphenyl; PBBs = polybrominated biphenyls; SIM = selected ion monitoring

Table 9-2. 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 pg/g	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 ng/g 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
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 impact; 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 = selected ion monitoring; SPE = solid phase extraction

and/or liquid chromatography (LC) (Sellström et al. 1993; Cramer et al. 1990; Meironyté Guvenius et al. 2001; Sellström et al. 1993; 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. 2002b; Meironyté Guvenius 1999a, 1999b; Sjödin et al. 1999).

9.2 ENVIRONMENTAL SAMPLES

Most environmental analyses have been performed using multiresidue methods involving solvent extraction of the analytes from the sample matrix, cleanup 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 parts-per-billion (ppb) to parts-per-trillion (ppt) range for water matrices and in the low parts-per-million (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 9-3 and 9-4, 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. 1980; Fawkes et al. 1982; Fehringer 1975b; Wolff et al. 1979b). 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 adsorbents are then Soxhlet extracted with acetone/hexane, and the extracts are cleaned up and analyzed by high-resolution GC techniques.

Table 9-3. 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 ng/g	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 ng/g	No data	Jacobs et al. 1978
Effluent and river water	Extract sample with hexane-ethyl ether	GC-ECD	0.1 ng/g	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 ng/g (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 ng/g	No data	Fehringer 1975
Plants	Cut, extracted with hexane/acetone; clean up with Florisil column	GC-ECD	0.3 ng/g 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

Table 9-4. 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 adsorbents 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 pg/L	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 µg/g	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 ng/g; <5 ng/g	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 µg/g 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
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 pg/g	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

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 Florisil, silica gel, alumina or activated charcoal column chromatography, gel permeation chromatography (GPC), and/or liquid chromatography (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 inter-laboratory study on PBDEs in environmental samples showed that there is good agreement for quantification of BDE 47 and 2,2’,4,4’,6-pentabromodiphenyl ether (BDE 100) congeners. However, improved methods are required for analysis of 2,2’,4,4’,5-pentabromodiphenyl ether (BDE 99), 2,2’,4,4’,5,5’-hexabromodiphenyl ether (BDE 153), 2,2’,4,4’,5,6’-hexabromodiphenyl ether (BDE 154), and BDE 209 congeners (de Boer 2000).

9.3 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 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.

9.3.1 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. 2002b; Eyster et al. 1983; Landrigan et al. 1979; Meironyté Guvenius 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. 2002b; Domino et al. 1980; Fawkes et al. 1982; Fehringer 1975a; Meironyté Guvenius 1999a, 1999b; Sjödin et al. 1999; Willet et al. 1978; Wolff et al. 1979a, 1979b). Additional 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 studies have been conducted to determine if known effects of PBBs and PBDEs 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; Covaci et al. 2003; 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 PBBs 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 PBDDs/PBDFs is achieved before analysis by GC-MS.

9.3.2 Ongoing Studies

No ongoing studies regarding analytical methods for determining PBBs and PBDEs residues or metabolites were located as a result of a search of the Federal Research in Progress Database (FEDRIP 2003).

10. REGULATIONS AND ADVISORIES

Table 10-1 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 exposure to PBBs. 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 lower brominated diphenyl ethers (BDEs). 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 a commercial pentaBDE mixture 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 lower brominated BDEs. The intermediate oral MRL is based on a minimal LOAEL of 2 mg/kg/day for liver effects in rats that were exposed to a commercial pentaBDE mixture for 90 days (WIL Research Laboratories 1984). A chronic-duration oral MRL was not derived for lower brominated BDEs due to insufficient data.

ATSDR has derived an MRL of 10 mg/kg/day for intermediate-duration oral exposure to decaBDE. This intermediate oral MRL is based on a NOAEL of 1000 mg/kg/day for developmental toxicity in rats exposed to decaBDE for 19 days during gestation (Hardy et al. 2002). No acute- or chronic-duration oral MRLs were derived for decaBDE due to insufficient data.

ATSDR has derived an MRL of 0.006 mg/m^3 for intermediate-duration inhalation exposure to lower brominated BDEs. The intermediate inhalation MRL is based on a NOAEL of 1.1 mg/m^3 for thyroid

Table 10-1. 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
	Suggested EPA method	8270	40CFR264,
	PQL	10 µg/L	Appendix IX
d. Food			
FDA	Indirect food additives; substances for use only as components of adhesives		FDA 2001 21CFR175.105 (c)(5)
	Hexabromo-1,1'-biphenyl		
e. 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]	
EPA	Oral reference dose (RfD)		IRIS 2002
	Decabromodiphenyl ether	$1x10^{-2}$ mg/kg/day	

Table 10-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a]

Agency	Description	Information		Reference
	Octabromodiphenyl ether	$3x10^{-3}$ mg/kg/day		
NATIONAL *(cont.)*				
EPA	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 10-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a]

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	Chemical substances known to be manufactured between 01/01/84 and date of promulgation		EPA 2002j 40CFR766.25 (a)(1)
	Decabromodiphenyl ether			
	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	06/30/98	01/11/90	
	Pentabromodiphenyl ether	01/11/90	06/30/98	

Table 10-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a]

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	
EPA	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	The significant new use is any use	EPA 2002n 40CFR721.1790
	Decabromodiphenyl		
	Hexabromo-1,1'-biphenyl		
	Octabromobiphenyl		
	Voluntary children's chemical evaluation program		EPA 2002o
	Decabromodiphenyl ether		
	Octabromodiphenyl ether		
	Pentabromodiphenyl ether		
NTP	Carcinogenicity classification		NTP 2002
	Decabromobiphenyl	Reasonably anticipated to be human carcinogens	
	Octabromobiphenyl		
	Polybrominated biphenyl		
STATE			
Regulations and Guidelines:			
a. Air		No data	
b. Water			
Florida	Drinking water guideline	10 µg/L	HSDB 2002
	p-Bromodiphenyl ether		
c. Food		No data	
d. Other			
Florida	Toxic substance		BLR 2002
	Polybrominated biphenyl		

Table 10-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a]

Agency	Description	Information	Reference
STATE *(cont.)*			
Massachusetts	Hazardous substances requires the labeling of containers of toxic substances in the workplace		BLR 2002
	Decabromobiphenyl	Extraordinary hazardous[g]	
	Decabromdiphenyl ether		
	Hexabromobiphenyl	Extraordinary hazardous[g]	
	Hexabromo-1,1'-biphenyl	Extraordinary hazardous[g]	
	Octabromobdiphenyl	Extraordinary hazardous[g]	
	p-Bromodiphenyl ether		
	Polybrominated biphenyl		
Michigan	Critical materials register; requires all businesses discharging waste products into the water or any sewer system to report the annual amount		BLR 2002
	p-Bromodiphenyl ether		
Minnesota	Hazardous substance		BLR 2002
	Decabromodiphenyl ether		
	Hexabromo-1,1'-biphenyl		
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		BRL 2002
	Decabromodiphenyl ether		
New York	Hazardous substance		BLR 2002
	p-Bromodiphenyl ether		
	Reportable quantity (air)	100 pounds	
	Reportable quantity (land)	100 pounds	

Table 10-1. Regulations and Guidelines Applicable to PBBs and PBDEs[a]

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

effects in rats that were exposed to a commercial octaBDE mixture for 13 weeks (Great Lakes Chemical Corporation 2001a, 2001b).

EPA derived reference doses (RfDs) for octaBDE and pentaBDE of $3x10^{-3}$ and $2x10^{-3}$ mg/kg/day, respectively (IRIS 2002). The current RfD for decaBDE is $1x10^{-2}$ mg/kg/day, but this is based on a study using a preparation that contained only 77% decaBDE; the RfD for decaBDE is currently under review by the IRIS program.

The National Academy of Sciences (NRC 2000) derived a RfD of 4 mg/kg/day for decabromodiphenyl oxide based on a NOAEL of 1,120 mg/kg/day for liver pathology in rats that were exposed for 103 weeks (NTP 1986).

IARC (1987) has classified decabromobiphenyl, hexabromobiphenyl, and octabromobiphenyl in Group 2B, possibly carcinogenic to humans. NTP (2002) has classified decabromobiphenyl, octabromobiphenyl, 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 nonabromodiphenyl 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.

The American Industrial Hygiene Association (AIHA) has established a Workplace Environmental Exposure Level (WEEL) of 5 mg/m^3 for decaBPE (AIHA 1996).

Industry is required to report health and safety data for PBDEs, including decabromodiphenyl ether, octabromodiphenyl ether, and pentabromodiphenyl ether, under the Toxic Substances Control Act (TSCA) (EPA 2002l).

The European Union has banned the sale of products containing more than 0.1% penta- and octaBDE effective August 15, 2004 (EU 2003b). In 2003, the state of California passed an identical ban, to go into effect January 1, 2008 (California Assembly 2003). A subsequent proposed bill would change the implementation date to June 1, 2006 (California Assembly 2004).

11. 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. Atlanta, GA: Subcommittee on Biomarkers of Organ Damage and Dysfunction.

*Agency for Toxic Substances and Disease Registry. 1994. Toxicological profile for chlorodibenzofurans. Atlanta, GA: U.S. Department of Health and Human Services.

*Agency for Toxic Substances and Disease Registry. 1998. Toxicological profile for chlorinated dibenzo-*p*-dioxins. Atlanta, GA: U.S. Department of Health and Human Services.

*Agency for Toxic Substances and Disease Registry. 2000. Toxicological profile for polychlorinated biphenyls. Atlanta, GA: U.S. Department of Health and Human Services.

*Ahmadizadeh M, Kuo C-H, Echt R, et al. 1984. Effect of polybrominated biphenyls, B-naphthoflavone 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. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 131-134.

Alaee M, Wenning RJ. 2002. The significance of brominated flame retardants in the environment: current understanding, issues and challenges. Chemosphere 46(5):579-582.

Alaee M, Arias P, Sjodin A, et al. 2003. An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. Environ Int 29:683-689.

---

*Cited in text

11. REFERENCES

Alaee M, Cannon C, Muir D, et al. 2001a. Brominated flame retardants. Spatial distribution and seasonal variation of PBDEs in Arctic and Great Lakes air. Organohalogen Compounds 52:26-29.

Alaee M, Luross M, Whittle DM, et al. 2002. Bioaccumulation of polybrominated diphenyl ethers in the Lake Ontario pelagic food web. Organohalogen Compounds 57:427-430.

*Alaee M, Sergeant DB, Ikonomou MG, et al. 2001b. 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.

Alcock RE, Jones KC. 1999. New directions "new" organic compounds in the environment. Atmos Environ 33(10):1645-1646.

Allchin CR, de Boer J. 2001. Brominated flame retardants. Results of a comprehensive survey for PBDEs in the River Tees, UK. Organohalogen Compounds 52:30-34.

*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.

Amirova Z, Matorova N, Kruglov E, et al. 2001. Human exposure. Cohort of firemen, Shelekhovo, Russia, PCDD/Fs, PCBs and PBDEs in blood lipids. Organohalogen Compounds 52:217-221.

*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.

11. REFERENCES

*Anderson HA. 1985. Utilization of adipose tissue biopsy in characterizing human halogenated hydrocarbon exposure. Environ Health Perspect 60:127-131.

*Anderson HA, Falk C, Hanrahan L, et al. 1998. Profiles of Great Lakes critical pollutants: a sentinel analysis of human blood and urine. Environ Health Perspect 106(5):279-289.

*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.

*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.

*Ankarberg E, Fredriksson A, Jakobsson E et al. 2001. Increased susceptibility to adult flame retardants exposure (PBDE 99) in mice neonatal exposed to nicotine. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 233-235.

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.

Arend MW, Jarman WM, Ballschmiter K. 2001. Levels in biotic compartments. Organohalogen POPs in fish of the northern Pacific. Organohalogen Compounds 58:437-440.

11. REFERENCES

*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 the U.S. Environmental Protection Agency under TSCA Section 8D. 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 the U.S. Environmental Protection Agency under TSCA Section 8E. 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. to the U.S. Environmental Protection Agency under TSCA Section 8E. 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: Pergamon 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.

11. REFERENCES

*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 AR. 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.

Behnish PA, Hosoe K, Brouwer A, et al. 2001. Dr.-calus-and erod-TEF values for dioxin-like compounds (PxBs/PxDDs/Fs; X=Br,Cl) and others (e.g. PAHs). Organohalogen Compounds 52:49-52.

*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.

11. REFERENCES

*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.

*BFRIP. 2002. Decabromodiphenyl ether (a.k.a. decabromodiphenyl oxide, DBDPO). Voluntary children's chemical evaluation program (VCCEP). Data Summary. Arlington, VA: American chemistry council's brominated flame retardant industry panel (BFRIP).

*Bidleman TF. 1988. Atmospheric processes. Wet and dry deposition of organic compounds are controlled by their vapor-particle partitioning. Environ Sci Technol 22:361-367.

*Bieniek D, Bahadir M, Korte F. 1989. Formation of heterocyclic hazardous compounds by thermal degradation of organic compounds. Heterocycles 28(2):719-722.

*Biesemeier J. 2004. Email communication to Hana Pohl, ATSDR, regarding ongoing non-clinical toxicity studies being conducted by Great Lakes Chemical Corporation (GLCC) in collaboration with Health Canada.. John Biesemeier, Manager, Regulatory Toxicology. West Lafayette, IN. June 08, 2004.

Birnbaum LS. 2001. Health effects of polybrominated dioxins and furans. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 81-84.

*Birnbaum LS, Darcey DJ, McKinney JD. 1983. Hexabromonaphthalene contaminants of polybrominated biphenyls: Chemical composition and disposition in the rat. J Toxicol Environ Health 12:555-573.

Bjorklund J, Tollback P, Ostman C. 2003. Large volume injection GC-MS in electron capture negative ion mode utilizing isotopic dilution for the determination of polybrominated diphenyl ethers in air. J Sep Sci 26:1104-1110.

11. REFERENCES

Blake BW, Enslein K, Gombar VK, et al. 1990. Salmonella mutagenicity and rodent carcinogenicity: quantitative structure-activity relationships. Mutat Res 241(3):261-271.

*Blanck H, 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.

*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.

Blanck H, Marcus M, Tolbert PE, et al. 1999. Age at menarche in girls exposed perinatally to polybrominated biphenyl. Am J Epidemiol 149:S21.

*Blay P, Nilsson C, Owman C, et al. 1993. Transthyretin expression in the rat brain: Effect of thyroid functional state and role in thyroxine transport. Brain Res 632(1-2):114-120.

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. Old Saybrook, CT: Business & Legal Reports, Inc.

*Bocio A, Llobet JM, Domingo JL, et al. 2003. Polybrominated diphenyl ethers (PBDEs) in foodstuffs: human exposure through the diet. J Agric Food Chem 7(51):3191-3195.

*Boethling SB, Mackay D. 2000. Handbook of Property Estimation Methods for Chemicals. Boca Raton, FL: CRC Press LLC.

*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.

Booij K, Zegers BN, Boon JP. 2002. 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*). Chemosphere 46(5):683-688.

Boon JP, Lewis WE, Tjoen-a-Choy MR, et al. 2002. Levels of polybrominated diphenyl ether (PBDE) flame retardants in animals representing different trophic levels of the North Sea food web. Environ Sci Technol 36:4025-4032.

*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.

*Boyages SC. 2000. The neuromuscular system and brain in hypothyroidism. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's the thyroid. Philadelphia, PA: Lippincott Williams & Wilkins, 803-810.

11. REFERENCES

*Braekevelt E, Tittlemier SA, Tomy GT. 2003. Direct measurement of octanol-water partition coefficients of some environmentally relevent brominated diphenyl ether congeners. Chemosphere 51(7):563-567.

*Branchi I, Alleva E, Costa LG. 2001. A preliminary characterization of behavioural alterations following perinatal exposure to a polybrominated diphenylether (PBDE 99). The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 75.

*Branchi I, Alleva E, Costa LG. 2002. Effects of perinatal exposure to a polybrominated diphenyl ether (PBDE 99) on mouse neurobehavioural development. Neurotoxicology 23(3):375-384.

*Brenner KS, Knies H. 1990. Formation of polybrominated dibenzofurans (PBDF's) and -dioxins (PBDDs) during extrusion production of a polybutyleneterephthalate (PBTP)/glass fiber resin blended with decabromodiphenylether (DBDPE)/antimony trioxide: Product and workplace analysis. Organohaolgen Compounds 2:319-324.

*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. Environmental Protection Agency under TSCA Section 8D. OTS052287.

Brouwer A. 1998. Structure-dependent multiple interactions of polyhalogenated aromatic hydrocarbons with the thyroid hormone system. Organohalogen Compounds 37:225-232.

Brouwer A, Meerts IATM, Bergman A, et al. 2001. Thyroidenic, estrogenic, and dioxin-like activity of polybrominated diphenyl ethers (PBDEs) in vitro. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 241-245.

Brown DJ, Van Overmeire I, Goeyens L, et al. 2001. Analysis of brominated flame retardants and brominated dibenzodioxins and biphenyls for Ah receptor activation using the Calux bioassay. Organohalogen Compounds 54:12-15.

Brown DJ, Van Overmeire I, Goeyens L, et al. 2004. Analysis of Ah receptor pathway activation by brominated flame retardants. Chemosphere 55:1509-1518.

*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.

11. REFERENCES

Brown V. 2003. Disrupting a delicate balance: Environmental effects on the thyroid. Environ Health Perspect 111(12):A642-A649.

*BSEF. 2002. An introduction to brominated flame retardants. Brussels, Belgium: Bromine Science and Environmental Forum, 1-28.

*BSEF. 2003. Major brominated flame retardants volume estimate. Total market demand by region in 2001. Brussels, Belgium: Bromine Science and Environmental Forum. http://www.bsef-site.com/bromine/our_industry/.

*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.

Bunce NJ, Chen G, Joyce EM, et al. 2001a. Capacity of PBDEs to induce CYPUA by the Ah receptor mediated pathway. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 77-79.

Bunce NJ, Konstantinov AD, Chittim BG. 2001b. New synthetic methods for polybrominated diphenyl ether congeners. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 183-186.

*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.

*Burreau S, Broman D, Zebuhr Y. 1999. Biomagnification quantification of PBDEs in fish using stable nitrogen isotopes. Organohalogen Compounds 40:363-366.

*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.

Butt CM, Truong J, Diamond ML, et al. 2003. Polybrominated diphenyl ether (PBDE), dioxin and furan (PCDD/F) concentrations in organic window films from southern Ontario. In: Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*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.

*California Assembly. 2003. Assembly Bill No. 302. An act to add Chapter 10 (Polybrominated diphenyl ethers) to Part 3 of Division 104 of the Health and Safety Code, relating to toxic substances. Approved August 9, 2003. http://www.leginfo.ca.gov/cgi-bin/calawquery?codesection=hsc.

*California Assembly. 2004. Assembly Bill No. 2587. A proposed act to amend Sections 108921 and 108922 of the Health and Safety Code, relating to toxic substances. Amended in Senate August 23, 2004. http://www.leginfo.ca.gov/cgi-bin/calawquery?codesection=hsc.

*Canton RF, Letcher R, Sanderson T, et al. 2003. Effects of brominated flame retardants on activity of the steroidogenic enzyme aromatase (CYP19) in H295R human adrenocortical carcinoma cells in culture. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65

*Capen CC. 1997. Mechanistic data and risk assessment of selected toxic points of the thyroid gland. Toxicol Pathol 25:39-48.

*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, Bunce NJ. 2001. PBDE congeners as Ah receptor agonist and antagonists. Organohalogen Compounds 53:353-356.

*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 JW, Harner T, Yang P, et al. 2003. Quantitative predictive models for octanol-air partition coefficients of polybrominated diphenyl ethers at different temperatures. Chemosphere 51(7):577-584.

Chen LC, Berberian I, Koch B, et al. 1992. Polychlorinated and polybrominated biphenyl congeners 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.

Choi J-W, Fujimaki S, Kitamura K, et al. 2002. Polybrominated dibenzo-*p*-dioxins (PBDEs), dibenzofurans (PBDFs) and diphenyl ethers (PBDEs) in Japanese human adipose tissue. Organohalogen Compounds 58:169-171.

Choi J-W, Fujimaki S, Kitamura K, et al. 2003. Historical trends of PBDD/Fs, PBDEs, PCDD/Fs and dioxin-like PCBs in sediment cores from Tokyo Bay. Organohalogen compounds. Boston, MA: Dioxins 2003. 60-65.

*Chou SF, Jacobs LW, Penner, D, et al. 1978. Absence of plant uptake and translocation of polybrominated biphenyls (PBBs). Environ Health Perspect 23:9-12.

Choudhry GG, Sundstrom G, Ruzo LO, et al. 1977. Photochemistry of chlorinated diphenyl ethers. J Agric Food Chem 25:1371-1376.

*Christensen JH, Platz J. 2001. Screening of polybrominated diphenyl ethers in blue mussels, marine and freshwater sediments in Denmark. J Environ Monit 3(5):543-547.

Christensen JH, Glasius M, Pecseli M, et al. 2002. Polybrominated diphenyl ethers (PBDEs) in marine fish and blue mussels from southern Greenland. Chemosphere 47(6):631-638.

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.

*Cordle F, Corneliussen P, Jelinek C, et al. 1978. Human exposure to polychlorinated biphenyls and polybrominated biphenyls. Environ Health Perspect 24:157-172.

Covaci A, Chu SG, Van de Vijver K, et al. 2002a. Levels in biotic compartments. Determination of POPs in harbour porpoises (*Phocoena phocoena*) stranded on the Belgian North sea coast. Organohalogen Compounds 58:443-436.

*Covaci A, de Boer J, Ryan JJ, et al. 2002b. 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.

Covaci A, de Boer J, Ryan JJ, et al. 2002c. Distribution of organobrominated and organochlorinated contaminants in Belgian human tissue. Environ Res 88:210-228.

Covaci A, Voorspoels S, de Boer J. 2003. Determination of brominated flame retardants with emphasis on polybrominated diphenyl ethers (PBDEs) in environmental and human samples- a review. Environ Int 29:735-756.

*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.

Crhova S, Cerna M, Grabie R, et al. 2002. Polybrominated flame retardants. Polybrominated flame retardants in human adipose tissue in Czech Republic inhabitants. The pilot study. Organohalogen Compounds 58:241-244.

*Crisp TM, Clegg ED, Cooper RL, et al. 1998. Environmental endocrine disruption: An effects assessment and analysis. Environ Health Perspect 106(1):11-56.

Cushing CA, Holocky KC, Pyatt DW, et al. 2003. Estimated children's exposure to decabromodiphenyl oxide in the US. Toxicol Sci 72(S-1):393.

*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, Aune M, Atuma S, et al. 2002. Time trend of polybrominated diphenyl ether (PBDE) levels in breast milk from Uppsala, Sweden, 1996-2001. Organohalogen Compounds 58:233-236.

*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, Allchin C. 2001. Brominated flame retardants. An indication of temporal trends in environmental PBDE levels in Europe. Organohalogen Compounds 52:13-17.

*de Boer J, Cofino WP. 2002. First world-wide interlaboratory study on polybrominated diphenyl ethers (PBDEs). Chemosphere 46(5):625-633.

de Boer J, Korytar P. 2001. Analysis of brominated flame retardants - Methodological issues. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 45-49.

*de Boer J, de Boer K, Boon JP. 2000a. Polybrominated biphenyls and diphenylethers. In: Paasivirta J., ed. Handbook of environmental chemistry Vol. 3 part K. Berlin Heidelberg: Springer-Verlag, 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 Monit 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.

de Boer J, Wester PG, van der Horst A, et al. 2003. Polybrominated diphenyl ethers in influents, suspended particulate matter, sediments, sewage treatment plant and effluents and biota from the Netherlands. Environ Pollut 122:63-74.

*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.

Devito M, Zhou T, Taylor M, et al. 2001. Effects of brominated diphenyl ethers on thyroid hormones in a short-term screen and in developmental studies. Organohalogen Compounds 53:1-4.

de Winter-Sorkina R, Bakker MI, Baumann RA, et al. 2003. Exposure assessment for Dutch nursing infants to brominated flame retardants via breast milk. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*de Wit CA. 2000. Levels and trends of BFRs in the European environment. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 135-138.

*de Wit CA. 2002. An overview of brominated flame retardants in the environment. Chemosphere 46(5):583-624.

*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.

*Di Carlo 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.

*Donnelly J, Grange AH, Nunn NJ, et al. 1987. Analysis of thermoplastic resins for brominated dibenzofurans. Biomed Envion Mass Spectrom 18(10):884-896.

*Doucette WJ, Andren AW. 1988. Estimation of octanol/water partition coefficients: Evaluation of six methods for highly hydrophobic aromatic hydrocarbons. Chemosphere 17:345-359.

*Dow Chemical Company. 1971. Results of 30 day dietary feeding studies on octabromodiphenyl SA-1902 and decabromodiphenyl oxide SA-1892.1. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0522265.

*Dow Chemical Company. 1975. Results of a reproduction study in rats maintained on diets containing decabromodiphenyl oxide. Submitted to U.S. Environmental Protection Agency under TSCA Section 8D. OTS0522252.

*Dow Chemical Company. 1985. Decabromodiphenyloxide: A summary of an oral teratology study in Sprague-Dawley rats. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0522284.

*Dumler R, Lenoir D, Thoma H, et al. 1990. Thermal formation of polybrominated dibenzofurans and dioxins from decamromodiphenyl ether flame retardants influence of antimony-III oxide and the polymer matrix. Chemosphere 20(10-12):1867-1874.

*Dumler R, Thoma H, Lenoir D, et al. 1989a. PBDF 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 decabromodiphenyl ether. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 37-39.

*Durst HI, Willett LB, Brumm CJ, 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, NY: 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 analysis of 40 polybrominated diphenyl ethers by gas chromatography/mass spectrometry. J Mass Spectrom 37(1):76-84.

*ENVIRON. 2003a. Voluntary children's chemical evaluation program pilot. Tier I assessment of the potential health risks to children associated with exposure to the commercial octabromodiphenyl ether product. CAS No. 32536-52-0. Emeryville, CA: ENVIRON Int. Corp.

*ENVIRON. 2003b. Voluntary children's chemical evaluation program pilot. Tier I assessment of the potential health risks to children associated with exposure to the commercial pentabromodiphenyl ether product. CAS No. 32534-81-9. Emeryville, CA: ENVIRON Int. Corp.

EPA. 1977. Market input/output studies. Task IV. Polybrominated biphenyls. U.S. Environmental Protection Agency. EPA560677017.

EPA. 1981. Development of test for determining anaerobic biodegradation potential: Washington, DC: U.S. Environmental Protection Agency.

*EPA. 1988a. Polybrominated biphenyl. Code of Federal Regulations: 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. EPA600890066A.

*EPA. 1995. Toxic chemical release inventory. Reporting form R and instructions. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA745K95051.

*EPA. 1997a. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.

*EPA. 1997b. 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. EPA749B98001.

*EPA. 2001. 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. EPA550B98003.

*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. 40CFR 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.

*EPA. 2004a. Decabromodiphenyl ether (CAS No. 1163-19-5). Voluntary children's chemical evaluation program. U.S. Environmental Protection Agency. Office of Pollution Prevention and Toxics. http://www.epa.gov/chemrtk/vccep/chem21.htm. June 24, 2004.

*EPA. 2004b. Pentabromodiphenyl ether (CAS No. 32534-81-9). Voluntary children's chemical evaluation program. U.S. Environmental Protection Agency. Office of Pollution Prevention and Toxics. http://www.epa.gov/chemrtk/vccep/chem22.htm. June 24, 2004.

*EPA. 2004c. Octabromodiphenyl ether (CAS No. 32536-52-0). Voluntary children's chemical evaluation program. U.S. Environmental Protection Agency. Office of Pollution Prevention and Toxics. http://www.epa.gov/chemrtk/vccep/chem23.htm. June 24, 2004.

*EPA. 2004d. NCER. STAR. Science to achieve results. National Center for Environmental Research. U.S. Environmental Protection Agency. http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/search.welcome. September 1, 2004.

*Eriksson J, Jakobsson E, Marsh G, et al. 2001a. Photo decomposition of brominated diphenylethers in methanol/water. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 203-206.

*Eriksson P, Anakarberg E, Viberg H, et al. 2001b. Neonatal exposure to toxicants defined critical period: altered adult susceptibility. Neurotoxicology 22(4):510.

Eriksson P, Fischer C, Karlsson H, et al. 2003. Interaction between a brominated flame-retardant (PBDE 99) and an ortho-substituted PCB (PCB 52) enhances developmental neurotoxic effects. Toxicol Sci 72(S-1):323-324.

*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. 2001c. Brominated flame retardants: a novel class of developmental neurotoxicants in our environment. Environ Health Perspect 109(9):903-908.

Eriksson P, Viberg H, Ankarberg E, et al. 2001d. Polybrominated diphenylethers (PBDEs): A novel class of developmental neurotoxicants in our environment. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 71-73.

*Eriksson P, Viberg H, Fischer C, et al. 2002a. A comparison on developmental neurotoxic effects of hexabromocyclododecane, 2,2',4,4',5,5'-hexabromodiphenyl ether (PBDE 153) and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153). Organohalogen Compounds 57:389-390.

*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. 2002b. 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.

*EU. 2002. Bis(pentabromophenyl) ether. European Union Risk Assessment Report. Luxembourg: Office for Official Publications of the European Committees. EINECS No. 214-604-9, 1-279.

*EU. 2003a. Diphenyl ether, octabromo derivative. European Union Risk Assessment Report. Luxembourg: Office for Official Publications of the European Committees, 1-279.

*EU. 2003b. Consolidated TEXT. CONSLEG system. Office for Official Publications of the European Communities. European Union. http://europa.eu.int/eru-lex/en/consleg/pdf/2003/en_2003L0011_do_001.pdf. September 01, 2004.

*EU. 2004. EU funded research projects. European Union. http://europa.eu.int/comm/research/endocrine/projects_ongoing_en.html. September 1, 2004.

*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.

Farrar NJ, Smith KEC, Lee RGM, et al. 2004. Atmospheric emissions of polybrominated diphenyl ethers and other persistent organic pollutants during a major anthropogenic combustion event. Environ Sci Technol 38:1681-1685.

Farrell TJ. 1980. Glass capillary gas chromatography of chlorinated dibenzofurans, chlorinated anisoles, and brominated biphenyls. J Chromatogr Sci 18:10-17.

Fattore E, Filipsson AF, Hanberg A, et al. 2001. Toxicity of a technical mixture of polybrominated diphenyl ethers following 28 days of oral exposure in male and female rats. Organohalogen Compounds 53:357-361

*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.

11. REFERENCES

*FEDRIP. 2003. 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.

*Fisher DA, Brown RS. 2000. Thyroid physiology in the prenatal period and during childhood. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's the thyroid. Philadelphia, PA: Lippincott Williams & Wilkins, 959-972.

Focant J-F, Sjodin A, Patterson DG. 2003. Qualitative evaluation of thermal desorption-programmable temperature vaporization-comprehensive two-dimensional gas chromatography-time-of-flight mass spectrometry for the analysis of selected halogenated contaminants. J Chromatogr A 1019(1-2):143-154.

*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 PJ, Aust SD. 1978. 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. J Nat Prod58(9):1384-1391.

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. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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 effects. 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 sulfation 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 detected 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 RD, Jenson A, eds. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam, NY: 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.

Gouin T, Thomas GO, Cousins I, et al. 2002. Air-surface exchange of polybrominated diphenyl ethers and polychlorinated biphenyls. Environ Sci Technol 36:1426-1434.

*Great Lakes Chemical Corporation. 1978. Octabromodiphenyl ether. Subacute inhalation toxicity study in rats. International Research and Development Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0522293.

*Great Lakes Chemical Corporation. 1984. 90-Day dietary study in rats with pentabromodiphenyl oxide (DE-71) (Final Report). Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0524336.

*Great Lakes Chemical Corporation. 2000. A 90-day inhalation toxicity study of octabromodiphenyl oxide in albino rats, dated 04/04/02. Submitted to the U.S. Environmental Protection Agency under TCSA Section 8E. OTS0574171-1.

*Great Lakes Chemical Corporation. 2001a. 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 the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0574171.

*Great Lakes Chemical Corporation. 2001b. Support: 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 the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0574171-1. [unpublished study]

*Great Lakes Chemical Corporation. 2004a. Technical information sheets for DE-60F special, DE-61, DE-62, and DE-71. http://www.el.greatlakes.com. February 17, 2004.

*Great Lakes Chemical Corporation. 2004b. Technical information sheet for DE-79. http://www.el.greatlakes.com. February 17, 2004.

*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 RA, Chou SFJ. 1981a. Attenuation of polybrominated biphenyls and hexachlorobenzene by earth materials. Cincinnati, OH: EPA600281191, 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.

Guvenius DM, Noren K. 2000. Multicomponent analysis of organochlorine and organobromine contaminants in human milk, blood plasma, liver and adipose tissue. Organohalogen Compounds 45:45-48.

*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.

11. REFERENCES

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.

Hackenberg R, Looser R, Froescheis O, et al. 2002. Trends of POPs in biota of the Atlantic Ocean - samples of 1981/82 reanalyzed and characterized with GC/ECD, GC/EI-MSD and GC/NCI-MSD. Organohalogen Compounds 56:495-498.

Haddad S, Poulin P, Krishnan K. 2000. Relative lipid content as the sole mechanistic determinant of the adipose tissue:blood partition coefficients of highly lipophillic organic chemicals. Chemosphere 40(8):839-843.

*Hagenmaier H, She J, Benz T, et al. 1992. Analysis of sewage sludge for polyhalogenated dibenzo-*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. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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. 2000a. 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. 2000b. 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, Letcher RJ. 2003. Metabolism in the toxicokinetics and fate of brominated flame retardants - a review. Environ Int 29:801-828.

*Hakk H, Huwe J, Lorentzsen M. 2001. A mass balance study of a commercial pentbromodiphenyl ether mixture in male Sprague-Dawley rats. Organohalogen Compounds 52:5-8.

Hakk H, Larsen G, Bergman A, et al. 2000. Metabolism, excretion and distribution of the flame retardant tetrabromobisphenol-A in conventional and bile-duct cannulated rats. Xenobiotica 30(9):881-890.

*Hakk H, Larsen 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 G, Klasson-Wehler E. 2002. Tissue disposition, excretion and metabolism of 2,2',4,4'5-pentabromodiphenyl ether (BDE-99) in the male Sprague-Dawley rat. Xenobiotica 32(5):369-382.

11. REFERENCES

*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 RC, Alaee M, Manchester-Neesvig JB, et al. 2003. Polybrominated diphenyl ether flame retardants in the North American environment. Environ Int 29:771-779.

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. 2001a. Brominated diphenyl ethers in land-spoiled sewage sludges in the US. BFR:149-152.

*Hale RC, La Guardia MJ, Harvey EP, et al. 2001b. Polybrominated diphenyl ether flame retardants in Virginia freshwater fishes (USA). Environ Sci Technol 35(23):4585-4591.

*Hale RC, La Guardia MJ, Harvey EP, et al. 2002. Potential role of fire retardant-treated polyurethane foam as a source of brominated diphenyl ethers to the US environment. Chemosphere 46(5):729-735.

*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.

Hamm S, Strikkeling M, Ranken PF, et al. 2001. Determination of polybrominated diphenyl ethers and PBDD/Fs during the recycling of high impact polystyrene containing decabromodiphenyl ether and antimony oxide. Chemosphere 44(6):1353-1360.

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 ML. 2001. Assessment of reported decabromodiphenyl oxide blood and air levels in Swedish workers and their workplace. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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.

*Hardy M, Biesemeier J, Manor O. 2001. Results of a prenatal developmental toxicity study of decabromodiphenyl oxide in rats. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 253-257.

*Hardy ML, Schroeder R, Biesemeier J, et al. 2002. Prenatal oral (gavage) developmental toxicity study of decabromodiphenyl oxide in rats. Int J Toxicol 21:83-91

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 of octanol-air partition coefficients (KOA) for polybrominated diphenyl ethers (PBDEs): Predicting partitioning in the environment. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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.

Harner T, Ikonomou M, Shieb M, et al. 2002. Passive air sampling results for polybrominated diphenyl ethers along an urban-rural transect. Organohalogen Compounds 57:33-36.

Harrad S, Wijesekera R, Hunter S, et al. 2004. Preliminary assessment of U.K. human dietary and inhalation exposure to polybrominated diphenyl ethers. Environ Sci Technol 38:2345-2350.

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.

Hayakawa K, Takatsuki H, Watanabe I, et al. 2002. Polybrominated diphenyl ethers (PBDEs), polybrominated dioxins/furans (PBDD/Fs) and monobromo-polychlorinated dioxins/furans (MoBPXDD/Fs) in atmospheric and bulk deposition in Kyoto, Japan. Organohalogen Compounds 59:299-302.

*HazDat. 2004. 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 lymphoma 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 polyhalogenated 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.

11. REFERENCES

Hirai T, Fortutani H, Myouren M, et al. 2002. Concentration of polybrominated diphenyl ethers (PBDEs) in the human bile in relation to those in the liver and blood. Organohalogen Compounds 58:277-280.

*Hites RA. 2004. Polybrominated diphenyl ethers in the environment and in people: A meta-analysis of concentrations. Environ Sci Technol 38(4):945-956.

*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.

Hooper K, She J. 2003. Lessons from the polybrominated diphenyl ethers (PBDEs): precautionary principle, primary prevention, and the value of community-based body-burden monitoring using breast milk. Environ Health Perspect 111(1):109-114.

*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.

Hori S, Akutsu K, Oda H, et al. 2002. Development of an analysis method for polybrominated diphenyl ethers and their levels in Japanese human mother's milk. Organohalogen Compounds 58:245-248.

Hovander L, Bergman A, Jakobsson K. 2001. PBDE levels among personnel employed at an electronics dismantling plant in the Stockholm area. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 295-297.

*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 congeners in C57BL/6N mice: quantitative 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.

*Hua I, Kang N, Jafvert CT, et al. 2003. Heterogeneous photochemical reactions of decabromodiphenyl ether. Environ Toxicol Chem 22:798-804.

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 epidemiological 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.

*Huwe JK, Hakk H, Lorentzsen M. 2002b. A mass balance feeding study of a commercial octabromodiphenyl ether mixture in rats. Organohalogen Compounds 58:229-223.

*Huwe JK, Lorentzsen M, Thuresson K, et al. 2002a. Analysis of mono- to deca-brominated diphenyl ethers in chickens at the part per billion level. Chemosphere 46:635-640.

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 Health 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, Rayne S. 2002. Chromatographic and ionization properties of polybrominated diphenyl ethers using GC/high-resolution MS with metastable atom bombardment and electron impact ionization. Anal Chem 74:5263-5272.

*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.

11. REFERENCES

Ikonomou MG, Fischer M, Antcliffe B, et al. 2001. PBDEs on the rise: as reflected by aquatic species from British Columbia and the Arctic. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 325-328.

*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.

Ikonomou MG, Rayne S, Addison RF. 2002a. Exponential increases of the brominated flame retardants, polybrominated diphenyl ethers, in the Canadian Arctic from 1981 to 2000. Environ Sci Technol 36:1886-1892.

*Ikonomou MG, Rayne S, Fischer M, et al. 2002b. Occurrence and congener profiles of polybrominated diphenyl ethers (PBDEs) in environmental samples from coastal British Columbia, Canada. Chemosphere 46(5):649-663.

*IRDC. 1974. Decabromodiphenyl ether. Acute toxicity studies in rats and rabbits. International Research and Development Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0523319.

*IRDC. 1975a. Octabromodiphenyl ether. Acute toxicity studies in rats and rabbits. International Research and Development Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS052222968.

*IRDC. 1975b Pentabromodiphenyl ether. Acute toxicity studies in rats and rabbits. International Research and Development Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0522286.

*IRDC. 1976. Decabromodiphenyl ether and octabromodiphenyl ether. A twenty-eight day toxicity study in rats. International Research and Development Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0523322.

*IRDC. 1977. Octabromodiphenyl ether. Thirteen week feeding study in rats. International Research and Development Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0522297.

*IRIS. 2002. Integrated Risk Information System. http://www.epa.gov/iris. April 18, 2002.

IRIS. 2004. Integrated Risk Information System. http://www.epa.gov/iris. September 01, 2004.

Jackson MA, Stack HF, Waters MD. 1993. The genetic toxicology of putative nongenotoxic carcinogens. Mutat Res 296(3):241-277.

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.

*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 pollutants in biological samples. Fresenius Z Anal Chem 340:439-445.

*Jansson B, Andersson R, Asplund L, et al. 1993. Chlorinated and brominated persistent organic compounds in biological samples from the environment. Environ Toxicol Chem 12(7):1163-1174.

*Jaret P. 2000. Health concerns: Defense systems under fire. Natl Wildl 38(6):36-41.

*Jaward FM, Meijer SN, Steinnes E, et al. 2004. Further studies on the latitudinal and temporal trends of persistent organic pollutants in Norwegian and U.K. background air. Environ Sci Technol 38:2523-2530.

*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-altered 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 occurrence 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, Kalantzi OI, et al. 2001. Environmental measurements and the global distribution of PBDEs. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 163-166.

Juchau MR. 1993. Chemical teratogenesis. Prog Drug Res 41:9-50.

Kaiser R, Marcus M, Blanck HM, et al. 2003. Polybrominated biphenyl exposure and benign breast disease in a cohort of US women. Ann Epidemiol 13(1):1-23.

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, Haragughi K, Yumoto S, et al. 2002. Metabolite of 2,2'4',5-tetrabromobiphenyl 3-methylsulphonyl-2,2'4',5-tetrabromobiphenyl, a potent inducer of CYP2B1/2 in rat. Xenobiotica 32(4):289-303.

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.

Kester MHA, Bulduk S, van Toor H, et al. 2002. Potent inhibition of estrogen sulfotransferase by hydroxylated metabolites of polyhalogenated aromatic hydrocarbons reveals alternative mechanism for estrogenic activity of endocrine disrupter. J Clin Endocrinol Metab 87(3):1142-1150.

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. 1999a. Dietary uptake and biological effects on decabromodiphenyl ether in rainbow trout (*Oncorhynchus mykiss*). Environ Sci Technol 33:1612-1617.

Kierkegaard A, Sellstrom U, Bignert A, et al. 1999b. Temporal trends of a polybrominated diphenyl ether (PBDE), a methoxylated OBDE, and hexabromocyclodoecane (HBCD) in Swedish biota. Organohalogen Compounds 40:367-370.

Kim TS, Shin SK, Hwang SR, et al. 2002. Method for the analysis of polybrominated biphenyls (PBBs) in environmental samples. Organohalogen Compounds 55:81-84.

*Kimbrough RD. 1987. Human health effects of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). Annu Rev Pharmacol Toxicol 27:87-111.

*Kimbrough R, Buckley J, Fishbein L, et al. 1978a. Animal toxicology. Environ Health Perspect 24:173-184.

*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.

Klamer HJC, Leonards EG, Bakker JF. 2002. Chemical and toxicological risk assessment of North sea surface sediments, brominated flame retardants and dioxin-type toxicity. Organohalogen Compounds 59:111-114.

*Klasson-Wehler EK, Hovander L, Bergman A. 1997. New organohalogen in human plasma-Identification and quantification. Organohalogen Compounds 33:420-425.

*Klasson Wehler E, Morck A, Hakk H. 2001. Metabolism of polybrominated diphenyl ethers in the rat. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 93-97.

*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. 2003. Differential effects of polybrominated diphenyl ethers and polychlorinated biphenyls on intracellular signaling in rat neuronal cultures. Organohalogen compounds. Dioxins:60-65.

*Kodavanti PRS, Derr-Yellin E. 2001. Differential effects of polybrominated diphenyl ethers and polychlorinated biphenyls on [3H]arachidonic acid release in rat neural cells. Organohalogen Compounds 53:185-189.

*Kodavanti PRS, Derr-Yellin EC. 2002. Differential effects of polybrominated diphenyl ethers and polychlorinated biphenyls on [3H]arachidonic acid release in rat cerebellar granule neurons. Toxicol Sci 68:452-457.

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.

*Kohler M, Zennegg M, Gerecke AC, et al. 2003. Increasing concentrations of decabromodiphenyl ether (DecaBDE) in Swiss sewage sludge since 1993. Organohalogen compounds. Dioxins:60-65.

*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 respiratory 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.

11. REFERENCES

*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.

Kucklick JR, Stahl KJ, McFee W, et al. 2002. Toxaphene and PBDEs in Atlantic white-sided and rough-toothed dolphins. Organohalogen Compounds 58:453-455.

*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.

Kuroki H, Sakoda S, Nakaoka H, et al. 2002. Anti-thyroid hormonal activity of the flame retardants, tetrabromobisphenol A and related compounds by a yeast two-hybrid assay. Organohalogen Compounds 56:119-121.

*Kuriyama S, Chahoud I. 2003. Maternal exposure to low dose 2,2',4,4',5 pentabromo diphenyl ether (PBDE 99) impairs male reproductive performance in adult rat offspring. In: Organohalogen Compounds. Dioxins 2003. Volumes 60-65.

Lacorte S, Guillamon M, Martinez E, et al. 2003. Occurrence and specific congener profile of 40 polybrominated diphenyl ethers in river and coastal sediments from Portugal. Environ Sci Technol 37:892-898.

Lacorte S, Martinez E, Guillamon M, et al. 2002. Determination of 40 PBDE in river sediments from Portugal. Organohalogen Compounds 58:175-178.

*Ladenson P, Singer P, Ain K, et al. 2000. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 160:1573-1575.

*LaFranchi S. 1999. Congenital hypothyroidism: Etiologies, diagnosis, and management. Thyroid 9(7):735-740.

*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 Environmental 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.

Larrazabal D, Angeles Martinez M, Fabrellas B. 2003. Innovative approach for the analysis of polybrominated diphenyl ethers (PBDEs) by quadrupole ion-trap mass spectrometry. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Lau F, Destaillats H, Charles MJ. 2003. Experimentally determined Henry's Law constants for six brominated diphenyl ether congeners. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Law RJ, Allchin CR. 2001. Brominated flame retardants in the UK environment. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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.

Law RJ, Allchin CR, Bennett ME, et al. 2002. Polybrominated diphenyl ethers in two species of marine top predators from England and Wales. Chemosphere 46(5):673-681.

*Laws SC, Ferrell JM, Hedge JM, et al. 2003. The effects of DE-71, a commercial polybrominated diphenyl ether mixture, on female pubertal development and thyroid function. Toxicologist 72(5-1):136.

Lebeuf M, Trottier S. 2001. The relationship between age and levels of polybrominated diphenyl ethers in Beluga whales from the St. Lawrence estuary, Canada. Organohalogen Compounds 52:22-25.

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.

Lee RGM, Jones KC. 2002. Atmospheric concentrations of PBDEs in western Europe. Organohalogen Compounds 58:193-196.

Lee S-J, Kim B-H, Kim H-S, et al. 2002. Human blood levels of polybrominated diphenyl ethers in Korea. Organohalogen Compounds 58:205-208.

*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 influence of water and metals on PBDD/F concentration in incineration of decabromobiphenyl ether in polymeric matrices. Chemosphere 28(11):1921-1928.

Leonards PEG, Santillo D, Brigden K, et al. 2001. Brominated flame retardants in office samples. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 299-302.

Letcher RJ. 2003. The state-of-the-science and trends of brominated flame retardants in the environment: present knowledge and future directions. Environ Int 29:663-664.

Letcher RJ, D'Sa I, Valters K, et al. 2003. Polybrominated diphenyl ethers and hydroxylated and methoxylated analogues in Detroit River fish. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

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.

Lichtensteiger W, Ceccatelli R, Faass O, et al. 2003a. Effect of polybrominated diphenylether and PCB on the development of the brain-gonadal axis and gene expression in rats. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*Lichtensteiger W, Ceccatelli R, Faass O, et al. 2003b. Effects of polybrominated diphenylether (PBDE) on reproductive organ and brain development and gene expression in rats. Toxicologist 72(5-1):133.

*Life Sciences Research Israel LTD. 1987. FR-1208: Teratology study in the rat. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4/8. OTS0513908.

Lind Y, Atuma S, Aune M, et al. 2001. Polybrominated diphenyl ethers (PBDEs) in breast milk from Uppsala women - extension and up-dating of data. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 117-264.

*Lind Y, Darnerud PO, Atuma S, et al. 2003. Polybrominated diphenyl ethers in breast milk from Uppsala County, Sweden. Environ Res 93(2):186-194.

*Lindstöm GUM. 1999. Aspects of polybrominated diphenyl ethers as indoor, occupational, and environmental pollutants. Organohalogen Compounds 43:445-446.

*Lindström 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.

Lindström 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.

*Lindström 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.

*Lioy PJ. 2002. Residues from the world trade center disaster in lower Manhattan and potential human exposures. Int J Toxicol 21(6):540.

Litz N. 2002. Some investigations into the behavior of pentabromodiphenyl ether (PEBDE) in soils. J Plant Nutr Soil Sci 165:692-696.

*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 polychlorinated biphenyls, polychlorinated/brominated dibenzo-*p*-dioxins and dibenzofurans, polybrominated biphenyl ethers, and extractable organic halogen in carp from the Buffalo River, New York. Environ Sci Technol 29(7):1832-1838.

Llansola M, Erceg S, Montoliu C, et al. 2001. Comparative study of PBDE 99 and Aroclor 1254 neurotoxicity. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 263-264.

*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.

Lorber M. 2003. Assessment of dioxin inhalation exposures and potential health impacts following the collapse of the world trade center towers. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*Luckey F, Fowler B, Litten S. 2001. Establishing baseline levels of polybrominated diphenyl ethers in Lake Ontario surface waters. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 337-339.

Ludewig G, Tampal NM, Robertson LW. 2003. Comparative study of PCB, PBB and PBDE mixtures on serum parameters in the rat. Toxicol Sci 72(S-1):365.

*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 polybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Great Lakes. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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.

*Luross JM, Alaee M, Sergeant DB, et al. 2002. Spatial distribution of polybrominated diphenyl ethers and polybromintated biphenyls in lake trout from the Laurentain Great Lakes. Chemosphere 46(5):665-672.

*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.

*MacPhail R, Farmer JD, Padnos BK, et al. 2003. Lack of effect of perinatal exposure to a polybrominated diphenyl ether mixture (DE-71) on the habituation of motor activity in adult rats. Toxicol Sci 72(S-1):123.

Madra S, Smith AG. 1992. Induction of cytochrome P450 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, Sonzogni WC, Hahm JL. 2003. A depth profile of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in sediments from Lake Michigan. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

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.

Marcus M. 2003. Pubertal development and exposure to polybrominated biphenyls (PBBs). Toxicol Sci 72(S-1):334.

Marcus M, Cheslack-Postava K, Tolbert PE, et al. 2002. Breast-feeding and PBBs: Response to Rogan and Weil. Environ Health Perspect 110(9):A504.

*Mariussen E, Fonnum F. 2002. The effect of pentabromodiphenyl ether, hexabromocyclododecane and tetrabromobisphenol-A on dopamine uptake into rat brain synaptosomes. Organohalogen Compounds 57:395-398.

*Mariuseen E, Fonnum F. 2003. The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. Neurochem Int 43(4-5):533-542.

*Mariussen E, Andersson PL, Patrik L, et al. 2003a. The effect of various substituents in ortho position of biphenyls on respiratory burst. intracellular calcium elevation in human granulocytes, and uptake of dopamine into rat synaptic vesicles and synaptosomes. Environ Toxicol Pharmacol 14(1-2):43-50.

Mariussen E, Fjeld E, Strand-Andersen M, et al. 2003b. Bioaccumulation of polybrominated diphenyl ethers in fish from the Norwegian Lake Mjosa. Organohalogen Compounds. Dioxins 2003. Boston, MA, 60-65.

Mariussen E, Fjeld E, Strand-Andersen M, et al. 2003c. Spatial distribution of polybrominated diphenyl ethers in trout from Norwegian lakes. Organohalogen Compounds. Dioxins 2003. Boston, MA, 60-65.

*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. NUREG 1575, EPA402R97016.

*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.

Matthews HB, Tuey DB, Anderson MW. 1977b. Pharmacokinetic models for lipophilic compounds. Environ Health Perspect 20:257-262.

11. REFERENCES

*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.

*Mazdai A, Dodder NG, Abernathy MP, et al. 2003. Polybrominated diphenyl ethers in maternal and fetal blood samples. Environ Health Perspect 111:1249-1252.

*McAllister D, Mazac CJ, Gorsich R et al. 1990. Analysis of polymers containing brominated diphenyl ethers as flame retardants after molding under various conditions. Chemosphere 10-12:1537-1541.

*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 sequelae 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.

*McKinney RF, Chaw SJK, Rickenbacher U et al. 1987. Polychlorinated biphenyls and related compound interactions with specific binding sites for thyroxine in rat liver nuclear extracts. J Med Chem 30:79-86.

*MDCH. 2002. http://www.michigan.gov.mdch. May 30, 2002.

Meerts IA, Lujiks E, Marsh G, et al. 1988. Polybrominated diphenylethers (PBDEs) as Ah-receptor agonists and antagonists. Organohalogen Compounds 37:147-150.

*Meerts IA, 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* estrogenicity 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.

Meijer L, Hafkamp AM, Bosman WE, et al. 2003. Non-absorbable fat increases the disposal of 2,2',4,4'-tetrabromodiphenyl (BDE-47) in rats through interruption of the enterohepatic circulation. Organohalogen Compounds. Dioxins 2003. Boston, MA, 60-65.

*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. 1999b. Polybrominated diphenyl ethers in human liver and adipose tissues. A pilot study. Organohalogen Compounds 40:372-382.

Meironyte Guvenius DM, Noren K. 2001. Polybrominated diphenyl ethers in Swedish human milk. The follow-up study. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 303-305.

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, Bergman A, Noren K. 2002. Occurrence and pre-and postnatal transfer of PBDEs, PCBs and OH-PCBs in humans. Organohalogen Compounds 55:271-274.

*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.

*Meylan WN, Howard PH. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere 26:2293-2299.

*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.

*Microbiological Associates Inc. 1996. Pentabromodiphenyloxide and octabromodiphenyl oxide. Maximization test in guinea pigs. Submitted to U.S. Environmental Protection Agency under TSCA Section FYI. OTS0001281.

Miguel R, Laboa G. 2001. Identification of brominated flame retardants in plastics from End of Life Electric and Electronic Equipments in view of WEEE directive. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 187-191.

*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 synthesis 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. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 153-157.

Moon H-B, Choi H-G, Kim S-S, et al. 2002a. Contaminations of polybrominated diphenyl ethers in marine sediments from the southern coastal areas of Korea. Organohalogen Compounds 58:217-220.

Moon H-B, Choi H-G, Kim S-S, et al. 2002b. Polybrominated diphenyls in marine sediments and bivalves from the coastal areas of Korea. Organohalogen Compounds 58:221-224.

*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, Hakk H, Orn U, et al. 2003. Decabromodiphenyl ether in the rat: absorption, distribution, metabolism, and excretion. Drug Metab Dispos 31:900-907.

*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. Reproductive 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.

Muir D, Teixeira C, Chigak M, et al. 2003. Current deposition and historical profiles of decabromodiphenyl ether in sediment cores. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Muir T, Alaee M. 2002. Costs and benefits of brominated flame retardants (BFRs) and alternatives. Organohalogen Compounds 58:237-240.

*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.

Nace CG, Maddaloni M, LaPosta D, et al. 2003. Measuring and evaluating impacts of dioxin-like compounds in residential apartments near the world trade center site. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Nagayama J, Takasuga T, Tsuji H. 2001. Contamination levels of brominated flame retardants, dioxins and organochlorine compounds in the blood of Japanese adults. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 113-116.

Nagayama J, Tsuji H, Takasuga T. 2000. Comparison between brominated flame retardants and dioxins or organochlorine compounds in blood levels of Japanese adults. Organohalogen Compounds 48:27-30.

*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-560677017.

NIES/EPA. 2002. Superfund Basic Research Program. Current research programs. http://benson.niehs.nih/sbrp/Program2000/program00.cfm.

Nikiforov VA, Karavan VS, Miltsov SA. 2003. Synthesis and characterization of methoxy- and hydroxy- polybromodiphenyl ethers. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*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.

*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.

*Norstrom RJ, Simon M, Moisey J, et al. 2002. Geographical distribution (2000) and temporal trends (1981-2000) of brominated diphenyl ethers in Great Lakes herring gull eggs. Environ Sci Technol 36:4783-4789.

*NRC. 1993. Pesticides in the diets of infants and children. National Research Council. 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 carcinogenesis 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.

*NTP. 2004. 2,2',4,4',5,5'-Hexabromodiphenyl ether. National Toxicology Program. http://ntp-server.niehs.nih.gov/htdocs/Results_status/ResstatH/M010078.html. September 1, 2004.

*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.

Oberg K, Warman K, Oberg T. 2002. Distribution and levels of brominated flame retardants in sewage sludge. Chemosphere 48(8):805-809.

*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. 2002a. Comparison of polybrominated diphenyl ethers in fish, vegetables, and meats and levels in human milk of nursing women in Japan. Chemosphere 46(5):689-696.

Ohta S, Nakao T, Nishimura H, et al. 2002b. Contamination levels of PBDEs, TBBPA, PCDDs/DFs, PBDDs/DFs and PXDDs/DFs in the environment of Japan. Organohalogen Compounds 57:57-60.

Ohta S, Nishimura H, Nakoa T, et al. 2001. Characterization of the photolysis of decabromodiphenyl ether and the levels of PBDEs as its photoproducts in atmospheric air of Japan. Organohalogen Compounds 52:321-324.

*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.

Oliaei F, King P, Phillips L. 2002. Occurrence and concentrations of polybrominated diphenyl (PBDEs) in Minnesota environment. Organohalogen Compounds 58:185-188.

*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.

*Palha J, Fernandes R, de Escobar G, et al. 2000. Transthyretin regulates thyroid hormone levels in the choroid plexus, but not in the brain parenchyma: Study in a transthyretin-null mouse model. Endocrinology 141(9):3267-3272.

*Palha J, Hays M, Morreale de Escobar G, et al. 1997. Transthyretin is not essential for thyroxine to reach the brain and other tissues in transthyretin-null mice. Am J Physiol 272(3 Pt 1):E485-E493.

Palm A, Cousins IT, Mackay D, et al. 2002. Assessing the environmental fate of chemicals of emerging concern: a case study of the polybrominated diphenyl ethers. Environ Pollut 117:195-213.

Papke O, Bathe L, Bergman A, et al. 2001. Determination of PBDEs in human milk from the United States. Comparison of results from three laboratories. Organohalogen Compounds 52:197-200.

*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. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 33-36.

Peng J-H, Cheng C-Y, Huang C-W, et al. 2003. Determination of polybrominated diphenyl ethers and polybrominated dibenzo-*p*-dixoins/dibenzofurans in flue gas analysis. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Pereg D, Ryan JJ, Ayotte P, et al. 2003. Temporal and spatial changes of brominated diphenyl ethers (BDEs) and other POPs in human milk from Nunavik (Arctic) and southern Quebec. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Peterman P, Orazio CE, Feltz KP. 2003. Sunlight photolysis of 39 mono-hepta PBDE congeners in lipid. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*Peters AJ, Coleman P, Jones KC. 1999. Organochlorine pesticides in UK air. Organohalogen Compounds 41:447-450.

Peters AK, Sanderson JT, Bergman A, et al. 2003a. Induction and inhibition of cytochrome P450 1A1, 1B1, and ethoxyresorufin-O-deethlation activity by polybrominated diphenyl ethers (PBDE) in MCF7 cells. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Peters L, Sanderson T, Bergman A, et al. 2003b. Agonistic and antagonistic effects on polybrominated diphenyl ethers (PBDE) in MCF7 cells. Toxicol Sci 72(S-1):369-370.

*Petreas M, She J, Brown FR, et al. 2002. High PBDE concentrations in California human and wildlife populations. Organohalogen Compounds 58:177-180.

*Petreas M, She J, Brown FR, et al. 2003. High body burdens of 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) in California women. Environ Health Perspect 111(9):1175-1179.

Pettersson A, Engwall M, Olsman H. 2001a. EROD-induction by polybrominated diphenyl ethers in cultured chick embryo livers. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 267-270.

*Pettersson A, Karlsson M, van Bavel B, et al. 2002. Concentrations of polybrominated diphenylethers and thyroid hormones in human plasma from exposed workers. Organohalogen Compounds 58:269-272.

Pettersson A, Westberg H, Engwall M, et al. 2001b. Concentrations in air and dust of polybrominated diphenyl ethers and tetrabromobisphenol A. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 223-226.

*Pettigrew A. 1993. Flame retardants (halogenated). In: Kroschwitz JI, Howe-Grant M, eds. Kirk-Othmer encyclopedia of chemical technology. Explosives and propellants to flame retardants for textiles. Vol. 10. 4th edition. New York, NY: John Wiley & Sons, 960-976.

*Pharmakon Associates Inc. 1984. Initial submission: Acute oral toxicity in rats (14 days) of Saytex 115 (pentabromodiphenyloxide). Submitted to the U.S. Environmental Protection Agency under TSCA Section FYI. 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.

Pirard C, De Pauw E, Focant J-F. 2003. Levels of selected PBDEs and PCBs in Belgian human milk. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*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.

11. REFERENCES

*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.

*Rao P, Kodavanti S, Zhang P. 2003. Effects of polybrominated diphenyl ethers and polychlorinated biphenyls on [^{3}H] phorbol ester binding in rat neurons. J Neurochem 85(suppl 1):13.

*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.

Rayn JJ, Patry B. 2001. Body burdens and food exposure in Canada for polybrominated diphenyl ethers (BDES). Organohalogen Compounds 51:226-229.

Rayne S, Ikonomou MG. 2002. Reconstructing source polybrominated diphenyl ether congener patterns from semipermiable membrane devices in the Fraser River, British Columbia, Canada: comparison to commercial mixtures. Environ Toxicol Chem 21(11):2292-2300.

*Rayne S, Ikonomou MG, Antcliffe B. 2003a. Rapidly increasing polybrominated diphenyl ether concentrations in the Columbia River system from 1992 to 2000. Environ Sci Technol 37(13):2847-2854.

*Rayne S, Ikonomou MG, Whale MD. 2003b. Anaerobic microbial and photochemical degradation of 4,4'-dibromodiphenyl ether. Water Res 37:551-560.

*Reistad T, Mariussen E, Fonnum F. 2002. The effect of brominated flame retardants on cell death and free radical formation in cerebellar granule cells. Organohalogen Compounds 57:391-394.

*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.

11. REFERENCES

*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.

*Rice CP, Chernyak SM, Begnoche L, et al. 2002. Comparisons of PBDE composition and concentration in fish collected from the Detroit River, MI and Des Plaines River, IL. Chemosphere 49(7):731-737.

*Rickenbacher U, McKinney JD, Oatley, SJ et al. 1986. Structurally specific binding of halogenated biphenyls to thyroxine transport protein. J Med Chem 29:641-648.

*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]pyrene 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.

Rogan WJ, Weil WB. 2001. Duration of breast-feeding and PBBs. Environ Health Perspect 110(9):A503.

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 *S. 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 Sprague-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.

11. REFERENCES

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. 2001a. Body burdens and exposure from food for polybrominated diphenyl ethers (BDEs) in Canada. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 103-106.

Ryan JJ, Patry B. 2001b. Body burdens and exposure from food for polybrominated diphenyl ethers (BDEs) in Canada. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 103-106.

Ryan JJ, Patry B, Mills P, et al. 2002. Recent trends in levels of brominated diphenyl ethers (BDES) in human milks from Canada. Organohalogen Compounds 58:173-176.

*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. 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, 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-halogenated 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. 2000. Toxicology of persistent organic pollutants. Eur J Lipid Sci Technol :52-53.

*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.

Sakai S-I. 2000. Thermal behavior of brominated flame retardants and PBDDs/DFs. Organohalogen Compounds 47:210-213.

11. REFERENCES

Sakai S-I, Morita M. 2003. Polybrominated dibenzo-*p*-dioxins, dibenzofurans, and diphenyl ethers in Japanese human adipose tissue. Environ Sci Technol 37:817-812.

Sakai S-I, Hayakawa K, Okamoto K, et al. 2002. Time trends and horizontal distribution of polybrominated diphenyl ethers (PBDEs) in sediment cores from Osaka Bay, Japan. Organohalogen Compounds 58:189-192.

Sakai S-I, Hirai Y, Tani H, et al. 2003. Time trends and fate analysis of polybrominated diphenyl ethers (PBDEs) in sediment cores. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*Sakai S-I, Honda Y, Takatsuki H, et al. 2001a. Polybrominated substances in waste electrical and electronic plastics and their behavior in the incineration plants. Organohalogen Compounds 52:35-38.

Saki S-I, Watanabe J, Honda Y, et al. 2001b. Combustion of brominated flame retardant and behavior of its byproducts. Chemosphere 42(5-7):519-531.

Sakai S-I, Watanabe J, Takatsuki H, et al. 2001c. Presence of PBDDs/DFs in flame retardant materials and their behavior in high temperature melting processes. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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.

*Sandholm A, Emanuelsson BM, Klasson-Wehler E. 2003. Bioavailability and half-life of decabromodiphenyl ether (BDE-209) in rat. Xenobiotica 33(11):1149-1158.

Santos FJ, Abalos M, Malavia J, et al. 2003. Ion trap MS/MS vs. HRMS for the analysis of PCDDs/Fs and dioxin-like PCBs in food samples. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*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.

Schecter A, Pavuk M, Papke O, et al. 2003a. Congener specific measurement of polybrominated diphenyl ethers in 47 individual milk samples from nursing mothers in the U.S.A. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*Schecter A, Pavuk M, Papke O, et al. 2003b. Polybrominated diphenyl ethers (PBDEs) in U.S. mother's milk. Environ Health Perspect 111(14):1723-1729.

*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.

*Sellström U, Jansson B. 1995. Analysis of tetrabromobisphenol A in a product and environmental samples. Chemosphere 31(4):3085-3092.

*Sellström U, Jansson B, Kierkegaard A, et al. 1993. Polybrominated diphenyl ethers (PBDE) in biological samples from the Swedish environment. Chemosphere 26(9):1703-1718.

*Sellström 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.

*Sellström 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.

Sellström U, Lindberg P, Haggberg L, et al. 2001. Higher brominated PBDEs found in eggs of peregrine falcons (*Falco peregrinus*) breeding in Sweden. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 159-162.

*Sellström 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, 143-172.

*Shah BP. 1978. Environmental considerations for the disposal of PBB-contaminated animals and wastes. Environ Health Perspect 23:27-35.

She J, Holden A, Tanner M, et al. 2003. High PBDE levels in piscivorous seabird eggs from the San Francisco Bay and Washington State. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

She J, Petreas M, Winkler J, et al. 2000a. Harbor seals as indicators of halogenated contaminants in San Francisco Bay. Organohalogen Compounds 49:422-425.

*She J, Petreas M, Winkler J, et al. 2002. PBDEs in the San Francisco Bay area: measurement in harbor seal blubber and human breast adipose tissue. Chemosphere 46(5):697-707.

*She J, Wrinkler J, Visita P, et al. 2000b. Analysis of PBDEs in seal blubber and human breast adipose tissue samples. Organohalogen Compounds 47:53-56.

Sheehan DM. 2003. Four different dose-response curve shapes for endocrine-disrupting chemicals - consequences for risk assessment. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Shelby MD, Witt KL. 1995. Comparison of results from mouse bone marrow chromosome aberration and micronucleus 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 568581813. PB84166495.

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 ^{125}I-thyroxin (T4) binding to choroid plexus by hydroxylated PCB metabolites. Organohalogen Compounds 37:241-244.

Sinkkonen S, Lahtipera M, Vattulainen A, et al. 2003. Analysis of known and new types of polyhalogenated aromatic substances in oven ash from recycled aluminum production. Chemosphere 52(4):761-775.

*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, Patterson DG, Bergman A. 2003. A review on human exposure to brominated flame retardants—particularly polybrominated diphenyl ethers. Environ Int 29:829-838.

*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.

*Smeds A, Saukko P. 2003. Brominated flame retardants and phenolic endocrine disrupters in Finnish human adipose tissue. Chemosphere 53:1123-1130.

*Smolnikar K, Dehnhardt M, Wiegand H. 2001. Perturbation by PBDE99 of calcium homeostasis after in vitro treatment. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 273.

Soderstrom G, Marklund S. 2002. PBCDD and PBCDF from incineration of waste-containing brominated flame retardants. Environ Sci Technol 36:1959-1964.

Soderström G, Sellström U, De Wit CA, et al. 2004. Photolytic debromination of decabromodiphenyl ether (BDE 209). Environ Sci Technol 38:127-132.

Solomon GM, Huddle AM. 2002. Low levels of persistent organic pollutants raise concerns for future generations. J Epidemiol Commun Health 56:826-827.

Sonzogni W, Manchester-Neesvig J. 2001. Polybrominated diphenyl ethers (PBDEs) in the Lake Michigan salmonids. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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.

*SRI. 2002. 2002 Directory of chemical producers- United States of America. Menlo Park, CA: Stanford Research Institution International.

*Stafford, CJ. 1983. Halogenated diphenyl ethers identified 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.

*Stapleton HM, Baker JE. 2003. Comparing polybrominated diphenyl ether and polychlorinated biphenyl bioaccumulation in a food web in Grand Bay, Lake Michigan. Arch Environ Contam Toxicol 45(2):227-234.

Stapleton HM, Alaee M, Letcher RJ, et al. 2003. Debromination of decabromodiphenyl ether by juvenile carp (*Cyprinus carpio*). Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*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.

*Stoker TE, Ferrell J, Hedge JM, et al. 2003. Assessment of SE-71, a commercial polybrominated diphenyl ether (PBDE) mixture, in the EDSP male pubertal protocol. Toxicologist 72(S-1):135-136.

*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. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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 10:89-105.

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.

Sun G, Yau A, Farias T. 2003. Analytical methods for trace levels of polybrominated diphenyl ethers (PBDEs). Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*Sundstrom G, Hutzinger O, Safe S, et al. 1976a. Identification of 2,2'4,4'5,5'-hexabromobiphenyl as the major component of flame retardant Firemaster® PB-6. Chemosphere 5:11-14.

*Sundstrom G, Hutzinger O, Safe S, et al. 1976b. The synthesis and gas chromatographic properties of bromobiphenyls. Sci Total Environ 6:15-29.

*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. Res 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.

Takasuga T, Tsuji H, Nagayama J. 2002. Gender specific dynamics of PCDD/DFs, PCBs, PBDEs and organochorines in blood of Japanese families over two-year study period. Organohalogen Compounds 58:297-300.

*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.

*Talsness CE, Shakibaei M, Kuriyama S, et al. 2003. Ultrastructural changes in the ovaries of adult offspring following a single maternal exposure to low dose 2,2'4,4',5-pentabromodiphenyl ether. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

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.

*Taylor MM, Hedge JM, DeVitro MJ, et al. 2002. Perinatal exposure to a polybrominated diphenyl ether mixture (DE-71) disrupts thyroid hormones but not neurobehavioral development. Toxicol Sci:133.

*Taylor MM, Hedge JM, Gilbert ME, et al. 2003. Perinatal exposure to polybrominated diphenyl ether mixture (DE-71): Disruption of thyroid homeostasis and neurobehavioral development. Toxicol Sci 72(S-1):124.

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.

ter Schure AFH, Larsson P. 2002. Polybrominated diphenyl ethers in precipitation in Southern Sweden (Skan, Lund). Atmos Environ 36:4015-4022.

ter Schure AFH, Larsson P, Merila J, et al. 2002. Latitudinal fractionation of polybrominated diphenyl ethers and polychlorinated biphenyls in frogs (*Rana temporaria*). Environ Sci Technol 36:5057-5061.

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 GO, Moss SEW, Jones KC, et al. 2003. Absorption of PBDEs and PCBs by grey seals (*Halichoerus gypus*). Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*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, Froshaug M, Leknes H, et al. 2003. Brominated flame retardants in breast milk from Norway. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Thomsen C, Haug LS, Leknes H, et al. 2002a. Comparing electron ionization high-resolution and electron capture low-resolution mass spectrometric determination of polybrominated diphenyl ethers in plasma, serum and milk. Chemosphere 46(5):641-648.

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 Monit 3(4):366-370.

Thomsen C, Lundanes E, Becher G. 2001c. Plasma concentration of brominated flame retardants in three Norwegian occupational groups. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 311-314.

Thomsen C, Lundanes E, Becher G. 2001d. A simplified method for determination of tetrabromobisphenol A and polybrominated diphenyl ethers in human plasma and serum. J Sep Sci 24:282-290.

Thomsen C, Lundanes E, Becher G. 2001e. A time related study on brominated flame retardants in serum samples from the general population in Norway. Organohalogen Compounds 52:206-209.

*Thomsen C, Lundanes E, Becher G. 2002b. 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.

Thuresson K, Jakobsson K, Hagmar L, et al. 2002a. Decabromodiphenyl ether exposure to workers manufacturing rubber and in an industrial setting producing rubber coated electric wires. Organohalogen Compounds 58:165-168.

Thuresson K, Jakobsson K, Hagmar L, et al. 2002b. Work related exposure to brominated flame retardants when recycling metals from printed circuit boards. Organohalogen Compounds 58:249-252.

*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.

*Tittlemier SA, Halldorson T, Stern GA, et al. 2002. Vapor pressures, aqueous solubilities, and Henry's Law constants of some brominated flame retardants. Environ Toxicol Chem 21(9):1804-1810.

Tollback P, Bjorklund J, Ostman C. 2003. Evaluation of gas chromatographic injection techniques for PBDE. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Tomy GT, Palace VP, Halldorson T, et al. 2004. Bioaccumulation, biotransformation, and biochemical effects of brominated diphenyl ethers in juvenile lake trout (*Salvelinus namaycush*). Environ Sci Technol 38:1496-1504.

Tomy G, Tittlemier S, Braekevelt E, et al. 2001. The physio-chemical properties of some brominated flame retardants. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 229-232.

*TRI 01. 2004. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

Tritscher A, Stadler R, Scanlan F, et al. 2003. Determination of polybrominated diphenylethers in samples of raw cow's milk, fish and egg. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

11. REFERENCES

*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.

*Tullo A. 2003. Great Lakes to phase out two flame retardants. Chemical & Engineering News 81(45):13. http://www.pubs.acs.org/cen/topstory/8145/print/8145notw3.html.

Tysklind M, Sellstrom U, Soderstrom G, et al. 2001. Abiotic transformation of polybrominated diphenylethers (PBDEs): photolytic debromination of decabromo diphenyl ether. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 51-54.

*Ueno D, Kajiwara N, Tanaka H, et al. 2003. Global pollution monitoring of polybrominated diphenyl ethers (PBDEs) using skipjack tuna as a bioindicator. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

Ueno D, Kajiwara N, Tanaka H, et al. 2004. Global pollution monitoring of polybrominated diphenyl ethers using skipjack tuna as a bioindicator. Environ Sci Technol 38:2312-2316.

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. 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, Dam M, Tysklind M, et al. 2001. Levels of polybrominated diphenyl ethers in marine mammals. Organohalogen Compounds 52:99-103.

van Bavel B, Hardell L, Kitti A, et al. 2002. High levels of PBDEs in 5% of 220 blood samples from the Swedish population. Organohalogen Compounds 58:161-164.

*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 thyroid hormone levels in vivo. Arch Toxicol 65:15-19.

11. REFERENCES

*van den Hove MF, Beckers C, Devlieger H, et al. 1999. Hormone synthesis and storage in the thyroid of human preterm and term newborns: Effect of thyroxine treatment. Biochimie 81:563-570.

*Van Vliet G. 1999. Merck AG thyroid symposium. Neonatal hypothyroidism: Treatment and outcome. Thyroid 9:79-84.

*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. 2001. Pattern of brominated compounds in top predations of marine food webs from four continents. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 379-383.

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. 2002a. Developmental exposure to a brominated flame-retardant, 2,2',4,4',5,5'-Hexabromodiphenyl ether (PBDE 153) affects behaviour and cholinergic nicorinic receptors in brain of adult mice. Toxicol Sci (suppl)66:132.

*Viberg H, Fredriksson A, Eriksson P. 2002b. 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.

*Viberg H, Fredrickson A, Eriksson P. 2003a. Neonatal PBDE 99 exposure causes dose-response related behavioural derangements that are not sex or strain specific in mice. Toxicol Sci 72(S-1):126.

Viberg H, Fredriksson A, Eriksson P. 2003b. Neurotoxicity of different polybrominated diphenyl ethers, including PBDE 209. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*Viberg H, Fredriksson A, Jakobsson E, et al. 2001a. Neonatal exposure to hexbromo-diphenyl ether (PBDE 153) affects behaviour and cholinergic nicotinic receptors in brain of adult mouse. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 275-278.

*Viberg H, Fredricksson A, Jakobsson E, et al. 2001b. Brominated flame retardant: Uptake, retention and developmental neurotoxic effects of decabromodiphenyl ether (PBDE 209) in the neonatal mouse. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 279-282.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Villeneuve DL, Kannan K, Priest BT, et al. 2002. In vitro assessment of potential mechanism-specific effects of polybrominated diphenyl ethers. Environ Toxicol Chem 21(11):2431-2433.

Vives I, Grimalt JO, Lacorte S, et al. 2004. Polybromodiphenyl ether flame retardants in fish from lakes in European high mountains and Greenland. Environ Sci Technol 38:2338-2344.

*von Meyerinck L, Hufnagel B, Schmoldt A, et al. 1990. Inductions of rat liver microsomal cytochrome P-450 by the pentabromo diphenyl ether bromkal 70 and half-lives of its components in the adipose tissue. Toxicology 61(2):259-274.

Voorspoels S, Covaci A, Schepens P. 2003. Polybrominated diphenyl ethers (PBDEs) in marine fish species of the Belgian North Sea and the Western Scheldt Estuary: Levels, profiles, and distribution. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*Vos JG, van Genderen H. 1973. Toxicological aspects of immunosuppression. Pesticide and environmental control symposium specialists. Miami, Florida, 527-545.

*Vulsma T, Gons MH, DeVijder JJM. 1989. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. N Eng J Med 321:13-16.

*Wania F, Dugani C. 2002. Assessing the long range transport potential of polybrominated diphenyl ethers: A comparison of four multimedia models. Final report. University of Toronto at Scarborough, Scarborough, Ontario.

*Waritz RS, 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. 1988. Behaviour of organobrominated compounds at the sediment phase in the environment. Koshu Eisei Hen 26:129-133.

Watanabe I, Sakai S-I. 2001. Environmental release and behavior of brominated flame retardants- an overview. Organohalogen Compounds 52:1-4.

Watanabe I, Sakai S-I. 2003. Environmental release and behavior of brominated flame retardants. Environ Int 29:665-682.

*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.

*Watanabe 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 RJ. 2001a. Probabilistic human health risk assessment of penta-, octa-, and deca- brominated dphenyl ethers. Organohalogen Compounds 52:39-42.

Wenning RJ. 2001b. Risk assessment of three commercial PBDEs: Probabilistic analysis of chronic daily intakes from different sources and comparison with European commission results. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 397-399.

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.

Wenning RJ, Von Burg A, Braithwaite S, et al. 2003. Health risk assessment of the commercial pentabromodiphenyl ether product in the United States. Organohalogen compounds. Dioxins 2003. Boston, MA, 60-65.

*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/.

*WHO. 1998. Brominated diphenyl ethers. International programme on chemical safety. Environmental Health Criteria. World Health Organization. http://www.inchem.org/documents/ehc/ehc/ehc205.htm.

*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.

*Wiegand H, Desaiah D, Dehnhardt M, et al. 2001. Polyhalogenated hydrocarbon induced perturbation of intracellular calcium homeostasis: From astrocytes to human macrophages. Organohalogen Compounds 53:182-184.

Wijesekera R, Halliwell C, Hunter S, et al. 2002. A preliminary assessment of UK human exposure to polybrominated diphenyl ethers (PBDEs). Organohalogen Compounds 55:239-242.

*WIL Research Laboratories. 1986. A range-finding teratology study in rats with DE-79. Submitted to U.S. Environmental Protection Agency under TSCA Section 8D. OTS0522298.

Wilford BH, Thomas GO, Alcock RE, et al. 2003. Polyurethane foam as a source of PBDEs to the environment. Organohalogen compounds. Dioxins 2003. Stockholm, Sweden, 60-65.

*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.

11. REFERENCES

*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.

Wolkers H, Van Bavel B, Derocher AE, et al. 2004. Congener-specific accumulation and food chain transfer of polybrominated diphenyl ethers in two Arctic food chains. Environ Sci Technol 38:1667-1674.

Wong A, Duan Lei Y, Alaee M, et al. 2001. Vapor pressure of the polybrominated diphenylethers. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 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.

Zegers BN, Lewis WE, Tjoen-A-Choy MR, et al. 2001a. Levels of some polybrominated diphenyl ether (PBDE) flame-retardants in animals of different trophic levels of the North Sea food web. Organohalogen Compounds 52:18-21.

Zegers BN, Lewis WE, Tjoen-A-Choy MR, et al. 2001b. Levels of some polybrominated diphenyl ether (PBDE) flame retardants in animals of different trophic levels of the North Sea food web. The second international workshop on brominated flame retardants. BFR 2001. Stockholm, Sweden, 143-147.

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, Haworth 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.

*Zennegg M, Kohker M, Gerecke AC, et al. 2003. Polybrominated diphenyl ethers in whitefish from Swiss lakes and farmed rainbow trout. Chemosphere 51(7):545-553.

*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, De Vito MJ, et al. 2000. Thyroid hormone disruptive effects of brominated diphenyl ethers following developmental exposure. Toxicologist 54(1):260-261.

*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.

Zhu LY, Hites RA. 2004. Temporal trends and spatial distribution of brominated flame retardants in archived fishes from the Great Lakes. Environ Sci Technol 38:2779-2784.

*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 MA, 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. Morbidity 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.

12. 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 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 that 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 of people that 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.

Lethal Concentration(LO) (LC_{LO})—The lowest concentration of a chemical in air that 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 that 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 group.

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, whereas 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 that 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.

q1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 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) (TD50)—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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS 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 100-fold 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 agency-wide 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 NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
[Lower Brominated Diphenyl Ethers]
CAS number(s): 32534-81-9 (pentaBDE), 32536-52-0 (octaBDE)
Date: September 2, 2004
Profile status: Final Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 3
Species: Rat

Minimal Risk Level: 0.006 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Great Lakes Chemical Corporation. 2000. A 90-day inhalation toxicity study of octabromodiphenyl oxide in albino rats, dated 04/04/02. Submitted to the U.S. EPA under TCSA Section 8E, Fiche no. OTS0574171-1.

Experimental design: This is an unpublished industry-sponsored study in which a commercial octaBDE product (Lot No. 9525DA23B, bromine content 78.7%, composition and purity not otherwise specified) was administered to groups of 10 male and 10 female Crl:CD(SD)IGS BR rats, via nose-only inhalation as a dust aerosol, in measured concentrations of 0 (filtered air-only), 1.1, 16 or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks. The mean MMADs in the low to high level groups were 2.0, 2.7, and 2.8 microns; the corresponding mean GSDs were 3.37, 3.72, and 3.01. Clinical and physical signs, body weight, food consumption, and survival were evaluated throughout the study. Ophthalmic, hematology (11 indices), serum chemistry (18 indices), and serum thyroid hormone (TSH, total T_3, and total T_4) evaluations were performed near the end of the exposure period. Urinalyses were not conducted. Comprehensive necropies, organ weight measurements, and histological examinations (including respiratory tract and thyroids) were performed following exposure termination.

Effects noted in study and corresponding doses: Hepatic, nasal, lung, thyroid, and ovarian effects were observed. The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at ≥16 mg/m^3 and liver weight (absolute and relative) at 202 mg/m^3. Total incidences of centrilobular hepatocellular hypertrophy in the 0, 1.1, 16, and 202 mg/m^3 groups were 1/10 (minimal), 0/10, 3/10 (all minimal), and 10/10 (6 minimal, 2 mild, 2 moderate) in males, and 0/10, 0/10, 3/10 (all minimal), and 6/10 (3 minimal, 3 mild) in females. Changes in nasal Goblet cells were increased at 202 mg/m^3, but showed no clear dose-related increasing trends for incidence and severity. Total incidences of Goblet cell hypertrophy (minimal or mild) were slightly increased in nasal level II of both sexes at ≥1.1 mg/m^3; incidences in 0, 1.1, 16, and 202 mg/m^3 exposure groups were 4/10 (all minimal), 9/10 (7 minimal, 2 mild), 6/10 (all minimal), and 10/10 (9 minimal, 1 mild) in males, and 2/10 (all minimal), 6/10 (all minimal), 4/10 (all minimal), and 8/10 (all minimal) in females. Goblet cell hypertrophy was also slightly increased in nasal level IV in males at 202 mg/m^3 (4/10, 0/10, 1/10, and 8/10, all minimal severity, not increased in females). Histological changes in the lungs included alveolar histiocytosis and chronic active inflammation that were only clearly induced at 202 mg/m^3. Total incidences of alveolar histiocytosis at 0, 1.1, 16, and 202 mg/m^3 were 3/10 (2 mild, 1 minimal), 5/10 (all minimal), 5/10 (all minimal), and 10/10 (5 minimal, 3 mild, 2 moderate) in males, and 0/10, 5/10 (all minimal), 2/10 (all minimal), and 10/10 (1 minimal, 7 mild, 2 moderate) in females. Corresponding total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10 (both minimal), and 10/10 (5 minimal, 4 mild, 1 moderate) in males, and 0/10, 1/10 (minimal), 1/10 (minimal), and 10/10 (2 minimal, 5 mild, 3 moderate) in females. Gross lung changes also occurred in both sexes at 202 mg/m^3; these included lung firmness and white discoloration and/or enlargement in the bronchial

and/or mediastinal lymph nodes. The lymph node effects correlated with the histological finding of granulomatous inflammation. There were no exposure-related gross or histopathological changes in the spleen, bone marrow, thymus, or other tissues, including thyroid. Thyroid hormone assessments, however, showed exposure-related decreases in mean thyroxine (total T_4) at ≥16 mg/m^3 in both sexes, and increases in thyroid stimulating hormone (TSH) at ≥16 mg/m^3 in males and 202 mg/m^3 in females. The changes were usually statistically significant ($p<0.05$ or $p<0.01$) compared to controls and considered to be consistent with chemical-induced hypothyroidism. There were no serum T_3 changes. Qualitative histological evaluations of step sections of ovaries showed an absence of corpora lutea in 3/10 females at 202 mg/m^3, compared to 0/10 in the control and lower exposure groups. This 30% incidence was interpreted to be a treatment-related effect because an absence of corpora lutea was considered unusual in rats at 20 weeks of age.

Other findings included some hematological alterations in 202 mg/m^3 females that were not considered to be exposure-related (slightly increased mean activated partial thromboplastin time, and decreased mean MCH and MCHC without effects on RBC counts, hematocrit, or hemoglobin levels). Serum chemistry evaluations showed that cholesterol was significantly increased (39.8% less than controls, $p<0.01$) in 202 mg/m^3 females, but the magnitude of the elevation was not considered toxicologically significant. Some other statistically significant serum chemistry alterations (increased mean globulin and total protein, decreased albumin/globulin ratio) also occurred in the 202 mg/m^3 females, but were not considered exposure-related due to small magnitudes of changes and lack of similar findings in the males.

Dose and end point used for MRL derivation: 1.1 mg/m^3

[X] NOAEL [ ] LOAEL

Considering the unclear adversity of minimal severity Goblet cell hypertrophy, lack of clear dose-related increasing trends for incidence and severity of this nasal effect, identification of both a NOAEL (1.1 mg/m^3) and LOAEL (16 mg/m^3) for changes in thyroid hormones, and abundant evidence for thyroid effects of PBDEs in oral studies, the NOAEL for effects on thyroid hormones is the most appropriate basis for derivation of the MRL.

Uncertainty factors used in MRL derivation:

[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability
[X] 3 modifying factor for incomplete data base

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

Was a conversion used from intermittent to continuous exposure? The NOAEL was adjusted to continuous exposure as follows: 1.1 mg/m^3 x 6 hours/24 hours x 5 days/7 days = 0.196 mg/m^3

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The human equivalent NOAEL ($NOAEL_{HEC}$) was calculated from the duration-adjusted NOAEL ($NOAEL_{ADJ}$) using EPA RfC methodology as follows:

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.196 \text{ mg/m}^3 \times 2.7 = 0.53 \text{ mg/m}^3$$

The regional deposited dose ratio (RDDR) for the extrathoracic (ET) region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculate

the RDDR of 2.7: mean particle size (MMAD) of 2.0 µm with a mean GSD (sigma g) of 3.37; default human body weight of 70 kg, and a default female F344 rat body weight of 180 g.

Based on these values, the MRL is derived as follows:

$$MRL = NOAEL_{HEC} \div (UF \times MF) = 0.53 \div (30 \times 3) = 0.006 \text{ mg/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: This is the only intermediate-duration inhalation study of PBDEs.

The thyroid is a sensitive target of lower brominated BDEs in orally exposed animals. A NOAEL for reduced serum T_4 hormone levels in fetal rats that were exposed to pentaBDE (Zhou et al. 2002) was used as the basis for the acute oral MRL for lower brominated BDEs. This study is supported by findings of reduced serum T_4 levels in weanling rats that were acutely exposed to octaBDE and pentaBDE as neonates (Zhou et al. 2001). Thyroid effects that mainly included reduced serum T_4 hormone levels and follicular cell hyperplasia were observed in a number of other animal studies of acute- or intermediate-duration oral exposure to penta- and octaBDEs (Fowles et al. 1994; Hallgren et al. 2001; WIL Research Laboratories 1984).

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Polybrominated Biphenyls (PBBs)
CAS number(s): 36355-01-8 (unspecified hexabromo mixture)
Date: September 2, 2004
Profile status: Final Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 4
Species: Rat

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm [ ] mg/m3

Reference: 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.

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.

Despite the fact that the inappropriate statistical test (t-test, rather than an ANOVA with multiple comparison tests) was used to analyze these data, ATSDR is confident with the designation of the NOAEL and LOAEL values. The data in the manuscript are presented graphically, with animal numbers presented as a range (8–11 animals/group); thus, an ANOVA could not be performed from the published report. However, using the graphical data, the change in plasma T4 levels in the 3 mg/kg/day groups is clearly on the order of 20–30%, which represents a biologically significant change. As such, the identification of 3 mg/kg/day as a LOAEL, and 1 mg/kg/day as a NOAEL, is not contraindicated by the lack of appropriate statistical analysis.

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. 1982a, 1982b; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978a; Norris et al. 1975a, 1975b, 1975c; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978).

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
[Lower Brominated Diphenyl Ethers]
CAS number(s): 32534-81-9 (pentaBDE), 32536-52-0 (octaBDE)
Date: September 2, 2004
Profile status: Final Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 27
Species: Rat

Minimal Risk Level: 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 (LED20) 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, mg/kg/day, respectively, 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, 1975b) 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, 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).

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name:	Polybrominated Diphenyl Ethers (PBDEs) [Lower Brominated Diphenyl Ethers]
CAS number(s):	32534-81-9 (pentaBDE), 32536-52-0 (octaBDE)
Date:	September 2, 2004
Profile status:	Final Post Public Comment
Route:	[ ] Inhalation [X] Oral
Duration:	[ ] Acute [X] Intermediate [ ] Chronic
Key to figure:	36
Species:	Rat

Minimal Risk Level: 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, 1975b), and 9 mg/kg/day for hepatocellular enlargement and increased liver weight in rats exposed to octaBDE or pentaBDE for 28 days (IRDC 1976).

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
[Decabromodiphenyl Ether (DecaBDPE)]
CAS number(s): 1163-19-5
Date: September 2, 2004
Profile status: Final Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 13
Species: Mouse

Minimal Risk Level: 10 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Hardy ML, Schroeder R, Biesemeier J, et al. 2002. Prenatal oral (gavage) developmental toxicity study of decabromodiphenyl oxide in rats. Int J Toxicol 21:83-91.

Experimental design: A commercial decaBDPE product (97.34% DBDPO, 2.66% nonaBDE/octaBDE) was administered to groups of 25 mated female Sprague-Dawley rats by gavage in corn oil in daily doses of 0, 100, 300, or 1,000 mg/kg/day on gestation days 0 through 19. Each female was sacrificed on gestation day 20 and necropsied. End points examined included maternal clinical observations, maternal body weight/weight gain and food consumption, maternal gravid uterine and liver weights, maternal gross lesions, total number of corpora lutea, uterine implantations, early and late resorptions, viable and nonviable fetuses, and fetal weight and sex. Fetuses were examined grossly (all fetuses), evaluated for skeletal/cartilaginous malformations and ossification variations (approximately half of each litter), and evaluated for visceral malformations (remaining fetuses). The experiment was designed to meet current (as of 2002) EPA/OPPTS and OECD guidelines for a prenatal developmental toxicity study.

Effects noted in study and corresponding doses: No effects on any maternal end points (e.g., clinical signs, body weight, pregnancy rate, implantation, liver weight, necropsy findings) or fetal endpoints (e.g., body weight, sex ratio, or external, visceral or skeletal malformations) were observed in any dose group.

Dose and end point used for MRL derivation: 1,000 mg/kg/day

[X] NOAEL [ ] LOAEL

No exposure-related maternal or developmental toxicity was found, indicating that the critical NOAEL is 1,000 mg/kg/day, the highest tested dose.

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

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: One intermediate-duration oral systemic toxicity study of a high purity decaBDE commercial product was conducted. A commercial decaBDE mixture (94–97% pure) was fed to F344 rats (10/sex/level) and B6C3F1 mice (10/sex/level) in dietary concentrations of 0, 3,100, 6,300, 12,500, 25,000, or 50,000 ppm for 13 weeks (NTP 1986). Corresponding estimated daily doses are 0, 496, 992, 2,000, 4,000, or 8,000 mg/kg/day in rats, and 0, 589, 1,178, 2,375, 4,750, or 9,500 mg/kg/day in mice. The daily doses (mg/kg body weight/day) were estimated by multiplying the dietary concentrations (ppm; mg/kg food) by food factors of 0.16 kg food/kg body weight/day for rats and 0.19 kg food/kg body weight/day for mice. The food factors are based on the averages of male and female subchronic reference values for food consumption and body weight in F344 rats and B6C3F1 mice (EPA 1988a). All animals were observed daily, weighed weekly, and necropsied at the end of the exposure period. Comprehensive histological examinations were also performed at the end of the study, but were limited to the control and high-dose groups. No compound-related clinical signs, deaths, body weight or food consumption changes, gross pathology, or histopathology were observed in either species at any level of exposure.

Based on the findings of the NTP (1986) study, the intermediate-duration NOAELs for systemic toxicity are 8,000 mg/kg/day in rats and 9,500 mg/kg/day in mice. The NOAEL for developmental toxicity is 1,000 mg/kg/day (Hardy et al. 2002). Because doses higher than 1,000 mg/kg/day have not been tested for developmental toxicity, and the NTP (1986) study indicates that this dose is also a NOAEL for systemic toxicity, the 1,000 mg/kg/day developmental toxicity NOAEL is used as the basis for the MRL.

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX B. USER'S GUIDE

Chapters 1 and 2

Public Health Statement

These chapters of the profile are health effects summaries written in non-technical language. Their intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statements 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 Statements 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.

Chapters 3 and 4

Relevance to Public Health

These chapters provide health effects summaries based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. These summaries are 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 chapters cover end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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.

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 5 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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.

MRLs 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. Chapters 3 and 4, "Relevance to Public Health," contain basic information known about the substance. Other sections such as Chapter 5 Section 5.9, "Interactions with Other Substances," and Section 5.10, "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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

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 no-observed-adverse-effect level (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 levels of significant exposure (LSE) Tables.

Chapter 5

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 5-1 and Figure 5-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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. Typically 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 5-1, 5-2, and 5-3, respectively). LSE figures are limited to the inhalation (LSE Figure 5-1) and oral (LSE Figure 5-2) 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 two "18r" data points in sample Figure 5-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapters 3 and 4, "Relevance to Public Health," cover the relevance of animal data to human toxicity and Section 5.4, "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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 11 of the profile.

(11) CEL. A 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 5-1 (page B-7)

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 acute and intermediate 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 one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 5-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
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

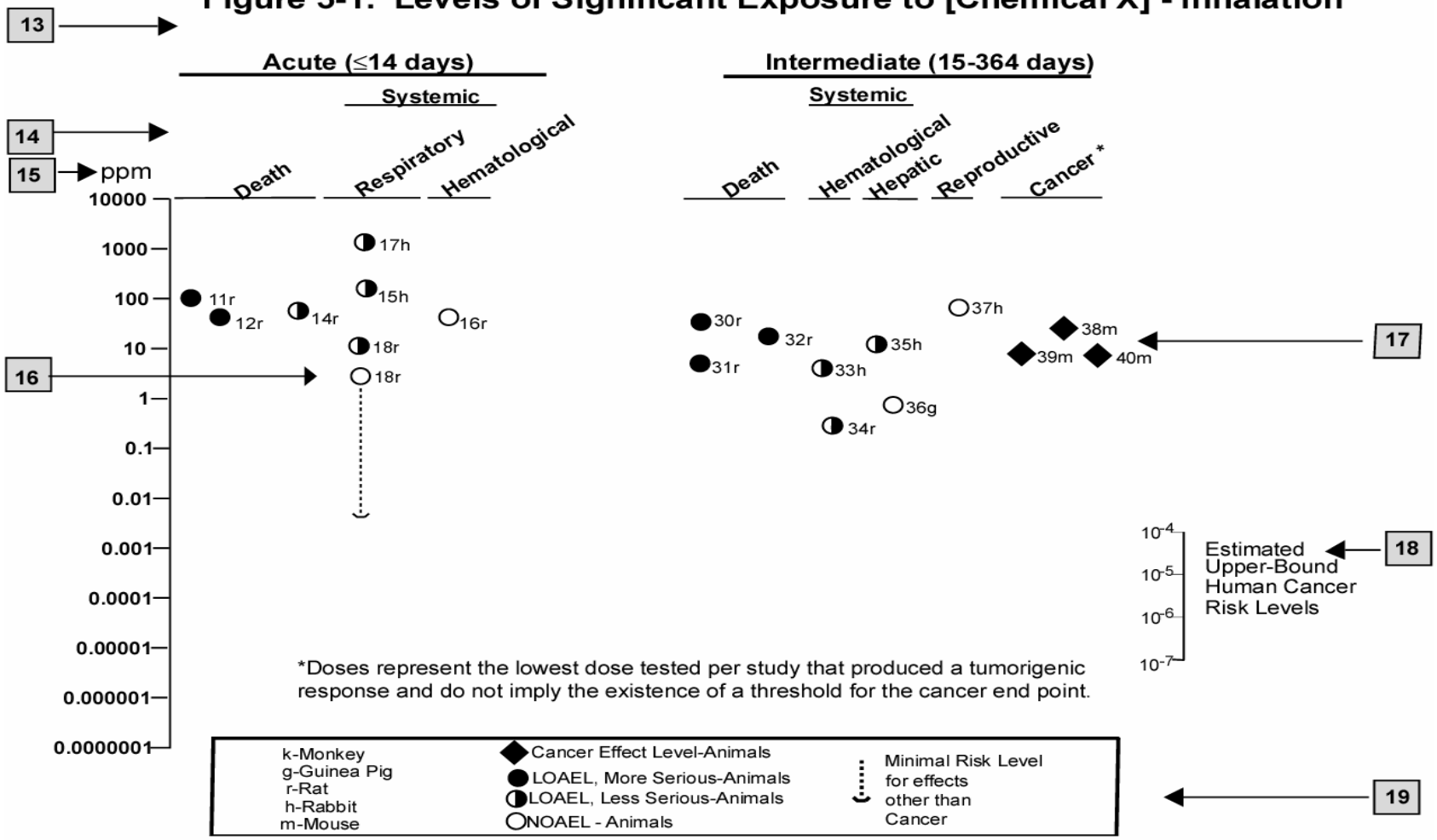
12 →

[a] The number corresponds to entries in Figure 5-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 5-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
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
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
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
BMD	benchmark dose
BMR	benchmark response
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
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
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
NHANES	National Health and Nutrition Examination Survey
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
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
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
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
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
<	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. INDEX

APPENDIX D