

TOXICOLOGICAL PROFILE FOR POLYBROMINATED BIPHENYLS

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

September 2004

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

UPDATE STATEMENT

A Toxicological Profile for PBBs, 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 and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30329-4027

This page is intentionally blank.

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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic 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. Staffs 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.



Patrick N. Breyse, Ph.D., CIH
Director, National Center for Environmental Health
and Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of 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. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

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: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

Internet: <http://www.atsdr.cdc.gov>

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

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

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

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

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.

Clinical Resources

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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • 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 and Human Health Sciences, Atlanta, GA

Stephen Bosch, B.S.
Richard J. Amata, M.S.
SRC, Inc., Noth 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 Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adhere nce to instructions in the Guidance.

This page is intentionally blank.

PEER REVIEW

A peer review panel was assembled for polybrominated biphenyls. 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 biphenyl'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.

This page is intentionally blank.

CONTENTS

| | |
|---|--------|
| DISCLAIMER | ii |
| UPDATE STATEMENT | iii |
| FOREWORD | v |
| QUICK REFERENCE FOR HEALTH CARE PROVIDERS..... | vii |
| CONTRIBUTORS | ix |
| PEER REVIEW | xi |
| CONTENTS..... | xiii |
| LIST OF FIGURES | xvii |
| LIST OF TABLES..... | xix |
| 1. PUBLIC HEALTH STATEMENT..... | 1 |
| 1.1 WHAT ARE PBBs? | 1 |
| 1.2 WHAT HAPPENS TO PBBs WHEN THEY ENTER THE ENVIRONMENT?..... | 2 |
| 1.3 HOW MIGHT I BE EXPOSED TO PBBs? | 2 |
| 1.4 HOW CAN PBBs ENTER AND LEAVE MY BODY? | 3 |
| 1.5 HOW CAN PBBs AFFECT MY HEALTH? | 4 |
| 1.6 HOW CAN PBBs AFFECT CHILDREN? | 6 |
| 1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PBBs? | 7 |
| 1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PBBs?..... | 7 |
| 1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?..... | 8 |
| 1.10 WHERE CAN I GET MORE INFORMATION? | 9 |
| 2. RELEVANCE TO PUBLIC HEALTH | 11 |
| 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PBBs IN THE UNITED STATES | 11 |
| 2.2 SUMMARY OF HEALTH EFFECTS..... | 13 |
| 2.3 MINIMAL RISK LEVELS | 21 |
| 3. HEALTH EFFECTS | 25 |
| 3.1 INTRODUCTION..... | 25 |
| 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE | 27 |
| 3.2.1 Inhalation Exposure | 29 |
| 3.2.1.1 Death..... | 29 |
| 3.2.1.2 Systemic Effects..... | 29 |
| 3.2.1.3 Immunological and Lymphoreticular Effects | 33 |
| 3.2.1.4 Neurological Effects..... | 33 |
| 3.2.1.5 Reproductive Effects..... | 34 |
| 3.2.1.6 Developmental Effects | 34 |
| 3.2.1.7 Cancer | 34 |
| 3.2.2 Oral Exposure | 34 |
| 3.2.2.1 Death..... | 34 |
| 3.2.2.2 Systemic Effects..... | 92 |
| 3.2.2.3 Immunological and Lymphoreticular Effects | 109 |
| 3.2.2.4 Neurological Effects..... | 112 |
| 3.2.2.5 Reproductive Effects..... | 115 |
| 3.2.2.6 Developmental Effects..... | 116 |

| | |
|---|-----|
| 3.2.2.7 Cancer | 121 |
| 3.2.3 Dermal Exposure | 128 |
| 3.2.3.1 Death | 128 |
| 3.2.3.2 Systemic Effects..... | 129 |
| 3.2.3.3 Immunological and Lymphoreticular Effects | 134 |
| 3.2.3.4 Neurological Effects..... | 134 |
| 3.2.3.5 Reproductive Effects..... | 134 |
| 3.2.3.6 Developmental Effects..... | 135 |
| 3.2.3.7 Cancer | 135 |
| 3.3 GENOTOXICITY | 135 |
| 3.4 TOXICOKINETICS..... | 139 |
| 3.4.1 Absorption | 139 |
| 3.4.1.1 Inhalation Exposure | 139 |
| 3.4.1.2 Oral Exposure | 140 |
| 3.4.1.3 Dermal Exposure..... | 140 |
| 3.4.2 Distribution | 141 |
| 3.4.2.1 Inhalation Exposure | 141 |
| 3.4.2.2 Oral Exposure | 141 |
| 3.4.2.3 Dermal Exposure..... | 144 |
| 3.4.2.4 Other Routes of Exposure | 144 |
| 3.4.3 Metabolism | 145 |
| 3.4.4 Elimination and Excretion | 148 |
| 3.4.4.1 Inhalation Exposure | 148 |
| 3.4.4.2 Oral Exposure | 148 |
| 3.4.4.3 Dermal Exposure..... | 150 |
| 3.4.4.4 Other Routes of Exposure | 150 |
| 3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models..... | 151 |
| 3.5 MECHANISMS OF ACTION | 154 |
| 3.5.1 Pharmacokinetic Mechanisms | 154 |
| 3.5.2 Mechanisms of Toxicity | 154 |
| 3.5.3 Animal-to-Human Extrapolations..... | 159 |
| 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS..... | 159 |
| 3.7 CHILDREN'S SUSCEPTIBILITY | 162 |
| 3.8 BIOMARKERS OF EXPOSURE AND EFFECT | 168 |
| 3.8.1 Biomarkers Used to Identify or Quantify Exposure to PBBs..... | 169 |
| 3.8.2 Biomarkers Used to Characterize Effects Caused by PBBs | 171 |
| 3.9 INTERACTIONS WITH OTHER CHEMICALS | 173 |
| 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE..... | 174 |
| 3.11 METHODS FOR REDUCING TOXIC EFFECTS | 175 |
| 3.11.1 Reducing Peak Absorption Following Exposure..... | 175 |
| 3.11.2 Reducing Body Burden..... | 176 |
| 3.11.3 Interfering with the Mechanism of Action for Toxic Effects | 177 |
| 3.12 ADEQUACY OF THE DATABASE | 178 |
| 3.12.1 Existing Information on Health Effects of PBBs..... | 178 |
| 3.12.2 Identification of Data Needs | 180 |
| 3.12.3 Ongoing Studies..... | 191 |
| 4. CHEMICAL AND PHYSICAL INFORMATION..... | 193 |
| 4.1 CHEMICAL IDENTITY..... | 193 |
| 4.2 PHYSICAL AND CHEMICAL PROPERTIES..... | 194 |

| | |
|--|-----|
| 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL | 207 |
| 5.1 PRODUCTION | 207 |
| 5.2 IMPORT/EXPORT | 208 |
| 5.3 USE..... | 208 |
| 5.4 DISPOSAL | 208 |
| 6. POTENTIAL FOR HUMAN EXPOSURE | 211 |
| 6.1 OVERVIEW | 211 |
| 6.2 RELEASES TO THE ENVIRONMENT | 213 |
| 6.2.1 Air | 214 |
| 6.2.2 Water..... | 214 |
| 6.2.3 Soil | 215 |
| 6.3 ENVIRONMENTAL FATE..... | 216 |
| 6.3.1 Transport and Partitioning | 216 |
| 6.3.2 Transformation and Degradation | 218 |
| 6.3.2.1 Air | 218 |
| 6.3.2.2 Water..... | 219 |
| 6.3.2.3 Sediment and Soil | 220 |
| 6.3.2.4 Other Media | 221 |
| 6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT | 221 |
| 6.4.1 Air | 222 |
| 6.4.2 Water..... | 222 |
| 6.4.3 Sediment and Soil | 222 |
| 6.4.4 Other Environmental Media..... | 223 |
| 6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE | 228 |
| 6.6 EXPOSURES OF CHILDREN | 231 |
| 6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES | 232 |
| 6.8 ADEQUACY OF THE DATABASE..... | 233 |
| 6.8.1 Identification of Data Needs | 233 |
| 6.8.2 Ongoing Studies..... | 237 |
| 7. ANALYTICAL METHODS..... | 239 |
| 7.1 BIOLOGICAL MATERIALS | 240 |
| 7.2 ENVIRONMENTAL SAMPLES..... | 242 |
| 7.3 ADEQUACY OF THE DATABASE..... | 244 |
| 7.3.1 Identification of Data Needs | 244 |
| 7.3.2 Ongoing Studies..... | 245 |
| 8. REGULATIONS AND ADVISORIES | 247 |
| 9. REFERENCES | 251 |
| 10. GLOSSARY | 323 |
| APPENDICES | |
| A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS | A-1 |
| B. USER'S GUIDE..... | B-1 |
| C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS..... | C-1 |

This page is intentionally blank.

LIST OF FIGURES

| | |
|--|-----|
| 3-1. Levels of Significant Exposure to Polybrominated Biphenyls—Oral | 83 |
| 3-2. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance | 153 |
| 3-3. Existing Information on Health Effects of PBBs..... | 179 |
| 6-1. Frequency of NPL Sites with PBB Contamination | 212 |

This page is intentionally blank.

LIST OF TABLES

| | |
|---|-----|
| 3-1. Levels of Significant Exposure to Polybrominated Biphenyls—Oral | 35 |
| 3-2. Levels of Significant Exposure to Polybrominated Biphenyls—Dermal | 130 |
| 3-3. Genotoxicity of PBBs <i>In Vivo</i> | 137 |
| 3-4. Genotoxicity of PBBs <i>In Vitro</i> | 138 |
| 3-5. Ongoing Studies on the Health Effects of PBBs | 192 |
| 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) Congeners | 195 |
| 4-2. Chemical Identity of Selected PBBs..... | 201 |
| 4-3. Physical and Chemical Properties of Selected PBBs..... | 202 |
| 4-4. Identified PBB Congeners in FireMaster® BP-6 and FireMaster® FF-1 | 204 |
| 6-1. Mean Concentrations of Nine PBB Congeners in Lake Trout from the Great Lakes (pg/g Wet Weight) | 225 |
| 6-2. Tissue Levels of PBBs in Michigan Residents..... | 229 |
| 7-1. Analytical Methods for Determining PBBs in Biological Materials | 241 |
| 7-2. Analytical Methods for Determining PBBs in Environmental Samples | 243 |
| 8-1. Regulations and Guidelines Applicable to PBBs | 248 |

This page is intentionally blank.

1. PUBLIC HEALTH STATEMENT

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

1. PUBLIC HEALTH STATEMENT

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 4 and 5.

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 6.

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

1. PUBLIC HEALTH STATEMENT

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 6.

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

1. PUBLIC HEALTH STATEMENT

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 breastfeeding. 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 3.

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.

1. PUBLIC HEALTH STATEMENT

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

1. PUBLIC HEALTH STATEMENT

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 3.

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

1. PUBLIC HEALTH STATEMENT

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 breastfeeding. 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

1. PUBLIC HEALTH STATEMENT

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 3 (Section 3.11) and Chapter 7 (Section 7.1).

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

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. 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. PUBLIC HEALTH STATEMENT

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. ATSDR can also provide publically available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or
- Write to:
Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
1600 Clifton Road NE
Mailstop F-57
Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site:
<http://www.atsdr.cdc.gov>.

1. PUBLIC HEALTH STATEMENT

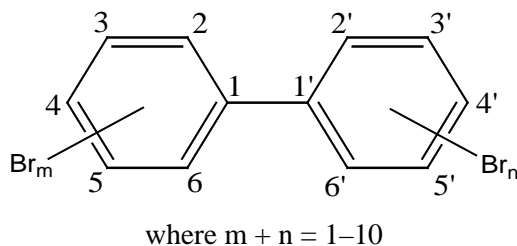
This page is intentionally blank.

2. RELEVANCE TO PUBLIC HEALTH

2.1 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 $m+n = 1-10$:



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 3.5, Mechanisms of Action).

2. RELEVANCE TO PUBLIC HEALTH

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 3.4, 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'-heptabromobiphenyl. Commercial octabromobiphenyl mixtures contained a large proportion (47.4–60.0%) of nonabromobiphenyl congeners, whereas commercial decabromobiphenyls contain predominately (96.8%) decabromobiphenyl congener.

Limited data are available on health effects of commercial decabromobiphenyl and octabromobiphenyl mixtures, although the hexabromobiphenyl mixtures FireMaster BP-6 and FireMaster FF-1 have been extensively tested. Most of the information on human health effects of PBBs comes from studies of Michigan residents who accidentally ingested milk, meat, and eggs that came from farms that used animal feed contaminated with FireMaster FF-1. In 1973, livestock on certain farms in Michigan were exposed to FireMaster FF-1 after it was mistaken as a feed supplement and mixed with feed that was distributed within the state for several months before being discovered. Health problems in dairy cattle, reported in the fall of 1973, were the first signs that this episode occurred, but the accidental addition of PBBs to animal feed was not identified as the cause of the problem until the spring of 1974.

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

2. RELEVANCE TO PUBLIC HEALTH

oral route via the food chain, and the inhalation and dermal routes represent the most likely routes of exposure to PBBs in occupational settings.

2.2 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 (T₄),

2. RELEVANCE TO PUBLIC HEALTH

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 T₄ and serum triiodothyronine (T₃) 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 T₄ 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 (aspartate aminotransferase [AST], serum alanine aminotransferase [ALT], 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.

2. RELEVANCE TO PUBLIC HEALTH

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

2. RELEVANCE TO PUBLIC HEALTH

correlation can be established between altered immune parameters and PBB levels in serum. Some have suggested that PBBs associated with white blood cells is possibly the cause of the immunological dysfunction resulting from exposure to PBBs. This would imply that total PBB in plasma is not necessarily a good marker for immune dysfunction. Continuous examination of this cohort may resolve the controversy.

Studies in animals, mostly intermediate-duration studies in rodents, indicate that a variety of immunological parameters such as spleen and thymus weights, antibody production, and lymphoproliferative responses can be affected by treatment with commercial PBB mixtures. The only chronic study found increased splenic hematopoiesis in mice, but no histological changes in the spleen, thymus, or lymph nodes of rats. It is apparent, however, that some of these effects are only seen at PBB levels that cause overt toxicity. Steroids are known to influence the immune response. Corticosterone levels were elevated in plasma of mice that were exposed to FireMaster BP-6 in the diet for 30 days, although the increase was not enough to be responsible for the observed immunological effect (reduced antibody-mediated response to sheep red blood cells). Thymic atrophy and a reduction in lymphocyte markers were reported in cows treated with PBB doses of 67 mg/kg/day for ≤ 60 days. However, these results should be interpreted with caution since the animals approached death at this dose. Based on the data available, it is difficult to suggest any particular species as the most sensitive. This is because different studies usually examined different end points, using different exposure protocols. It is unclear whether morphological changes in the reticuloendothelial system are more sensitive indicators of altered immune status than are functional changes. Although the limited data on humans are largely inconclusive, PBBs have altered immune responses in a variety of animal species, which suggests that humans may also be affected.

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

2. RELEVANCE TO PUBLIC HEALTH

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

2. RELEVANCE TO PUBLIC HEALTH

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/m³) 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.

2. RELEVANCE TO PUBLIC HEALTH

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 F₁ or F₂ 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. Embryo-lethal 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

2. RELEVANCE TO PUBLIC HEALTH

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

2. RELEVANCE TO PUBLIC HEALTH

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.

2.3 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 3, Section 3.5.2, 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

2. RELEVANCE TO PUBLIC HEALTH

many of the most toxic congeners resemble the structural configuration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (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, chlorinated dibenzo-*p*-dioxins [CDDs], chlorinated dibenzofurans [CDFs], and polybrominated diphenyl ethers [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 of 1 mg/kg/day for decreased serum levels of thyroid T₄ hormone identified in groups of 8–11 male rats that were treated with 0, 1, 3, or 6 mg/kg/day doses of an

2. RELEVANCE TO PUBLIC HEALTH

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 T₄ 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 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.

Decreased serum T₄ 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 T₃ and T₄ 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; Gupta and Moore 1979; Kasza et al. 1978a; Norris et al. 1975a, 1975b; NTP 1983; 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

2. RELEVANCE TO PUBLIC HEALTH

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 3.2.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of polybrominated biphenyls (PBBs). 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 are a class of brominated hydrocarbons that are used as flame retardant additives in plastics, textiles, and other materials. This class of chemicals is 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 (monobrominated through decabrominated), each containing one or more isomers.

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, octabromobiphenyl, and decabromobiphenyl. The most prevalent hexabromobiphenyl PBB mixtures had the trade names FireMaster BP-6 and FireMaster FF-1. FireMaster FF-1 was produced by grinding FireMaster BP-6 and adding 2% calcium polysilicate as an anticaking agent. The hexabromobiphenyl mixtures contained varying proportions (depending on lot number) of di- through octabrominated homologues, and 2,2',4,4',5,5'-hexabromobiphenyl (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

3. HEALTH EFFECTS

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).

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

3. HEALTH EFFECTS

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 3.4.2.2, it is reasonable to assume that mainly unchanged penta-, hexa-, and heptabromobiphenyl congeners in animal products were consumed.

Toxicity data for individual PBB congeners are included in some discussions in this profile when these data corroborate or provide information on effects not documented for the PBB mixtures. Congener-specific toxicity data are currently not practical for determining exposure levels of PBB 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 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 to which people may be exposed may be different from the original PBB source because of possible changes in congener composition resulting from differential partitioning and transformation in the environment and/or differential biological metabolism and retention.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies.

3. HEALTH EFFECTS

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. 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

3. HEALTH EFFECTS

example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

3.2.1 Inhalation Exposure

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

3.2.1.1 Death

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 $5,000 \text{ mg/m}^3$ 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.

3.2.1.2 Systemic Effects

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

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to PBBs.

3. HEALTH EFFECTS

Slight dyspnea was observed in five male and five female rats that were exposed to a decabromobiphenyl dust mixture at 5,000 mg/m³ concurrently with starch dust (6 mg/m³) for 6 hours/day, 5 days/week for 4 weeks (Millischer et al. 1980). This effect was not observed at 500 mg/m³ 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 $\approx 1,000$ in the high exposure group.

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

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

Hematological Effects. 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/m³ concurrently with starch dust (6 mg/m³) 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.

Hepatic Effects. 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/m³ 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 $\mu\text{g}/\text{m}^3$, 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.

3. HEALTH EFFECTS

Relative liver weight was increased $\approx 25\%$ in groups of 5 or 10 rats that were exposed to a decabromobiphenyl dust mixture at concentrations of 50–5,000 mg/m³ concurrently with starch dust (6 mg/m³) for 6 hours/day, 5 days/week for 4 weeks (Millischer et al. 1980). The increased liver weight was not accompanied by hepatic histologic changes, and therefore may be an adaptive response because PBBs are hepatic inducers and cause cellular proliferation (see Section 3.2.2.2 Hepatic Effects). No effects on liver weight or histology were observed at 5 mg/m³.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to PBBs.

Groups of six rats were exposed to 0.00035 $\mu\text{g}/\text{m}^3$ 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/m³ concurrently with starch dust (6 mg/m³) 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.

Endocrine Effects. Hypothyroidism was diagnosed in 4 of 35 men who were occupationally exposed to unspecified PBBs and/or decabromo diphenyl ether (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 $\mu\text{U}/\text{ml}$ normal range), low or borderline low serum T₄ levels (4.4 versus 4.5–11.5 $\mu\text{g}/\text{dL}$) and free-

3. HEALTH EFFECTS

thyroxine indices (3.7 versus 3.8–10.8), and markedly elevated thyroid antimicrosomal antibody titers (1:6,400 or above). Serum T₄ 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 T₄ 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.

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

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

Ocular Effects. No studies were located regarding ocular effects in humans after inhalation exposure to PBBs.

3. HEALTH EFFECTS

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/m³ concurrently with starch dust (6 mg/m³) 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/m³ and lower concentrations.

3.2.1.3 Immunological and Lymphoreticular Effects

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.

3.2.1.4 Neurological Effects

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.

3. HEALTH EFFECTS

3.2.1.5 Reproductive Effects

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.

3.2.1.6 Developmental Effects

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

3.2.1.7 Cancer

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

3.2.2 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 PBBs are recorded in Table 3-1 and plotted in Figure 3-1 .

3.2.2.1 Death

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

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | Reference Chemical Form | |
|----------------------------|-------------------------|---|---------|----------------------|---|----------------------------|--|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | | Serious (mg/kg/day) |
| 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 | ^b 1 | 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) |

3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------------|---|---------|----------------------|--|------------------------|--------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------------|---|-----------|----------------------|-----------------------------|--|-----------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|---------|----------------------|------------------------------------|--|----------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 9 | Rat (Sherman) | once 2-14 mo observ (GO) | Resp | 1000 | | | Kimbrough et al. 1978b (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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|---------|----------------------|--------------------------------|------------------------|---------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|-----------|----------------------|---|------------------------|---------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---|---|---------|----------------------|---|------------------------|---------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|----------------------------|--------------------------|---|---------|----------------------|---|-----------------------------------|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|-----------|----------------------|-----------------------------|---|-----------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|----------------------------|-------------------------|---|--------|----------------------|---|---|--|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|----------------------------|-------------------------------------|---|--------|----------------------|---|--|------------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------------|---|--------|----------------------|-----------------------------|--|---------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|--------|----------------------|-----------------------------|---|-------------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | Reference Chemical Form |
|----------------------------|--------------------|---|---------|----------------------|---|-----------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|---------|----------------------|---|--|--|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|-----------|----------------------|---|------------------------|------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|--------|----------------------|--|------------------------|------------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|---------|----------------------|--|------------------------|----------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|---------|----------------------|-------------------------------|------------------------|-------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|---------------------------|---|---------|----------------------|---|------------------------|--------------------------------|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------------|---|-----------|----------------------|-----------------------------|--|------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 (Holtzman) (F) | 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|---------|----------------------|--|------------------------|---------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 55 | Rat (Holtzman) | 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------------------|---|---------|----------------------|-----------------------------|--|---------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 58 | Rat (Sprague- Dawley CFY) | 13 wk (F) | Gastro | 100 | | | Millischer et al. 1980 (DBB) |
| | | | Hemato | 100 | | | |
| | | | Hepatic | 25 | 100 | (11% increased liver weight, hepatocyte hypertrophy and vacuolization, slightly increased liver lipids) | |
| | | | Renal | 100 | | | |
| | | | Bd Wt | 100 | | | |

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|---------|----------------------|--------------------------------------|------------------------|------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|---------|----------------------|-----------------------------|------------------------|------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------------|---|-----------|----------------------|---|--|----------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|---------|----------------------|-----------------------------|------------------------|----------------------------------|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|-----------|----------------------|---|------------------------|---------------------------------|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|---------|----------------------|---|------------------------|-------------------------------|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|---------|----------------------|---|------------------------|---|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|---------------------|---|-----------|----------------------|--|------------------------|-----------------------------|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 68 | Mouse (B6C3F1) | 30 d 5 d/wk 1x/d (GO) | Resp | 30 | | | Gupta et al. 1981 (FF-1) |
| | | | Cardio | 30 | | | |
| | | | Gastro | 30 | | | |
| | | | Hemato | | 30 F (decreased PCV) | | |
| | | | Musc/skel | 30 | | | |
| | | | Hepatic | 0.3 | 3 (hepatocyte enlargement and necrosis) | | |
| | | | Renal | 30 | | | |
| | | | Ocular | 30 | | | |
| | | | Bd Wt | 3 | 30 M (significant decrease in weight gain) | | |
| | | | Other | 30 | | | |

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral (continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------|---|---------|----------------------|-----------------------------|---|------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|-----------|----------------------|--|--|----------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|---------------------|---|---------|----------------------|--|---|---------------------------------|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 72 | Gn Pig (NS) | 30 d ad lib (F) | Resp | 20 M | | | Sleight and Sanger 1976 (NS) |
| | | | Hepatic | | 0.04 M (vacuolation and fatty changes) | | |
| | | | Bd Wt | 0.4 M | | 4 M (severe weight loss prior to death) | |

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL | | Reference Chemical Form |
|-------------------------------|---------------------|---|---------|----------------------|--|------------------------|-----------------------------------|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|----------------------|---|---------|----------------------|--|--|--|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 75 | Mink (NS) | 313 d ad lib (F) | Cardio | 2.4 | | | Aulerich and Ringer 1979; Ringer et al.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) | |
| 76 | Rat (Fischer 344) | Immuno/ Lymphoret 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------|---|--------|----------------------|---|--|--|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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- ad lib (F) | | 1.25 F | 2.5 F (reduced lymphocyte response to mitogen stimulation) | | Howard et al. 1980 (BP-6) |

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|----------------------------|-------------------------------|---|--------|----------------------|--|---|-----------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 Holtzman) | 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|----------------------------|----------------------|---|--------|-----------------------------|---|---|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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) |

3. HEALTH EFFECTS

3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---|---|--------|----------------------|---------------------------------------|---|------------------------------------|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 (Holtzman 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|-----------------------------|---|--------|----------------------|--|--|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|--------|----------------------|--|--|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 et al. 1981 (FF-1) |

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|----------------------------|---------------------------|---|--------|----------------------|-----------------------------|--|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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: hepatocellular 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 3-1 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 | | Reference Chemical Form |
|-------------------------------|---------------------|--|--------|----------------------|-----------------------------|--------------------------------|---|
| | | | | | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 113 | Mouse (B6C3F1) | 116 wks Gd 0-ppd 56 (weaning) 105wks post-weaning ad lib (F) | | | | 1.3 F (44% decreased survival) | NTP 1992, Chhabra et al. 1993 (FF-1) |
| | Systemic | | | | | | |
| 114 | Monkey (Rhesus) | 66 wk ad lib (F) | Hemato | 0.012 | | | Lambrecht et al. 1978 (FF-1) |
| | | | Bd Wt | | 0.012 (7.4% weight loss) | | |

Table 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------------|---|-----------|----------------------|---|------------------------|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------|---|-----------|----------------------|---|-------------------------------------|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|-------------------------------|---------------------------|---|--------|---------------------------------|--|------------------------|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| | | | | | | | |
| 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 3-1 Levels of Significant Exposure to Polybrominated Biphenyls - Oral

(continued)

| Key to figure ^a | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | LOAEL | | | Reference Chemical Form |
|----------------------------|------------------------|---|--------|----------------------|-----------------------------|--|---|
| | | | | NOAEL (mg/kg/day) | Less Serious (mg/kg/day) | Serious (mg/kg/day) | |
| 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) 0.5 (CEL: hepatocellular adenoma and carcinoma) | NTP 1992, Chhabra et al. 1993 (FF-1) |
| 123 | Mouse (B6C3F1) | 116 wks Gd 0- ppd 56 105wks post-weaning (F) | | | | 3.9 (thyroid follicular cell adenoma) 1.3 (CEL: hepatocellular adenoma and carcinoma) | NTP 1992, Chhabra et al. 1993 (FF-1) |

3. HEALTH EFFECTS

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)

Acute (≤ 14 days)

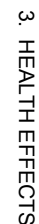


Figure 3-1. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

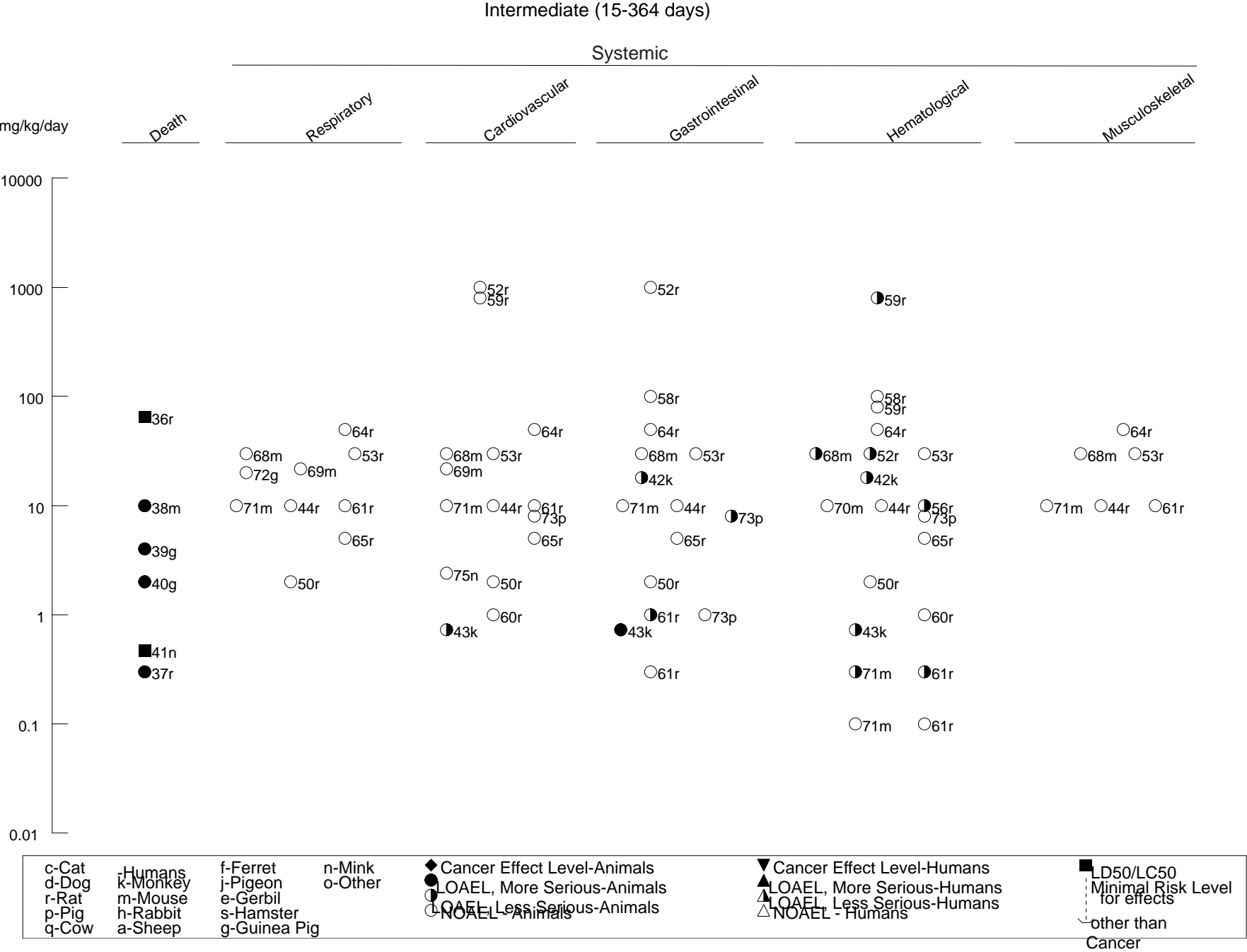


Figure 3-1. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

Intermediate (15-364 days)

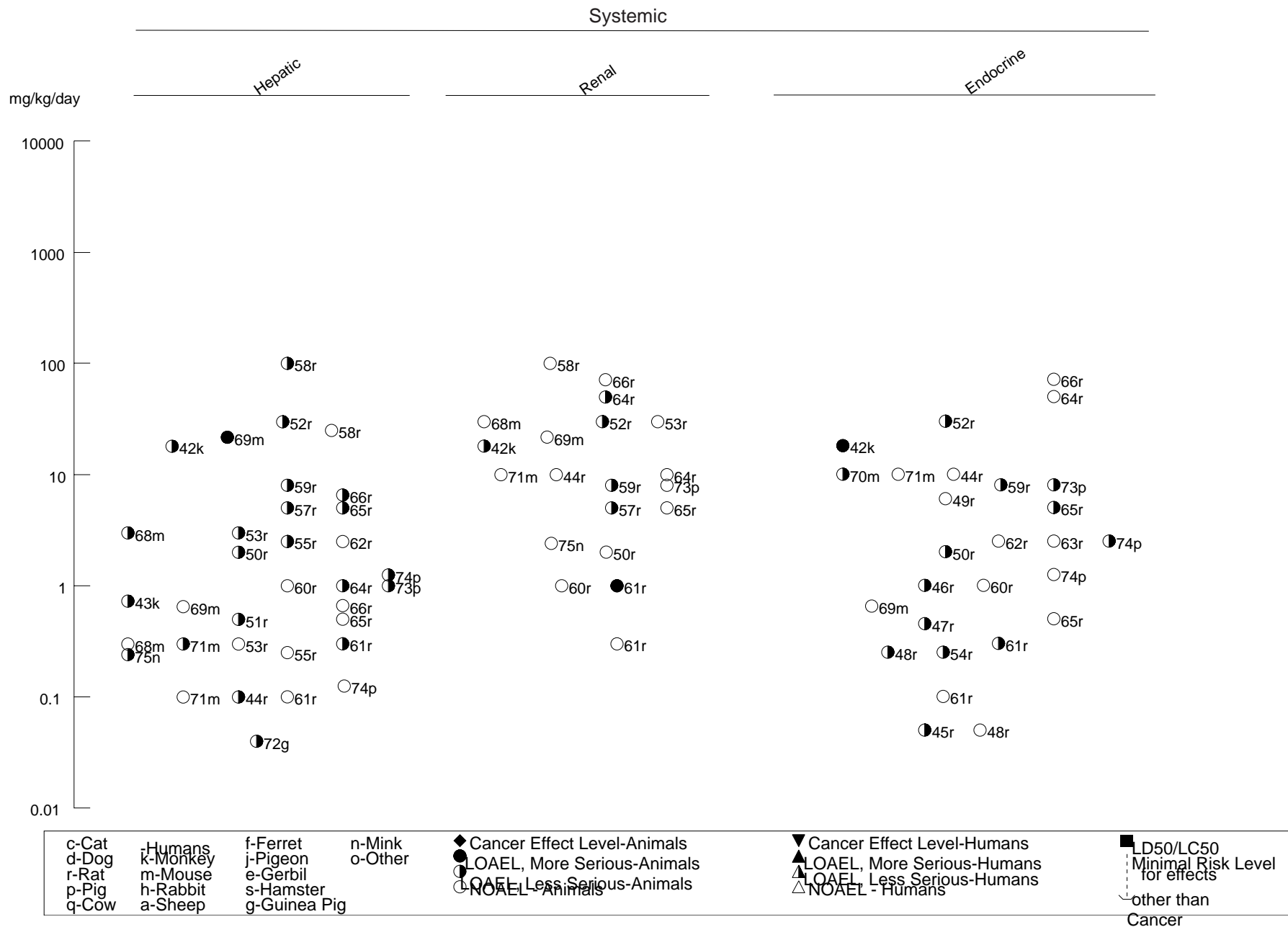


Figure 3-1. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)
Intermediate (15-364 days)

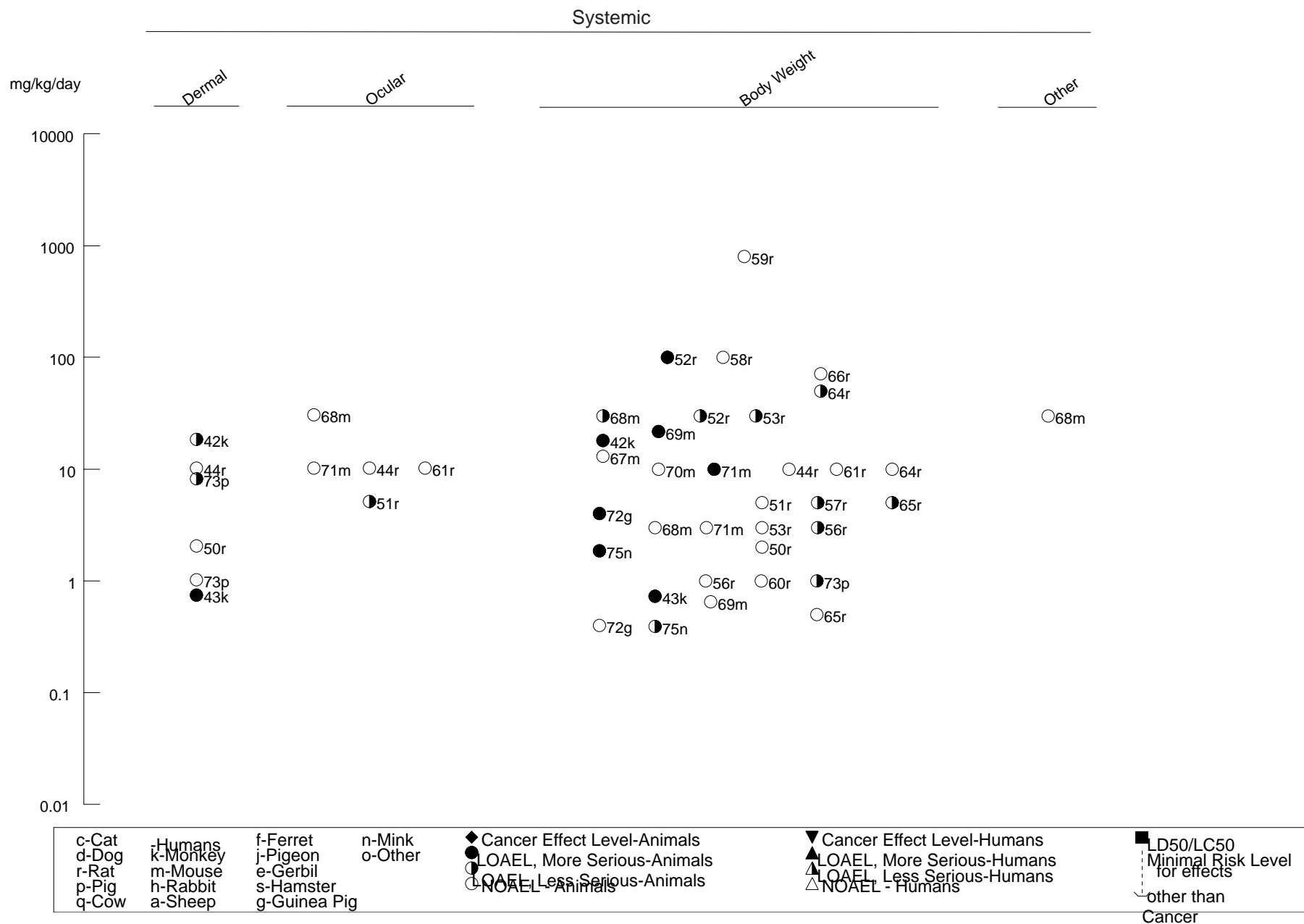


Figure 3-1. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)
Intermediate (15-364 days)

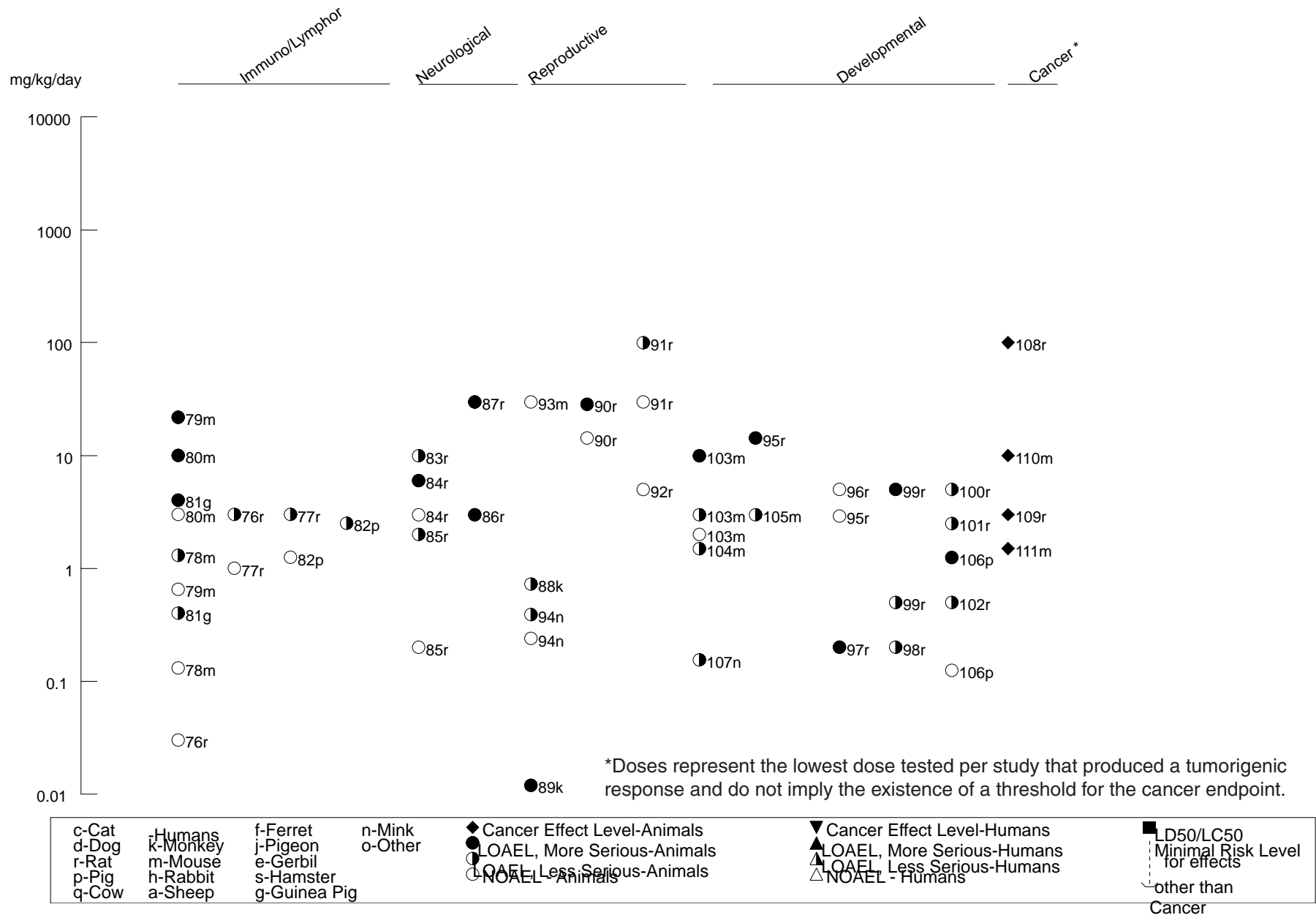
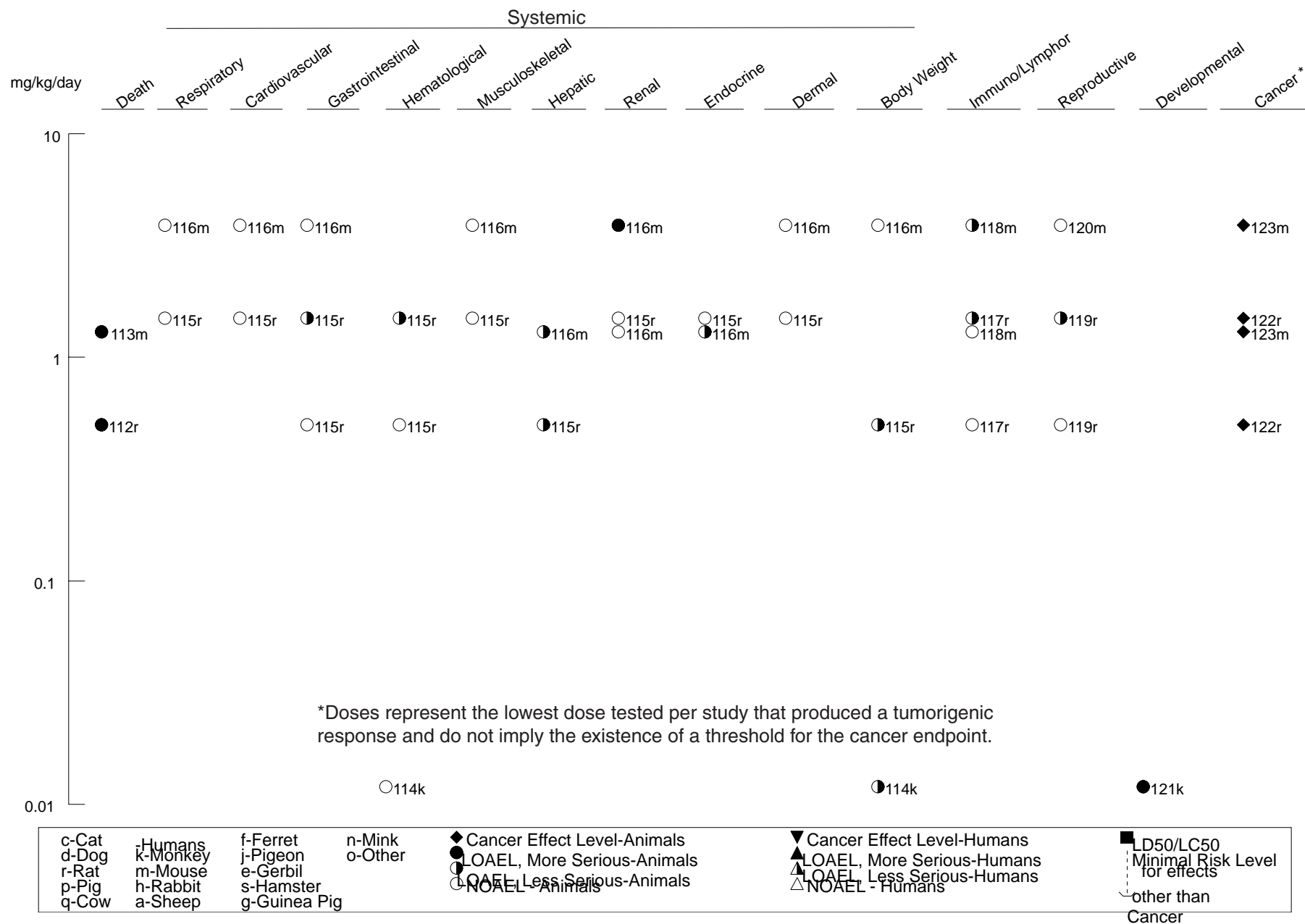


Figure 3-1. Levels of Significant Exposure to Polybrominated Biphenyls- Oral (*Continued*)

Chronic (≥ 365 days)



3. HEALTH EFFECTS

(5 days/week), however, caused 100% mortality in rats; the mean time to death was 12.3 days in females and 11.0 days in males (Gupta and Moore 1979). The cause of death was not specifically reported, but a general statement indicated that the rats had hunchback posture, rough coat, and sunken eyes, were lethargic, and appeared dehydrated and emaciated. No deaths occurred in rats administered octabromobiphenyl mixture in a single dose $\leq 1,000$ 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 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

3. HEALTH EFFECTS

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) 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 LD₅₀ 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

3. HEALTH EFFECTS

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 LD₅₀ value and reliable LOAEL values for death in each species in the acute- and intermediate-duration categories are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

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

Respiratory Effects. 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

3. HEALTH EFFECTS

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.

Cardiovascular Effects. 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 $\leq 1,000$ 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.

3. HEALTH EFFECTS

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.

Gastrointestinal Effects. 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 $\leq 1,000$ 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

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

Hematological Effects. 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

3. HEALTH EFFECTS

≤ 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.

Musculoskeletal Effects. 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

3. HEALTH EFFECTS

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.

Hepatic Effects. 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 3.8.2, suggest that PBBs may have induced hepatic microsomal enzymes in exposed Michigan residents (Lambert et al. 1990).

Hepatic effects of PBBs are documented in various animal species although rats have been the species tested most extensively. The changes appear to be similar among species and reversible when mild. Characteristic hepatic effects include proliferation of the smooth endoplasmic reticulum, microsomal enzyme induction, increased serum levels of liver-associated enzymes indicative of possible hepatocellular damage, liver enlargement, hepatocyte vacuolation and fat deposition, fibrosis, and

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

(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

3. HEALTH EFFECTS

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.

Renal Effects. 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

3. HEALTH EFFECTS

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 shrunk and glomerular tufts were shrunk, 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 ammoniogenesis 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

3. HEALTH EFFECTS

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.

Endocrine Effects. 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

3. HEALTH EFFECTS

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 3-2 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 $\leq 1,000$ mg/kg and up to 2 years posttreatment observation (Kimbrough et al. 1978b, 1981) or dosages of $\leq 1,000$ 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 decreased 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

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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).

Dermal Effects. 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),

3. HEALTH EFFECTS

≤ 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). Dermatitis 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 dermatitis (a nonspecific term used to denote any cutaneous lesion or group of lesions), and histologic examinations were not completed.

Ocular Effects. 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).

Body Weight Effects. 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

3. HEALTH EFFECTS

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 $\leq 2,000$ 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

3. HEALTH EFFECTS

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.

3.2.2.3 Immunological and Lymphoreticular Effects

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

3. HEALTH EFFECTS

different among the three groups. Furthermore, there was no correlation between a poor mitogenic response and low numbers of T-lymphocytes (Silva 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 3.2.2.6.

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

3. HEALTH EFFECTS

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 $\geq 15\%$ 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 typhosa* 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

3. HEALTH EFFECTS

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

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

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

3.2.2.4 Neurological Effects

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

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

activity was apparent at 6 mg/kg/day, compared with controls. Weakness of the hind limb was noted in rats treated with 10 mg/kg/day FireMaster FF-1 for 6 months compared with control rats (Cabe and Tilson 1978). Histological examination of brain and/or spinal nerve tissue found no FireMaster FF-1-related alterations in rats or mice administered up to 10 mg/kg/day for 25 weeks (NTP 1983) or 3.9 mg/kg/day for up to 105 weeks (NTP 1992).

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

Postnatal neurodevelopmental effects were also evaluated in offspring of rats that received 0.2 or 2 mg/kg/day doses of FireMaster BP-6 dissolved in peanut butter from day 6 of gestation through day 24 postpartum and observed until postnatal day 60 (Henck et al. 1994). Multivariate analysis of variance of neurodevelopmental end points showed significant PBB-related effects for acquisition of forward locomotion, cliff avoidance, cage emergence, and open-field activity in male and female offspring of the rats exposed to 2 mg/kg/day. The most prominent behavioral effects were delays in acquisition of forward locomotion and suppressed open-field activity. Other effects in the offspring included reduced crown-rump length and body weight at birth and reduced postnatal body weight as summarized in Section 3.2.2.6 (Developmental Effects).

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

3. HEALTH EFFECTS

3.2.2.5 Reproductive Effects

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 breastfeeding of 4.1 ± 5.3 months. The numbers of women who breastfed their first infant after the initial serum PBB level and had previously breast-fed were 293 (65.7%) and 49 (11.0%), respectively. Exposure was treated as a categorical variable by dividing the women into groups of low (reference) exposure (≤ 1 ppb, $n=260$, serum levels at or below the detection limit), moderate exposure (>1 – ≤ 7 ppb, $n=141$), and high exposure (>7 ppb, $n=45$, levels above the 90th percentile). Three outcomes of interest were analyzed: (1) the decision to breastfeed (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

3. HEALTH EFFECTS

progesterone was decreased in the same four females that showed this effect prebreeding. In a multiple-generation study in which only F₀ 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 F₁ or F₂ generations (McCormack et al. 1981). Implantation was completely blocked in two of five and two of three female rats that survived gavage administration of 28.6 or 57.1 mg/kg/day FireMaster BP-6, respectively, on alternate days between GDs 0 and 14 (Beaudoin 1979). Histological examination of reproductive organs in male and female rats and mice revealed no abnormalities following gavage treatment with doses up to 10 mg/kg/day FireMaster FF-1 for 25 weeks or 30 mg/kg/day for 4–5 weeks (Gupta and Moore 1979; Gupta et al. 1981; NTP 1983). Necrosis, hyperplasia, and metaplasia in the epithelial lining of the ductus deferens were observed in male rats that died following 100 mg/kg/day FireMaster FF-1 for 4–5 weeks (Gupta and Moore 1979). Treatment of male and female mink with diets providing up to 0.39 mg/kg/day FireMaster FF-1 for 6–7 months before breeding did not affect reproductive performance with respect to fertility or litter size (Aulerich and Ringer 1979; Ringer et al. 1981). In the only chronic study, histological examination of male and female reproductive organs showed increased cystic endometrial hyperplasia in rats exposed to 1.5 mg/kg/day FireMaster FF-1 for up to 104 weeks, but no changes were observed in mice exposed to ≤ 3.9 mg/kg/day for up to 105 weeks (NTP 1992). Following 6–7 months of exposure to 0.012 mg/kg/day FireMaster FF-1 in the diet, four of seven female monkeys displayed a lengthening of the menstrual cycle from 28 to 31 days and decreased serum progesterone; prior to the treatment, they had at least 2 years of normal cycles (Allen et al. 1979; Lambrecht et al. 1978). All seven of these monkeys conceived after one to four matings with control males (controls required one to three breedings), but two displayed prolonged implantation bleeding and another two had fetuses that were aborted or stillborn (see Developmental Effects). Reduced spermatogenesis was observed in a male monkey that died after 25 weeks on a diet providing 0.73 mg/kg/day FireMaster FF-1 (Allen et al. 1978).

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

3.2.2.6 Developmental Effects

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,

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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. 1982b). 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 $\leq 1,000$ mg/kg/day decabromobiphenyl mixture on GDs 6–15 (Millischer et al. 1980).

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

3. HEALTH EFFECTS

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 F₁ 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 F₁ offspring of dams treated with 0.5 mg/kg/day (McCormack et al. 1981). Although survival of F₂ and F₃ generations was not affected by the 5 mg/kg/day treatment of the F₀ rat dams, F₂ offspring, but not F₃ 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, T₄, 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 adrenocorticotrophic 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

3. HEALTH EFFECTS

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 T₃ and T₄ hormones were observed in 4-week-old offspring of swine fed 2.5 mg/kg/day FireMaster BP-6 in the diet during the second half of gestation and during lactation; 1.25 mg/kg/day produced similar effects on the thyroid, but no necrosis in the liver of 4-week-old nursing pigs (Werner and Sleight 1981). Examination of several parameters of immune function in 4-week-old offspring of sows fed ≤ 2.5 mg/kg/day FireMaster BP-6 during gestation and lactation provided no conclusive evidence for immunosuppressive effects (Howard et al. 1980). An abortion and a stillbirth occurred among seven female monkeys that were fed 0.012 mg/kg/day FireMaster FF-1 in the diet for 7 months prior to conception and during pregnancy (Allen et al. 1979; Lambrecht et al. 1978). The surviving five infants had reduced birth weight and postnatal body weight gain, but no gross abnormalities. The incidence of dystocia (difficult birthing) was 50% increased among first- and second-generation offspring of cows treated with 0.65 mg/kg/day FireMaster BP-6 by gelatin capsule for 180 or 202 days during late pregnancy (Willett et al. 1982). The same dosage for 60 days caused a 21.6% increased incidence of dystocia, but this increase was not statistically significant ($p=0.08$). Stillbirths and preweaning deaths were not significantly increased, but all mortality was attributable to dystocia. Incidences of dystocia and calf mortality appeared to be related to higher birth weight, which in turn were correlated with concentrations of PBBs in maternal blood and tissues. Growth and development were not affected in the surviving calves. Of six pregnant cows that were similarly treated with a maternolethal dosage (67 mg/kg/day) of FireMaster BP-6, three aborted after 30–38 days, and three retained dead fetuses (Moorhead et al. 1977).

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

3. HEALTH EFFECTS

3.2.2.7 Cancer

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

3. HEALTH EFFECTS

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

Another study of the Michigan PBB registry evaluated associations between levels of serum PBBs and risks of various site-specific cancers (Hoque et al. 1998). Primary cancers (195 malignancies) were identified in 187 persons among 3,899 registrants enrolled in 1976 and followed through 1993. Controls were 696 randomly selected cancer-free individuals who were frequency matched to cases by age (in 5-year strata) and sex in a 4:1 ratio (except above age 70 years when, due to lower numbers, all eligible controls were used). PBB levels in the cases were measured at the time of registry enrollment. Serum PBB concentration ranges was categorized into four groups (not detectable–3 ppb, 4–20 ppb, 21–50 ppb, >50 ppb) defined by the median and the 90th and 95th percentiles. Conditional logistic regression was used to calculate univariate and multivariate (adjusted) ORs by cancer site for the three highest serum PBB categories compared to the reference (≤ 3 ppb) group. The multivariate ORs were adjusted for family history of cancer, smoking status, alcohol use, age, serum PCB level, and sex. Digestive system cancer (12 cases) and lymphoma (not otherwise specified) (8 cases) showed increasing dose-response relationships for risk as PBB concentrations increased. Digestive system cancer was a grouping that comprised of the following sites: liver (five cases), stomach (five cases), esophagus (one case) and pancreas (one case). Adjusted ORs for digestive system cancer were 1.00 (reference), 8.23 (95% CI=1.27–53.3), 12.3 (0.80–191), and 22.9 (1.34–392) for the ≤ 3 , 4–20, 21–50, and >50 ppb categories, respectively. The corresponding adjusted ORs for PBB level and lymphoma risk were 1.00, 3.85 (0.32–46.2), 19.6 (1.52–253), and 48.9 (4.09–585). The lymphoma ORs were incompletely adjusted due to missing data for serum PCB level and family cancer history in the reference category. Increased risks were also observed for breast cancer in the 4–20 ppb category (nine cases, adjusted OR=2.41, 95%

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

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.

3. HEALTH EFFECTS

Eight F₀:F₁ 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 ($p \leq 0.002$) except for carcinoma in 0:0.5 mg/kg/day males and females and 0:1.5 mg/kg/day females ($p > 0.05$). Combined perinatal and adult exposure significantly enhanced the development of liver tumors in female rats, as shown by comparisons with females receiving adult exposure only. Compared to the 0:0.5 mg/kg/day female adult-only exposed group, incidences of hepatocellular adenoma were 22 of 50 ($p = 0.01$) and 35 of 50 ($p < 0.001$); of carcinoma, 1 of 50 ($p = 0.05$) and 8 of 50 ($p = 0.048$); and of hepatocellular adenoma or carcinoma (combined), 22 of 50 ($p = 0.03$) and 39 of 50 ($p < 0.001$) in the 0.15:0.5 and 0.5:0.5 mg/kg/day groups, respectively. Compared to the 0:1.5 mg/kg/day female adult-only exposed group, incidences of hepatocellular adenoma, carcinoma, and hepatocellular adenoma or carcinoma (combined) were 45 of 50 ($p = 0.049$), 22 of 50 ($p < 0.001$), and 47 of 50 ($p = 0.016$), respectively, in the 0.5:1.5 mg/kg/day group. This enhancing influence of perinatal exposure did not occur in the males. Perinatal-only exposure did not cause significantly increased incidences of liver or other tumors in rats of either sex.

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

3. HEALTH EFFECTS

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 ($p \leq 0.05$ in males; $p \leq 0.01$ in females). For males, there was also a marginally significant ($p \leq 0.05$) increase associated with F_0 exposure.

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

3. HEALTH EFFECTS

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

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

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

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

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

3. HEALTH EFFECTS

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'-hexabromobiphenyl (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 3.5.2.

The tumor initiating potential of PBBs is not well characterized. Numbers of GGT-altered foci were significantly increased in partially hepatectomized rats that were administered a single 1–10 mg/kg oral dose of 3,3',4,4'-tetrabromobiphenyl (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).

3.2.3 Dermal Exposure

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

3.2.3.1 Death

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

3. HEALTH EFFECTS

cause of death was not reported. A commercial mixture of decabromobiphenyl in corn oil was not lethal in rats that were observed for 14 days following application of a single dose as high as 5,000 mg/kg to covered intact skin (Millischer et al. 1980). The octabromobiphenyl LOAEL of 5,000 mg/kg is reported in Table 3-1. 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.

3.2.3.2 Systemic Effects

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

Systemic effects that have been observed in humans and animals following dermal exposure to PBBs are described below. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 3-2.

Hepatic Effects. 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 $\geq 1,000$ 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/deca (1:9) applied once a day for 5 days to the ear of three rabbits caused no histopathological effects in the liver (Hass et al. 1978).

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

Table 3-2 Levels of Significant Exposure to Polybrominated Biphenyls - Dermal

| Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL | LOAEL | | Reference Chemical Form |
|---------------------|---|---------|---------------------|-------------------|--|-------------------------------------|
| | | | | Less Serious | Serious | |
| 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 3-2 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)

3. HEALTH EFFECTS

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

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

Dermal Effects. As discussed in Section 3.2.1.2, results from a medical history survey study of workers in a PBB manufacturing plant and a nonexposed group of Wisconsin farm residents indicated an association between occupational exposure to PBBs and the occurrence of acne (Chanda et al. 1982). The survey covered a period of 3 years of potential exposure, but exposure levels were not reported. No adverse dermal effects were observed on the arms or legs of subjects after a 6-day application of polymer fibers containing commercial octabromobiphenyl mixture under an occlusive covering; no additional information was reported (Waritz et al. 1977).

Several studies examined the acute dermal effects of commercial PBB mixtures in rabbits. Application of 0.19 mg/kg FireMaster FF-1 for 5 days, in toluene vehicle, to the inner surface of the left ear of two rabbits (right ear served as control) induced moderate hyperkeratosis, which included marked dilation of the hair follicles, with moderate proliferation of the epithelium and partial atrophy of the sebaceous glands (Needham et al. 1982). There was also evidence of excess keratin and debris in the subjacent hair follicles. Application of either a dry or water-moistened formulation of octabromobiphenyl mixture (amount not reported) for 24 hours did not adversely affect intact skin in rabbits, but slight erythema and edema were observed in abraded skin (Norris et al. 1975a). Repeated applications over a 2-week period of the dry octabromobiphenyl mixture formulation (amount not reported) to occluded intact or abraded skin caused no skin response, but the water-moistened formulation caused slight and transient erythema (Norris et al. 1975a). None of these studies reported the number of animals used. Rough skin with mild erythema was observed in occluded intact shaved dorsal skin of a group of rabbits after repeated

3. HEALTH EFFECTS

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.

Ocular Effects. 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.

Body Weight Effects. 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

3. HEALTH EFFECTS

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).

3.2.3.3 Immunological and Lymphoreticular Effects

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.

3.2.3.4 Neurological Effects

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.

3.2.3.5 Reproductive Effects

Polybrominated Biphenyls. Eleven workers in a PBB manufacturing company in Michigan displayed no differences in the distribution of sperm counts, motility, or morphology compared with a control group of

3. HEALTH EFFECTS

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.

3.2.3.6 Developmental Effects

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

3.2.3.7 Cancer

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.

3.3 GENOTOXICITY

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

3. HEALTH EFFECTS

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

In vitro studies indicate that PBBs are not directly genotoxic. As summarized in Table 3-4, PBBs did not exhibit mutagenic activity when tested in the prokaryotic organisms *S. typhimurium* (Haworth et al. 1983; Millischer et al. 1980; NTP 1983) and *E. coli* (Rossman et al. 1991) with or without activation systems in the limited number of studies available. *In vitro* testing in eukaryotic cells resulted in negative genotoxic responses in hamster cells (Galloway et al. 1987; Kavanagh et al. 1985; Williams et al. 1984), rat liver cells (Kavanagh et al. 1985; Williams et al. 1984), mouse liver and lymphoma cells (Myhr and Caspary 1991; Williams et al. 1984), and human fibroblasts (Williams et al. 1984).

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

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

3. HEALTH EFFECTS

Table 3-3. Genotoxicity of PBBs *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: | | | |
| <i>Salmonella typhimurium</i> (mouse hosted-mediated) | Gene mutation | – | Millischer et al. 1980 (DBB) |
| Micronucleus test: | | | |
| Mouse bone marrow erythrocytes | Chromosome aberration (micronuclei) | – | Millischer et al. 1980 (DBB) |

– = negative result; DBB = decabromobiphenyl commercial mixture; DNA = deoxyribonucleic acid; FF-1 = FireMaster FF-1; PBBs = polybrominated biphenyls

3. HEALTH EFFECTS

Table 3-4. Genotoxicity of PBBs *In Vitro*

| Species (test system) | End point | Results | | Reference |
|---|---------------------------|-----------------|--------------------|----------------------------------|
| | | With activation | Without activation | |
| PBBs | | | | |
| Prokaryotic organisms: | | | | |
| <i>Salmonella typhimurium</i> (plate incorporation) | Gene mutation | — | — | NTP 1983 (FF-1) |
| <i>Salmonella typhimurium</i> (plate incorporation) | Gene mutation | — | — | Haworth et al. 1983 (HBB) |
| <i>Salmonella typhimurium</i> (plate incorporation) | Gene mutation | — | — | Millischer et al. 1980 (DBB) |
| <i>Escherichia coli</i> (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) |

– = negative result;; 2,4,5-HBB = 2,2',4,4',5,5'-hexabromobiphenyl; 3,4,5-HBB = 3,3',4,4',5,5'-hexabromobiphenyl; 3,4-TBB = 3,3',4,4'-tetrabromobiphenyl;; BP-6 = FireMaster BP-6; DBB = decabromobiphenyl commercial mixture; DNA = deoxyribonucleic acid; FF-1 = FireMaster FF-1; HBB = hexabromobiphenyl (unspecified); PBB = unspecified mixture; PBBs = polybrominated biphenyls

3. HEALTH EFFECTS

3.4 TOXICOKINETICS

Data regarding the toxicokinetics of PBBs in humans are limited to information derived from cases of accidental ingestion of food contaminated with PBBs and cases of occupational exposure by the inhalation and dermal routes. These data provide qualitative evidence that PBBs are absorbed in humans by the inhalation, oral, and dermal routes. Limited quantitative data in animals indicate that some PBB congeners are well absorbed after oral exposure. Dermal absorption data for animals are insufficient for estimating absorption rates, and no inhalation absorption data were located. In blood, 80% of PBBs are bound to protein and 20% are associated with lipids. The distribution pattern of PBBs did not differ significantly between humans and animals and among animal species. Due to their lipophilic nature, PBBs, especially the highly brominated congeners, tend to accumulate in lipid-rich tissues. Greater relative amounts of PBBs are usually found in the liver, adipose, skin, and breast milk. Certain components of PBB mixtures are metabolized by the microsomal monooxygenase system catalyzed by cytochrome P-450 of the type induced by phenobarbital. The rate of metabolism of some PBB congeners depends on the bromine substitution pattern. PBB congeners of low bromine content are transformed into hydroxylated derivatives that are predominately eliminated in the urine. Highly brominated congeners are either retained or excreted unchanged in the feces. As discussed in Section 3.3.2, 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.

3.4.1 Absorption**3.4.1.1 Inhalation Exposure**

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

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

3. HEALTH EFFECTS

3.4.1.2 Oral Exposure

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

Absorption of PBBs from the gastrointestinal tract in animals can be inferred from the numerous reports of adverse effects (Section 3.2.2) and increased residue levels in tissues following oral administration of these compounds (Section 3.4.2.2); however, few quantitative data exist. By comparing the amount of radioactivity in the feces of rats administered a single 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 $\approx 93\%$ of the oral dose was absorbed over a 24-hour period (Matthews et al. 1977a). 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 $\geq 90\%$ was absorbed over a dose range of 1–30 mg/kg (Matthews et al. 1977a). 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.

3.4.1.3 Dermal Exposure

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).

3. HEALTH EFFECTS

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

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.

3.4.2.2 Oral Exposure

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

Analysis of postmortem tissue samples from 15 subjects in the Grand Rapids, Michigan area indicated that renal fat had the highest single PBB concentration (1.65 µg/g wet weight) and the highest mean concentration (0.475 µg/g) (Miceli et al. 1985). In regards to adipose, PBB concentrations in different

3. HEALTH EFFECTS

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. 1977a). 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. 1977a). 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 3.4.5 (Physiologically Based Pharmacokinetic/Pharmacodynamic Models), human intake of 9.8 g of the congener over a 230-day period would result in peak concentrations of 720 and 2.1 ppm in fat and blood, respectively, 5 years after the onset of exposure. The model also predicted that the body burden after 5 years would be 5.2 g and the half-life 6.5 years. This half-life is shorter than the 12 years (median, range 4–97 years) calculated for hexabromobiphenyl in a Michigan cohort (Lambert et al. 1990) (see Section 3.8.1).

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

3. HEALTH EFFECTS

The distribution and elimination of PBBs from tissues were examined in rats over a period of 112 days after a single oral dose of FireMaster FF-1 (Domino et al. 1982). Elimination from blood was best described by a three-compartment model, and an elimination half-life from whole blood of 145 days was estimated. Relative to the three compartments (C1, C2, and C3): C1 consisted of heart, kidney, spleen, and whole blood; C2 included liver, lung, cerebrum, cerebellum, and testes; and C3 included subcutaneous fat. PBB residues in C1 rose quickly, peaked within 5 hours of dosing and then fell rapidly; a half-life of 3.62 hours was estimated. PBB peaked in C2 at 12 hours and then decreased; the half-life was 17.6 hours. In C3, levels of PBB peaked only after 1 week and remained elevated for several weeks; the estimated half-life was 31.1 days. Tissues with PBBs in order of increasing concentration were: blood, spleen, kidney, and heart in C1, and testes, cerebrum, cerebellum, lung, and liver in C2. Simulations of different body fat proportions showed that reduction in body fat decreased the half-life of the chemical considerably. According to the investigators (Domino et al. 1982), tissues within C1 and C2 may be at greater risk of toxicity during the subacute phase of PBB ingestion. In their view, this could explain the fact that blood PBB levels in Michigan families were not positively correlated with toxic symptoms of exposure to PBBs (see Section 3.2).

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

Several studies have examined the distribution of PBB residues in offspring after maternal exposure to PBBs during gestation and/or lactation. In 4-week-old pigs exposed *in utero* and via lactation to FireMaster BP-6, PBBs accumulated preferentially in adipose tissue and liver on a wet tissue basis. Over a wide range of doses, however, adipose had at least two times the PBB concentration compared to the liver (Werner and Sleight 1981). PBB levels in tissues of sows were comparable to those measured in tissues of 4-week-old pigs. On a fat basis, the liver had the highest concentration of PBBs in both sows

3. HEALTH EFFECTS

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).

3.4.2.3 Dermal Exposure

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.

3.4.2.4 Other Routes of Exposure

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. 1977a). 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 $\geq 60\%$ 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,

3. HEALTH EFFECTS

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, $>1 \mu\text{g/g}$ 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.

3.4.3 Metabolism

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 would not be expected

3. HEALTH EFFECTS

since the temperatures reached during these processes is probably not high enough. As discussed in Chapter 4, temperatures must exceed $\approx 500^\circ\text{C}$ 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 mono-hydroxylated 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

3. HEALTH EFFECTS

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'-hexabromobiphenyl (Gardner et al. 1979). This metabolite was not found in the liver, but the parent compound was identified. Since hydroxylation in position 6 of highly substituted congeners is unlikely, it was postulated that the metabolite found in the feces was formed by microbial metabolism of the PBB in the intestinal tract. The *in vitro* metabolism of 2,2',4,4',5,5'-hexabromobiphenyl (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

3. HEALTH EFFECTS

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 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).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

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

3.4.4.2 Oral Exposure

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

3. HEALTH EFFECTS

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 ($\text{BMI} \geq 23$). Increasing number of pregnancies between the first and last measurement was also associated with slower decay, but the effect was of borderline statistical significance ($p=0.06$). Breastfeeding 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 $\mu\text{g/kg}$, with a median of 250 $\mu\text{g/kg}$, 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 $\mu\text{g/kg}$.

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

3. HEALTH EFFECTS

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. 1977a). 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. (1977a) 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.

3.4.4.3 Dermal Exposure

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

3.4.4.4 Other Routes of Exposure

Rats given a single intravenous dose of ^{14}C -2,2',4,4',5,5'-hexabromobiphenyl excreted a cumulative 0.96, 3.3, and 6.6% of the dose in the feces 1, 7, and 42 days after dosing, respectively (Matthews et al. 1977a). 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, \approx 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

3. HEALTH EFFECTS

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.

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

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

3. HEALTH EFFECTS

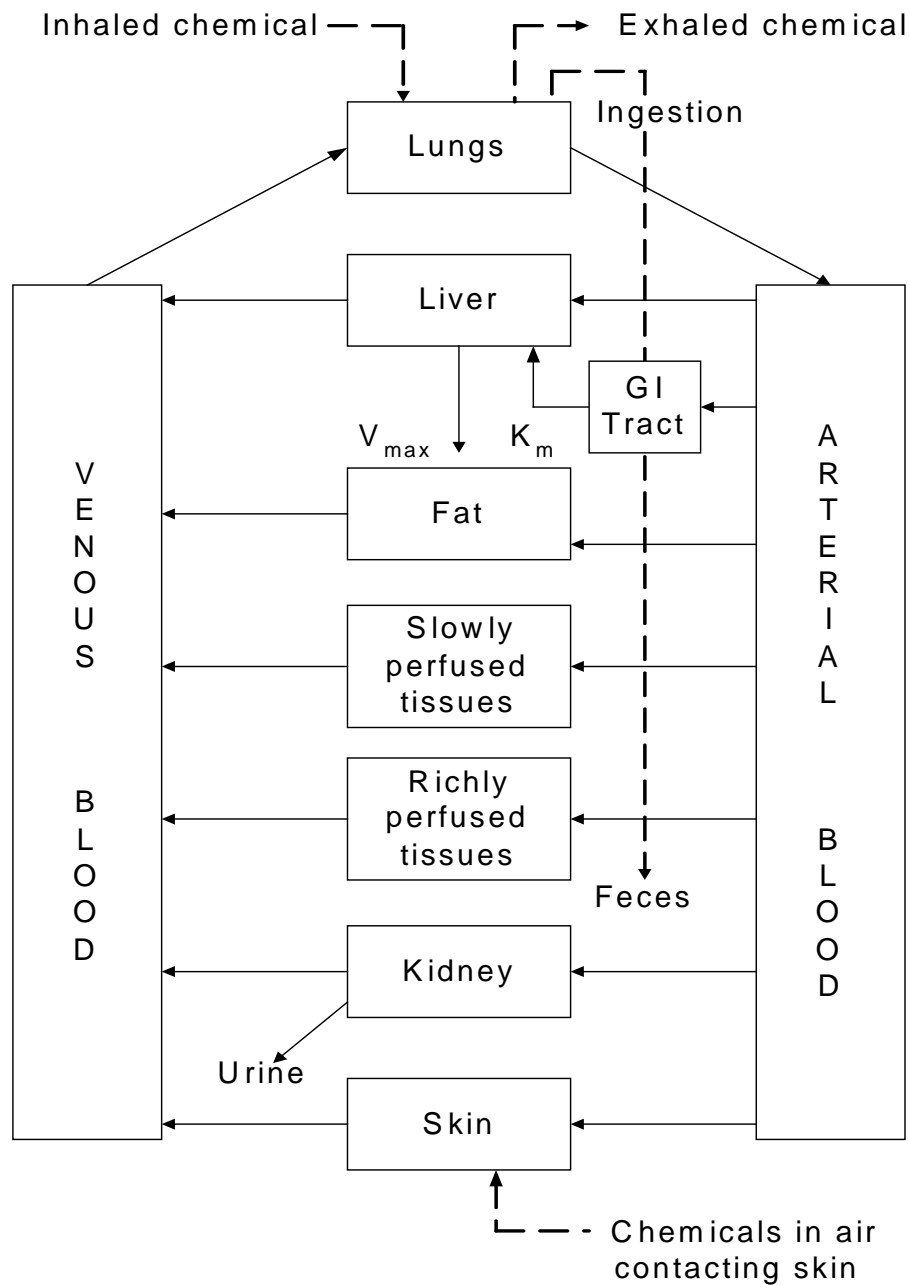
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many 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 3-2 shows a conceptualized representation of a PBPK model.

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. 1977b). 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

3. HEALTH EFFECTS

Figure 3-2. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

3. HEALTH EFFECTS

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 3.4.4 (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.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

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.

3.5.2 Mechanisms of Toxicity

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, CDDs, CDFs, and other structurally related halogenated aromatic hydrocarbons are believed to share a common

3. HEALTH EFFECTS

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 μ M) greater than tetrachlorodibenzo-*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 that 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

3. HEALTH EFFECTS

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 peroxidase 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'-tetrabromo-

3. HEALTH EFFECTS

biphenyl (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).

3. HEALTH EFFECTS

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, β -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 3.2 in which more than one strain was tested (mice or other species) do not address the possible strain-dependency of the toxic responses observed. It must be mentioned, however, that differences in the response between tissues, strains, or species, do not exclusively indicate differences in receptor affinities, but most likely reflect the fact that the battery of enzyme activities (see below) controlled by the Ah locus varies within the tissue, strain, and animal species.

Initial binding of a PBB congener to the 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

3. HEALTH EFFECTS

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.

3.5.3 Animal-to-Human Extrapolations

Residue levels of PBBs 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 congeners in human milk do not resemble the pattern of any of the commercial mixtures. As discussed in Chapter 6, residue analyses indicate that tetra- to hexa-congeners predominate in humans, aquatic mammals, birds, fish, and other biota, indicating that the biological fate of PBB 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.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the 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

3. HEALTH EFFECTS

in the natural environment. Examples of natural hormone mimics are the isoflavonoid 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, 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.

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 T₄ and T₃ 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

3. HEALTH EFFECTS

FSH, low or borderline low serum T₄, and increased thyroid antimicrosomal antibody titers (Bahn et al. 1980).

Serum levels of the adrenal hormones corticosterone B, dehydroepiandrosterone, and dehydroepiandrosterone 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 F₁ 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 breastfeeding (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 breastfeeding, as either a continuous variable or as categorized by duration (<3, 3–9, or >9 months), was not associated with serum PBB decay, although increasing number of pregnancies was weakly associated with a slower rate of serum PBB decay (the effect had borderline statistical significance). Additional information on the design and results of this study is provided in Section 3.8.1. Thomas et al. (2001) found no relationship between serum levels of PBBs and the frequency and duration of lactation in Michigan women. Characteristics of the study cohort included a mean initial serum PBB level of 17.5 ppb, an estimated mean serum PBB level at delivery of 9.4 ppb, mean duration of breastfeeding as main source of nutrition of 2.6 months, and mean total duration of breastfeeding of

3. HEALTH EFFECTS

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 breastfeed (yes/no), (2) the duration (months) of breast-feeding as the main source of nutrition, and (3) the total duration (months) of breast-feeding. None of the three outcomes was significantly associated with serum PBB levels. Additional information on the design and results of this study is provided in Section 3.2.2.5.

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

3.7 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a

3. HEALTH EFFECTS

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 in the same manner as the general population, primarily via consumption of contaminated foods. Exposure also may occur by transfer of PBBs that have accumulated in women's bodies to the fetus across the placenta. Because PBBs 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 on sensitive immature tissues, organs, and systems, with potentially serious long-lasting consequences. Transfer of PBBs via

3. HEALTH EFFECTS

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 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 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 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 with other chemicals in children or adults. No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to PBBs, 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.

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-

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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 T₄ 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 adrenocorticotrophic hormone. Serum concentrations of T₃ and T₄ 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 T₄ and T₃ 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 T₄, 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

3. HEALTH EFFECTS

(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). Breastfeeding as either a continuous variable or as categorized by duration (<3, 3–9, or >9 months) was not associated with serum PBB decay. Additional information on the design and results of this study is provided in Section 3.8.1. Another study of women exposed to PBBs during the Michigan contamination episode similarly found no relationship between serum levels of PBBs and the frequency and duration of lactation (Thomas et al. 2001). Characteristics of the study cohort included a mean initial serum PBB level of 17.5 ppb, an estimated mean serum PBB level at delivery of 9.4 ppb, a mean duration of breast-feeding as the main source of nutrition for 2.6 months, and a mean total duration of breast-feeding of 4.1 months. Exposure was treated as a categorical variable by dividing the women into groups of low (reference) exposure (≤ 1 ppb), moderate exposure ($>1\text{--}\leq 7$ ppb), and high exposure (>7 ppb). Three outcomes of interest were analyzed: (1) the decision to breastfeed (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

3. HEALTH EFFECTS

confounding determinants, including histories of previous breast-feeding and thyroid disorders. Additional information on the design and results of this study is provided in Section 3.2.2.5.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The 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 are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by PBBs are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or

3. HEALTH EFFECTS

other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to PBBs

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 $\approx 1:300$ 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 $\mu\text{g/day}$; overweight individuals had an excretion rate of 4.1 $\mu\text{g/day}$. 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

3. HEALTH EFFECTS

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 ($\text{BMI} \geq 23$). Increasing number of pregnancies between the first and last measurement was also associated with slower decay, but the effect was of borderline statistical significance ($p=0.06$). Breastfeeding as either a continuous

3. HEALTH EFFECTS

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).

3.8.2 Biomarkers Used to Characterize Effects Caused by PBBs

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 3.2.2.2, 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 T₄, 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 T₄ and T₃ 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 T₄ 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 T₄ and T₃ 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,

3. HEALTH EFFECTS

CDDs, and CDFs (Lambert et al. 1992a, 1992b). 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. 1992a, 1992b). 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 3.2.

3. HEALTH EFFECTS

3.9 INTERACTIONS WITH OTHER CHEMICALS

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 LD₅₀ 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 LD₅₀ value of 1,2-dibromo-3-chloropropane (DBCP) but had no effect on the LD₅₀ 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).

3. HEALTH EFFECTS

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to PBBs than will most persons exposed to the same level of PBBs 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, or compromised function of organs affected by PBBs. Populations who are at greater risk due to their unusually high exposure to PBBs are discussed in Section 6.7, Populations with Potentially High Exposures.

Information was located on a small part of the U.S. population that might be unusually susceptible to PBBs. As indicated in Section 3.4.4.2, breast milk constitutes the most important route of excretion of PBBs in lactating females. Therefore, women with high body burdens of PBBs 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 as they are for other thyroid hormone disrupting chemicals (Glinioer et al. 1990; McDonald 2002; Morreale de Escobar et al. 2000). 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

3. HEALTH EFFECTS

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).

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 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.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

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. There is no indication of hazards associated with the treatments. The methods are particularly appropriate for trying under conditions of acute exposure, but PBBs 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.

3.11.1 Reducing Peak Absorption Following Exposure

Ingested PBBs are absorbed by the gastrointestinal tract of humans and animals (see Section 3.4). Although there are no specific recommendations for clinical treatment of acute intoxication from ingested PBBs, 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

3. HEALTH EFFECTS

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 and PBBs is unknown (HSDB 2002). 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 and Takahashi 1991), but it is unclear if rice bran would be of benefit in poisoned humans.

The detection of PBBs in the serum and fat of people who were occupationally exposed to these chemicals indicates that PBBs 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 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 2002). 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.

3.11.2 Reducing Body Burden

PBBs tend to accumulate in lipid-rich tissues and are slowly metabolized and eliminated from the body (see Section 3.4). Several methods to enhance the elimination of PBBs from the body have been examined in animals, 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 3.8.1, a rapid breakdown of fat, as might occur in dieting, might lead to a transient increase in PBB 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;

3. HEALTH EFFECTS

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 CDFs (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 from adipose tissue is not recommended in individuals with hepatic or renal disease (Lemesh 1992).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are no known methods for interfering with the mechanism of action of PBBs. Although the mechanism of action of PBBs is not completely understood, experimental evidence 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 3.5). It appears, therefore, that interfering with the initial step, binding to the receptor, or with any of the subsequent steps, would possibly prevent the expression of the toxic effects. 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.

PBBs 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.

3. HEALTH EFFECTS

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PBBs 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.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of PBBs

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PBBs are summarized in Figure 3-3. The purpose of this figure is to illustrate the existing information concerning the health effects of PBBs. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments.

Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As indicated in Figure 3-3, 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.

3. HEALTH EFFECTS

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

| | Systemic | | | | | | | | | |
|------------|----------|-------|--------------|---------|-------------------------|------------|--------------|---------------|-----------|--------|
| | Death | Acute | Intermediate | Chronic | Immunologic/Lymphoretic | Neurologic | Reproductive | Developmental | Genotoxic | Cancer |
| Inhalation | | | | ● | | ● | ● | | | |
| Oral | | | | ● | ● | ● | ● | ● | | ● |
| Dermal | | ● | | ● | ● | ● | ● | | | |

Human

| | Systemic | | | | | | | | | |
|------------|----------|-------|--------------|---------|-------------------------|------------|--------------|---------------|-----------|--------|
| | Death | Acute | Intermediate | Chronic | Immunologic/Lymphoretic | Neurologic | Reproductive | Developmental | Genotoxic | Cancer |
| Inhalation | ● | ● | ● | | | | | | | |
| Oral | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Dermal | ● | ● | ● | | | | | | | ● |

Animal

● Existing Studies

3. HEALTH EFFECTS

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.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. 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.

Intermediate-Duration Exposure. 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

3. HEALTH EFFECTS

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

3. HEALTH EFFECTS

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.

Chronic-Duration Exposure and Cancer. 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.

Genotoxicity. 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

3. HEALTH EFFECTS

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.

Reproductive Toxicity. 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 F₁ or F₂ generations of female F₀ 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

3. HEALTH EFFECTS

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.

Developmental Toxicity. 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 embryoletality 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.

Immunotoxicity. 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.

3. HEALTH EFFECTS

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). 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.

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

3. HEALTH EFFECTS

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.

Epidemiological and Human Dosimetry Studies.

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.

Biomarkers of Exposure and Effect.

Exposure. 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

3. HEALTH EFFECTS

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 T₄, and increased thyroid antimicrosomal antibody titers (Bahn et al. 1980), and effects in exposed rats included reduced levels of serum T₄ and T₃ (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.

Effect. 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 T₄ 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.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding absorption in humans via the inhalation route, but data from occupationally exposed individuals and

3. HEALTH EFFECTS

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'-hexabromobiphenyl) 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. 1977a). Little information regarding distribution of PBBs could be drawn from the limited number of studies in animals administered PBBs by the inhalation or dermal routes. Additional well-conducted studies by these routes of exposure would provide useful information regarding possible route-dependent distribution patterns. Studies regarding distribution through the placenta after inhalation and dermal exposure were not available.

Data regarding biotransformation of PBBs in humans are limited to individuals who accidentally consumed food contaminated with PBBs or who were exposed to PBBs in the workplace (Wolff and Aubrey 1978; Wolff et al. 1979a). The use of human cell systems in culture might be considered a useful addition to whole animal studies for studying the metabolic fate of PBBs. There are studies regarding the metabolism of some PBB congeners after oral administration to rats (Sparling et al. 1980), rabbits (Kohli et al. 1978), and pigs (Kohli and Safe 1976). However, the PBBs mainly studied were monobromobiphenyls and dibromobiphenyls, which are only trace components of FireMaster mixtures. Therefore, studies on the *in vivo* metabolism of the main components of commercial PBB mixtures would provide valuable information regarding the metabolic disposition of highly brominated congeners. A limited amount of information is available on the metabolism of PBBs in farm animals (e.g., dairy cows,

3. HEALTH EFFECTS

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.

Comparative Toxicokinetics. 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. 1977a). 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. 1977a; 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'-hexabromobiphenyl (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

3. HEALTH EFFECTS

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.

Methods for Reducing Toxic Effects. 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.

Children's Susceptibility. 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

3. HEALTH EFFECTS

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.

Child health data needs relating to exposure are discussed in Section 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies that are relevant to health effects of PBBs, as identified in the Federal Research in Progress database (FEDRIP 2002) and the websites of various U.S. government agencies, are listed in Table 3-5.

3. HEALTH EFFECTS

Table 3-5. Ongoing Studies on the Health Effects of PBBs

| Investigator | Affiliation | Research description | Sponsor | Source |
|------------------|---|--|---------------------------|-------------|
| 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 |
| Karmaus W et al. | Michigan State University, East Lansing, Michigan | An effort to determine if exposure to halogenated organic compounds (including PBBs) via breastfeeding creates a risk to the immune system of the child | EPA | EPA 2004d |
| Marcus M | Emory University, Atlanta, Georgia | Investigation of the effect PBBs have on pubertal development, reproductive health, and ovarian function | NIEHS | FEDRIP 2003 |
| 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 <i>in vivo</i> ; 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 |

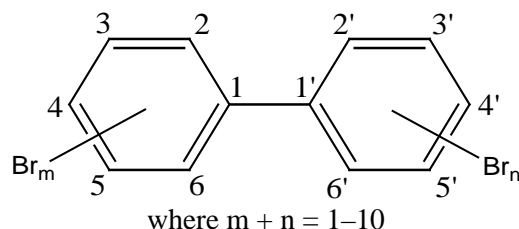
^aNIEHS/EPA Superfund Basic Research Program

EPA = U.S. Environmental Protection Agency; EU = European Union; NIEHS = National Institute of Environmental Health Sciences; PBB = polybrominated biphenyl; PBDE = polybrominated diphenyl ether; PCB = polychlorinated biphenyl

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 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:



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

4. CHEMICAL AND PHYSICAL INFORMATION

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 2002a).

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 4-1 (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 4-2.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information found in the literature regarding the physical and chemical properties of hexabromobiphenyl, octabromobiphenyl, decabromobiphenyl, and BB 153 is presented in Table 4-3. The data for the properties listed in Table 4-3 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).

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) Congeners

| IUPAC No. ^a | Compound/ substituents | CAS No. ^b |
|------------------------|------------------------|----------------------|
| | Biphenyl | 92-52-4 |
| | Monobromo- | 26264-10-8 |
| 1 | 2 | 2052-07-7 |
| 2 | 3 | 2113-57-7 |
| 3 | 4 | 92-66-0 |
| | Dibromo- | 27479-65-8 |
| 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 |
| 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 | |
| 36 | 3,3',5 | |
| 37 | 3,4,4' | 6683-35-8 |

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) Congeners

| IUPAC No. ^a | Compound/ substituents | CAS No. ^b |
|------------------------|------------------------|----------------------|
| 38 | 3,4,5 | 115245-08-4 |
| 39 | 3,4',5 | 72416-87-6 |
| | Tetrabromobiphenyl | 40088-45-7 |
| 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 | |
| 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 | |

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) Congeners

| IUPAC No. ^a | Compound/ substituents | CAS No. ^b |
|------------------------|------------------------|----------------------|
| 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 |
| 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 | |
| 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 |

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) Congeners

| IUPAC No. ^a | Compound/ substituents | CAS No. ^b |
|------------------------|------------------------|----------------------|
| 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 |
| 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' | |
| 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 | |

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) Congeners

| IUPAC No. ^a | Compound/ substituents | CAS No. ^b |
|------------------------|------------------------|----------------------|
| 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 |
| 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 | |
| 192 | 2,3,3',4,5,5',6 | |
| 193 | 2,3,3',4',5,5',6 | |
| | Octabromobiphenyl | 27858-07-7 |
| 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 |

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Polybrominated Biphenyl (PBB) Congeners

| IUPAC No. ^a | Compound/ substituents | CAS No. ^b |
|------------------------|--------------------------|----------------------|
| 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 | 119264-61-8 |
| 204 | 2,2',3,4,4',5,6,6' | |
| 205 | 2,3,3',4,4',5,5',6 | |
| | Nonabromobiphenyl | 27753-52-2 |
| 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 |
| 209 | 2,2',3,3',4,4',5,5',6,6' | 13654-09-6 |

^aBallschmitter and Zell 1980^bNot all PBBs have been assigned CAS numbers^cWHO 1994b

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Chemical Identity of Selected PBBs^a

| Characteristic | Hexabromo-biphenyl | Octabromo-biphenyl | Decabromo-biphenyl | 2,2',4,4',5,5'-Hexabromobiphenyl |
|--------------------------|---|---|--|--|
| Synonym(s) | FireMaster BP-6 ^b ; FireMaster FF-1 ^b | Bromkal 80 ^b | Flammex B 10 ^b ; Adine 0102 ^b ; Berkflam B 10 ^b | 2,2',4,4',5,5'-hexabromo-1,1'-biphenyl |
| Registered trade name(s) | FireMaster BP-6; FireMaster FF-1 | Bromkal 80 | Flammex B 10; Adine 0102; Berkflam B 10 | None |
| Chemical formula | C ₁₂ H ₄ Br ₆ | C ₁₂ H ₂ Br ₈ | C ₁₂ Br ₁₀ | C ₁₂ H ₄ Br 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 |

^aAll information obtained from IARC (1986) except where noted.

^bThese 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

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-3. 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; 365–367 °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 | 5.2x10 ⁻⁸ mmHg at 25 °C ^h ; 5.6x10 ⁻⁶ mm Hg (liquid sub-cooled) ^c | 7x10 ⁻¹¹ mmHg at 28 °C ⁱ | No data | 7.6x10 ⁻⁵ mm Hg at 90 °C ^d |
| Henry's law constant | 3.9x10 ⁻⁶ atm-m ³ /mol ^j ; 1.38x10 ⁻⁶ atm-m ³ /mol ^c | No data | No data | 5.7x10 ⁻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 |

^aAll information obtained from IARC (1978) and Norris et al. (1973) unless otherwise noted.^bSundstrom et al. 1976b^cTittlemier et al. 2002^dHardy (2002a)^eDoucette and Andren 1988^fThe 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.^gEstimated from the Freundlich adsorption constants given by Jacobs et al. (1978).^hJacobs et al. 1976ⁱWaritz et al. 1977^jEstimated from the ratio of vapor pressure and water solubility.

4. CHEMICAL AND PHYSICAL INFORMATION

Of the 209 possible congeners of PBBs, only about 42 have been synthesized in pure form even on a laboratory scale (Sundstrom et al. 1976b). The PBBs produced for commercial use were mixtures of PBBs with other non-PBB impurities. The technical products were FireMaster BP-6, FireMaster FF-1, Bromkal 80, and Flammex B 10 (or Adine 0102 or Berkflam B 10) (IARC 1986). FireMaster FF-1, a white powder, was made by grinding brown flakes of FireMaster BP-6 and adding 2% calcium silicate as an anticaking agent (Fries 1985b). The exact composition of FireMaster BP-6 or FireMaster FF-1 seems to have varied between and within batches (Sundstrom et al. 1976a). Table 4-4 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

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-4. 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 | |
| <i>Dibromobiphenyls</i> | | | | |
| 4 | 2,2'- | 0.020 | | Moore et al. 1979 |
| <i>Tribromobiphenyls</i> | | | | |
| 18 | 2,2',5- | 0.050 | | Robertson et al. 1984b |
| 26 | 2,3',5- | 0.024 | | |
| 31 | 2,4',5- | 0.015 | | |
| 37 | 3,4,4'- | 0.021 | | |
| <i>Tetrabromobiphenyls</i> | | | | |
| 49 | 2,2',4,5'- | 0.025 | | Orti et al. 1983 Robertson et al. 1984b |
| 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 | |
| | | 0.159 | | |
| | | | | |
| <i>Pentabromobiphenyls</i> | | | | |
| 95 | 2,2',3,5',6- | 0.020 | | Orti et al. 1983 |
| 99 | 2,2',4,4',5- | | <0.08 | Robertson et al. 1984b Aust et al. 1981 Orti et al. 1983 Krüger 1988 Robertson et al. 1984b Robertson et al. 1984b Krüger 1988 |
| 101 | 2,2',4,5,5'- | 2.69 | | |
| | | 4.50 | 3.70 | |
| | | | 1.54 | |
| | | 2.60 | | |
| 118 | 2,3',4,4',5- | 2.94 | | |
| | | | 0.70 | |
| | | 3.20 | | |
| 126 | 3,3',4,4',5- | | <0.01 | Robertson et al. 1984b |
| | | 0.079 | | |
| | | | | |
| <i>Hexabromobiphenyls</i> | | | | |
| 132 | 2,2'3,3',4,6'- | 1 | | Krüger 1988 |
| 138 | 2,2',3,4,4',5'- | 12.3 | | Robertson et al. 1984b |
| | | 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. 1984b |
| | | 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. 1984b |
| | | 47.8 | 47.1 | Aust et al. 1981 |
| | | 55.2 | | Orti et al. 1983 |
| | | 58.5 | | Krüger 1988 |

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-4. 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. 1984b |
| | | 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. 1984b |
| | | 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. 1984b |
| | | 5.5 | | Krüger 1988 |
| 169 | 3,3',4,4',5,5'- | 0.294 | | Robertson et al. 1984b |
| <i>Heptabromobiphenyls</i> | | | | |
| 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. 1984b |
| | | | 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. 1984b |
| | | | 1.0 | Krüger 1988 |
| 189 | 2,3,3',4,4',5,5'- | | 0.51 | Orti et al. 1983 |
| <i>Octabromobiphenyls</i> | | | | |
| 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

^aBallschmitter and Zell 1980

4. CHEMICAL AND PHYSICAL INFORMATION

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

Hexabromonaphthalene 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, hexabromonaphthalene was shown to be a 60:40 mixture of 1,2,3,4,6,7-hexabromonaphthalene and 2,3,4,5,6,7-hexabromonaphthalene.

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

5.1 PRODUCTION

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 2002a). Hexabromobiphenyl constituted about 11.8 million pounds (ca 88%) and octa- and decabromobiphenyl constituted ≈ 1.5 million pounds together of this total (Neufeld et al. 1977). Over 98% of the hexabromobiphenyl was produced as FireMaster BP-6 and the residual as FireMaster FF-1 (Hesse and Powers 1978). Michigan Chemical Corporation, St. Louis, Michigan, the sole producer of hexabromobiphenyl in the United States, stopped producing this PBB in 1975. White Chemical Co., Bayonne, New Jersey, and Hexcel Corporation, Sayreville, New Jersey, manufactured octa- and decabromobiphenyl in the United States until 1979 (IARC 1986; Neufeld et al. 1977). Shortly after the 1973–1974 agriculture contamination episode in Michigan (see Section 3.2), PBB production in the United States was voluntarily discontinued (Hardy 2000a); 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 2000a).

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

5.2 IMPORT/EXPORT

PBBs are no longer being imported or exported except possibly in small quantities for laboratory uses. PBBs have not been imported from other countries into the United States, except in finished products (Neufeld et al. 1977). The two companies that manufactured octa- and decabromobiphenyl in the United States between 1976 (0.805 million pounds) and 1978 exported all of their products to Europe (Neufeld et al. 1977).

5.3 USE

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 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 (acrylonitrile-butadiene-styrene, ABS) used in electronic equipment housings (Hardy 2002a). 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).

5.4 DISPOSAL

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.

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

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).

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

This page is intentionally blank.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

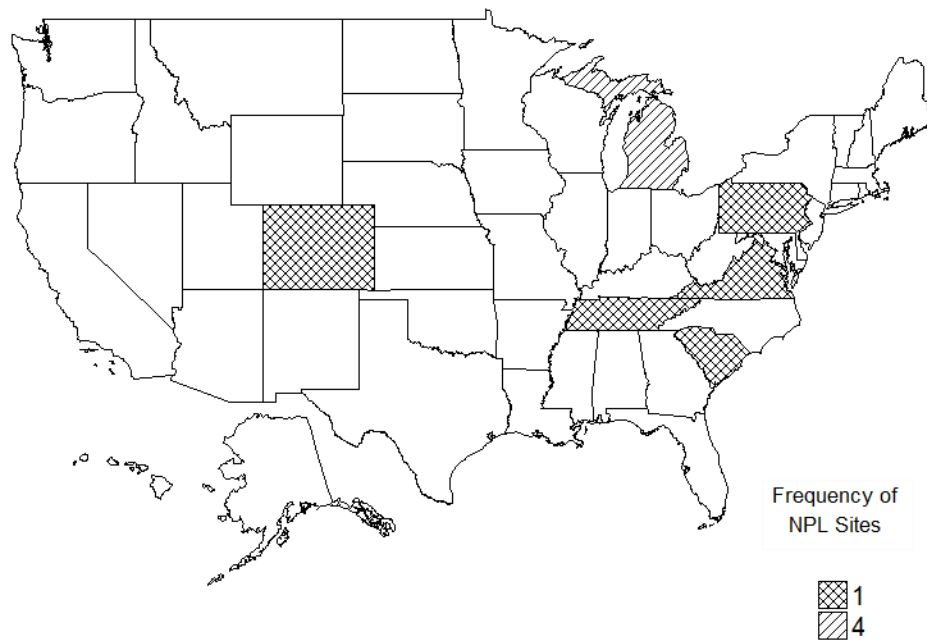
PBBs have been identified in at least 9 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for PBBs is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 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 3.2 for additional details concerning this incident). By June 1975, 412 farms had been quarantined. Disposal of contaminated feed, animal carcasses (poultry, dairy cattle, swine), and animal products (dairy, meat, eggs) contributed to environmental contamination (Dunckel 1975; Kay 1977). No information was located on the current levels of contamination at these locations.

PBBs can exist 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;

6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-1. Frequency of NPL Sites with PBB Contamination

Derived from HazDat 2004

6. POTENTIAL FOR HUMAN EXPOSURE

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; Oppenhuizen 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. Studies have identified PBBs in marine mammals from coastal seas and the Atlantic Ocean (de Boer et al. 1998c). 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.

6.2 RELEASES TO THE ENVIRONMENT

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

6. POTENTIAL FOR HUMAN EXPOSURE

FireMaster BP-6 with cattle feed in a number of farms in the lower peninsula in Michigan (see Section 3.2 for additional details concerning this incident). By June 1975, 412 farms had been quarantined. Disposal of contaminated feed, animal carcasses (poultry, cattle, swine), and animal products (meat, milk, eggs) contributed to environmental contamination (Dunckel 1975; Kay 1977).

6.2.1 Air

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).

6.2.2 Water

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 98–503 ppm (Di

6. POTENTIAL FOR HUMAN EXPOSURE

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).

6.2.3 Soil

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

6. POTENTIAL FOR HUMAN EXPOSURE

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).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

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 adsorb 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 5.2×10^{-8} mm Hg at 25 °C (Jacobs et al. 1976). The vapor pressure of octabromobiphenyl is 7.0×10^{-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 3.9×10^{-6} atm·m³/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

6. POTENTIAL FOR HUMAN EXPOSURE

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

6. POTENTIAL FOR HUMAN EXPOSURE

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 adsorption 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.

6.3.2 Transformation and Degradation

Photolysis appears to be the dominant transformation process for PBBs. 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 PBBs.

6.3.2.1 Air

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

6. POTENTIAL FOR HUMAN EXPOSURE

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.

6.3.2.2 Water

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. Although photolysis mainly produces debromination products, unlike in the case of an individual PBB congener, it has been indicated that 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).

6. POTENTIAL FOR HUMAN EXPOSURE

Several investigators assessed the biodegradation potential of PBBs under aerobic conditions, with activated sludge or pure cultures of microorganisms as microbial inoculum, and concluded that although the lower substituted biphenyls might biodegrade in aerobic water and sediment (Kong and Sayler 1983; Sugiura 1992; Yagi and Sudo 1980), the higher substituted biphenyls are resistant to aerobic biodegradation (Kawasaki 1980; Sasaki 1978; Shelton and Tiedje 1981). This is consistent with biodegradation studies in soil (see Section 6.3.2.3). It has been proposed that complete mineralization of 4-bromobiphenyl to carbon dioxide occurs via a 4-bromobenzoate intermediate by mixed bacterial cultures obtained from PBB-contaminated river sediment (Kong and Sayler 1983). However, complete mineralization was not observed for 2- and 3-bromobenzoate (Kong and Sayler 1984).

Although higher brominated biphenyls do not biodegrade in water or sediment under aerobic conditions, it has been shown that anaerobic microorganisms 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).

6.3.2.3 Sediment and Soil

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 6.3.2.2, higher brominated PBBs may biodegrade in an anaerobic region of river sediment and possibly soil polluted with PCBs and PBBs to form lower brominated products. Biodegradation of the photolysis products of hexa- and heptabromobiphenyl in soil (which produces lower brominated products) was only minor ($\approx 3\%$ 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

6. POTENTIAL FOR HUMAN EXPOSURE

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.

6.3.2.4 Other Media

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

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Evaluation of the potential for human exposure to PBBs 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 concentrations as technical mixtures, as homologs, or as congeners. Chemical analysis procedures are discussed in greater detail in Chapter 7. Recent monitoring data for PBBs are very limited. Historical monitoring data indicate that environmental PBB concentrations are confined to areas near former manufacturing facilities and regions of Michigan effected by the farm catastrophe of the early 1970's (see Section 6.1).

6. POTENTIAL FOR HUMAN EXPOSURE

6.4.1 Air

Historically, PBBs were released to the atmosphere during three stages of the manufacturing process, and an estimate of the maximum amount of PBBs expected to be lost to the air during the manufacture of PBBs in the United States is available (see Section 6.2.1) (Neufeld et al. 1977). Monitoring data on the ambient air levels of PBBs are very limited. The concentration of hexabromobiphenyl in air samples collected downwind and crosswind from the White Chemical Company plant in Bayonne, New Jersey was 0.06 ng/m³ (DeCarlo 1979).

6.4.2 Water

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.

6.4.3 Sediment and Soil

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

6. POTENTIAL FOR HUMAN EXPOSURE

surface soil of control farms (that did not use contaminated manure) were $<25 \mu\text{g/kg}$ (Fries and Jacobs 1980).

Concentrations of PBBs in sediments upstream from the Michigan Chemical Corporation plant were below the detection limit ($100 \mu\text{g/kg}$) with the exception of one sample (Hesse and Powers 1978). The concentration of PBBs in sediment from one upstream sample was $350 \mu\text{g/kg}$. 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 $\leq 77.0 \text{ mg/kg}$. 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 $<10 \mu\text{g/kg}$ 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).

6.4.4 Other Environmental Media

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, $1\text{--}2 \text{ mg/kg}$; cheese, $1.4\text{--}15.0 \text{ mg/kg}$; and canned milk, $1.2\text{--}1.6 \text{ mg/kg}$ (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 $4,600 \text{ mg/kg}$ and up to $2,700 \text{ mg/kg}$, 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 $>0.3 \text{ mg/kg}$ 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 $>0.6 \text{ mg/kg}$, and a market basket survey in Michigan showed detectable PBBs in only 1/102 meat samples (Di Carlo et al. 1978).

6. POTENTIAL FOR HUMAN EXPOSURE

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 $\mu\text{g/kg}$ (fat basis) in fish from embayments and tributaries of Lake Huron, but not from Lake Superior. 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 6-1).

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 ($\mu\text{g/g}$) 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 ($\mu\text{g/g}$) 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 ($\mu\text{g/g}$) and not detected to 1.8 mg/kg ($\mu\text{g/g}$), respectively (Hesse and Powers 1978). Three bottlenose dolphins (*Tursiops truncatus*) collected during 1987–1988 from the U.S. mid-Atlantic contained PBBs at concentrations of 14–20 $\mu\text{g/kg}$ (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 ($\mu\text{g/g}$), respectively (Kaiser et al. 1980). Twenty-two other specimens did not contain detectable levels

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-1. 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

6. POTENTIAL FOR HUMAN EXPOSURE

(<0.03 mg/kg [$\mu\text{g/g}$]) 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 ($\mu\text{g/g}$) 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 (and Asplund 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 $\mu\text{g/kg}$ (ng/g) wet weight from harbor seals collected from the North Sea (decaBB <1 $\mu\text{g/kg}$ [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 $\mu\text{g/kg}$ (ng/g) wet weight, respectively. Tetra-, penta-, and deca-BBs concentration ranges were 1.1–1.9, 0.4–0.9, and <0.5 $\mu\text{g/kg}$ (ng/g) wet weight, respectively, in sperm whales from the Atlantic Ocean (de Boer et al. 1998c).

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 3.5.1).

Hexabromobiphenyl was detected (detection limit 6.6 $\mu\text{g/kg}$ [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 United States ranged from 1 to 2 $\mu\text{g/kg}$ (ng/g) (Lewis and Sovocool 1982). PBB levels in the adipose tissues of 15 quarantined dairy farm residents in mid-

6. POTENTIAL FOR HUMAN EXPOSURE

Michigan (where the mix-up involving FireMaster BP-6 occurred) ranged from 0.104 to 174 mg/kg ($\mu\text{g/g}$) (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 $\mu\text{g/kg}$ [ng/g]; serum, 1.7 $\mu\text{g/L}$) and were lowest in the upper peninsula (median: adipose tissue, 15 $\mu\text{g/kg}$ [ng/g]; serum, 0.2 $\mu\text{g/L}$), farthest from the source of contamination. Levels in the rest of the state were in between (median: adipose tissue, 240 $\mu\text{g/kg}$ [ng/g]; serum, 0.9 $\mu\text{g/L}$) (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.

6. POTENTIAL FOR HUMAN EXPOSURE

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 [$\mu\text{g/L}$]).

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 6-2. 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).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

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,

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. 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 |
| | 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 |
| | Exposed mothers | <1 µg/L | No data | Eyster et al. 1983 |
| Placenta | Exposed mothers | 370 µg/kg (fat basis) | No data | Eyster et al. 1983 |
| Breast milk | 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 |
| | | | | |

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. 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 |

^aWhen 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

6. POTENTIAL FOR HUMAN EXPOSURE

especially in the immediate vicinity of the PBB contaminated areas of this region, exposure to PBBs may still be occurring today. However, environmental levels have decreased since the 1970s and current exposure, if any, will be at low levels. For other regions of the United States, the levels of exposure will either be very low or none.

In the past, the general population may have been exposed to PBBs by inhaling contaminated air, ingesting contaminated water and food, and using consumer products containing PBBs. Other than in air in the vicinity of PBB production plants (see Section 6.1), no current or historical data exist that would indicate that PBBs might be present in ambient air. There are no current or historical data on the direct exposure of humans to PBBs from water. The general population may have been exposed to low levels of PBBs from the consumption of contaminated foods, but no estimate is available that quantitated this exposure. Historical monitoring and body burden data indicate that low level exposures to PBBs were limited to the population within the state of Michigan (see Section 6.4 and Table 6-2). The level of exposure to PBBs was slightly higher for the people residing in the lower peninsula of Michigan and highest among people residing in the immediate vicinity of the contaminated dairy farms, where people consumed contaminated meat, eggs, and dairy products (see Section 6.4 and Table 6-2). Consumer exposure in the past (plastics containing PBBs may not be in circulation anymore since PBB production ceased in the 1970s) from using PBB-containing plastics (e.g., typewriters, calculators, projector housings, and movie equipment cases) is expected to be very low since the PBBs were incorporated into the plastic and their mobilization could only have occurred under conditions such as combustion (Di Carlo et al. 1978).

Workers involved in the historical production of PBBs, PBB-containing plastics, and PBB-containing plastic products could have been exposed to PBBs via inhalation of dust and vapor and/or dermal contact. Both workplace environmental monitoring and body burden monitoring data of workers (see Table 6-2) (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.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7 Children's Susceptibility.

6. POTENTIAL FOR HUMAN EXPOSURE

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).

Infants who consume breast milk may have had a higher exposure to PBBs than children who drink formula milk, especially children exposed during the Michigan episode (see Section 6.4.4). No additional information was found in the literature about the exposure of children to PBBs (WHO 1994b).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

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. 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 breastfed by exposed mothers in the contaminated areas may also be at higher risk (Jacobson et al. 1989).

6. POTENTIAL FOR HUMAN EXPOSURE

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PBBs 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.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Many of the relevant physical and chemical properties of the PBBs are not available (see Table 4-3). More data on the physical and chemical properties of hexabromobiphenyl are available relative to octabromo- and decabromobiphenyl. Even in the case of hexabromobiphenyl, not all relevant data are available, and the quality of data 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.

Production, Import/Export, Use, Release, and Disposal. 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

6. POTENTIAL FOR HUMAN EXPOSURE

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.

Environmental Fate. 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). de Boer et al. (1998c) 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.

Bioavailability from Environmental Media. Available information regarding the rate of absorption of PBBs following inhalation, oral, or dermal contact is discussed in the Toxicokinetics Section (Section 3.4). Although no data on the bioavailability of PBBs from inhalation of contaminated air, or ingestion of or dermal contact with water, or inhalation of or dermal contact with soil are available,

6. POTENTIAL FOR HUMAN EXPOSURE

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 progressively 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.

Food Chain Bioaccumulation. 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.

Exposure Levels in Environmental Media. 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.

Exposure Levels in Humans. 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,

6. POTENTIAL FOR HUMAN EXPOSURE

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.

Exposures of Children. Children may be exposed to PBBs by a variety of exposure pathways. Levels will be highest for children living in the vicinity of the area affected by the Michigan contamination episode. The most important pathway appears to be consumption of contaminated mother's milk (see Section 6.4.4). More data are needed on the levels of PBB exposure in nursing women from consumption of fish and from those of the general population. Exposure and body burden studies related to consumption of fish in the U.S. population are needed to determine exposure levels, particularly in children of recreational and subsistence fishers. Information related to the exposure of children living near hazardous waste sites is also needed. In particular, information is needed that is related to the potential for children to be exposed to PBBs bound to soil and dust particles through pica or unintentional hand-to-mouth activity within homes located in these areas. Quantitative information regarding the bioavailability and amount of PBBs that children are exposed to through contact with contaminated soils are unavailable. Therefore, any information concerning this subject would be useful in evaluating children's exposure. Additional information on weight-adjusted intakes would be helpful for determining the health risks for young children. Infants and young children consume a greater amount of food per kilogram of body weight and, therefore, may have a proportionately greater exposure to PBBs than adults.

Child health data needs relating to susceptibility are discussed in Section 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. 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

6. POTENTIAL FOR HUMAN EXPOSURE

contact with this cohort, updates health questionnaires, and collects blood samples to be analyzed (MDCH 2002).

6.8.2 Ongoing Studies

A search in Federal Research in Progress (FEDRIP 2002) did not identify ongoing research studies for PBBs.

6. POTENTIAL FOR HUMAN EXPOSURE

This page is intentionally blank.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring polybrominated biphenyls (PBBs), its metabolites, and other biomarkers of exposure and effect to PBBs. 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 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 and the primary analytical technique was gas chromatography-electron capture detection (GC-ECD) with packed columns (i.e., noncongener specific).

Covaci et al. (2003) reviewed the determination of brominated flame retardants in environmental and human samples. The analysis methodology for PBBs 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. 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 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 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

7. ANALYTICAL METHODS

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 CO₂ 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. 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 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 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 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 congeners.

7.1 BIOLOGICAL MATERIALS

Methods for the determination of organobromine compounds such as PBBs 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 in blood or serum, urine, feces, adipose tissue, liver, and breast milk. The methods for determining PBB residues in biological samples are given in Table 7-1.

7. ANALYTICAL METHODS

Table 7-1. Analytical Methods for Determining PBBs in Biological Materials

| Sample matrix | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|----------------------------------|--|-------------------|------------------------|-------------------------|---------------------|
| Serum | Extract denatured sample with hexane-ethyl ether; clean up by Florisil column chromatography | GC-ECD | 1 µg/L | 100.6–106.8 at 100 µg/L | Burse et al. 1980 |
| Serum | Extract denatured sample with hexane-ether; clean up by Florisil column chromatography | GC-ECD | 1 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 chromatography | 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. 1979a |
| 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

7. ANALYTICAL METHODS

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).

7.2 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. Analytical methods for the determination of PBBs in environmental samples are given in Table 7-2.

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

7. ANALYTICAL METHODS

Table 7-2. 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) | Fehrerger 1975b |
| Dairy products | Fat extracted by methanol/ether; clean up by GPC, 25% toluene in ethyl acetate | GC-ECD | 7 ng/g | No data | Fehrerger 1975a |
| 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

7. ANALYTICAL METHODS

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).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PBBs 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.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods used as biomarkers for exposure to PBBs 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 in adipose tissue, serum, and breast milk (Burse et al. 1980; Covaci et al. 2002b; Domino et al. 1980; Fawkes et al. 1982; Fehring 1975a; Meironyté Guvenius 1999a, 1999b; Sjödin et al. 1999; Willet et al. 1978; Wolff et al. 1979a, 1979b). Additional congener standards are needed for PBBs analysis. Metabolites are also important biomarkers for exposure to PBBs. However, these compounds are mostly unknown, and standards are not available.

7. ANALYTICAL METHODS

Effect. No studies have been conducted to determine if known effects of PBBs exposure can be quantitatively correlated with PBB 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 in environmental samples (Akutsu et al. 2001; Andersson and Blomkvist 1981; Covaci et al. 2003; Fehring 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).

7.3.2 Ongoing Studies

No ongoing studies regarding analytical methods for determining PBBs residues or metabolites were located as a result of a search of the Federal Research in Progress Database (FEDRIP 2003).

7. ANALYTICAL METHODS

This page is intentionally blank.

8. REGULATIONS AND ADVISORIES

Table 8-1 summarizes international, national, and state regulations and guidelines on human exposure to PBBs.

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 after 1 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.

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.

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to PBBs^a

| Agency | Description | Information | Reference |
|-----------------------------|---|--|------------------------------------|
| <u>INTERNATIONAL</u> | | | |
| Guidelines: | | | |
| IARC | Carcinogenicity classification | | IARC 1987 |
| | Decabromobiphenyl | Group 2B ^b | |
| | Hexabromobiphenyl | Group 2B ^b | |
| | Octabromobiphenyl | Group 2B ^b | |
| <u>NATIONAL</u> | | | |
| 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 | | | |
| | 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 | Chemical substances subject to proposed or final TSCA rules or orders | Regulated under <u>TSCA section(s)</u> | EPA 1998 |
| | Decabromobiphenyl | 5(a)(2) | |
| | Hexabromo-1,1'-biphenyl | 5(a)(2) | |
| | Octabromobiphenyl | 5(a)(2) | |
| | 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) |
| | Polybrominated biphenyls | 01/01/87 | |

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to PBBs^a

| Agency | Description | Information | Reference |
|---------------------------------------|---|--|----------------------------|
| <u>NATIONAL</u> <i>(cont.)</i> | | | |
| EPA | TSCA; significant new uses subject to reporting of polybrominated biphenyl Decabromodiphenyl Hexabromo-1,1'-biphenyl Octabromobiphenyl | The significant new use is any use | EPA 2002n 40CFR721.1790 |
| NTP | Carcinogenicity classification Decabromobiphenyl Octabromobiphenyl Polybrominated biphenyl | Reasonably anticipated to be human carcinogens | NTP 2002 |

^aPolybrominated biphenyls category includes: decabromobiphenyl (CAS# 13654-09-6); hexabromobiphenyl (CAS# 59080-40-9); hexabromo-1,1'-biphenyl (CAS# 36355-01-8); ; octabromobiphenyl (CAS# 27858-07-7); octabromobiphenyl (CAS# 61288-13-9) (CAS# 32534-81-9); polybrominated biphenyl (CAS# 59536-65-1); and polybrominated biphenyl mixture (CAS# 67774-32-7).

^bGroup 2B: possibly carcinogenic to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; 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; REL = recommended exposure limit; TLV = threshold limit value; TSCA = Toxic Substances Control Act; TWA = time-weighted average

8. REGULATIONS AND ADVISORIES

This page is intentionally blank.

9. REFERENCES

- *Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. *Dev Med Child Neurol* 27:532-537.
- *Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. *Environ Health Perspect Suppl* 103(7):103-112.
- *Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Notice. *Federal Register* 54(174):37618-37634.
- Agency for Toxic Substances and Disease Registry. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems. 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

9. 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 (*Phalacrocorax 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.

9. 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. Bioaccumulation of dyestuffs and organic pigments in fish. Relationships to hydrophobicity and steric factors. *Chemosphere* 17:1631-1644.
- Anonymous. 1981. Workplace environmental exposure level guide- decabromodiphenyl 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.

9. REFERENCES

- Argus Research Laboratories. 1984. Dosage-range embryo/fetal toxicity & teratogenic potential of Saytex 115 administered orally via gavage to CrI: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 CrI: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 CrI:COBS[®] CD[®] (SD) BR presumed pregnant rats. Submitted 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 dibenzofurans. *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.

9. 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 organohalogens in 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 hexabromocyclododecane 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.
- Behnisch PA, Hosoe K, Brouwer A, et al. 2001. DR.-CALUX- 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* 320:717-728.
- *Bekesi JG, Holland JF, Anderson HA, et al. 1978. Lymphocyte function of Michigan dairy farmers exposed to polybrominated biphenyls. *Science* 199:1207-1209.
- *Bekesi JG, Roboz J, Fischbein A, et al. 1985. Immunological, biochemical, and clinical consequences of exposure to polybrominated biphenyls. In: Dean JH, Luster MI, Munson AE, et al., eds. *Immunotoxicology and immunopharmacology*. New York, NY: Raven Press, 393-406.
- *Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. *Endometriosis: Advanced management and surgical techniques*. New York, NY: Springer-Verlag.
- Bergman A. 2000. Brominated flame retardants-a burning issue. *Organohalogen Compounds* 47:35-40.
- Bergman A, Athanasiadou M, Wehler EK, et al. 1999. Polybrominated environmental pollutants. Human and wildlife exposures. *Organohalogen Compounds* 43:89-92.

9. REFERENCES

- 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.
- Blake BW, Enslein K, Gombar VK, et al. 1990. Salmonella mutagenicity and rodent carcinogenicity: Quantitative structure-activity relationships. *Mutat Res* 241(3):261-271.

9. REFERENCES

Blanck H, Marcus M, Hertzberg V, et al. 2000a. Determinants of polybrominated 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* 51(5):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.

Braekevelt E, Tittlemier SA, Tomy GT. 2003. Direct measurement of octanol-water partition coefficients of some environmentally relevant brominated diphenyl ether congeners. *Chemosphere* 51(7):563-567.

9. REFERENCES

- 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 (PBDFs) and -dioxins (PBDDs) during extrusion production of a polybutyleneterephthalate (PBTP)/glass fiber resin blended with decabromodiphenylether (DBDPE)/antimony trioxide: Product and workplace analysis. *Organohalogen Compounds* 2:319-324.
- Brenner KS, Knies H. 1993. Workplace of PBDFs and 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 mixture 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, Nixon 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.
- 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.

9. REFERENCES

- 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 CYP1A 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.
- Bureau 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.
- Bureau S, Broman D, Zebuhr Y. 1999. Biomagnification quantification of PBDEs in fish using stable nitrogen isotopes. *Organohalogen Compounds* 40:363-366.
- Bureau 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 Technol* 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.

9. REFERENCES

- 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.

9. REFERENCES

- Choi J-W, Fujimaki S, Kitamura K, et al. 2002. Polybrominated dibenzo-*p*-dioxins (PBDEs), dibenzofurans (PDBFs) 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.
- *Clewett 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. XXI. 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.

9. REFERENCES

- *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 chromatography/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.

9. REFERENCES

- *Dannan GA, Sleight SD, Aust SD. 1982a. Toxicity and microsomal enzyme induction effects of several polybrominated biphenyls fo Firemaster. *Fundam Appl Toxicol* 2:313-321.
- *Dannan GA, Sleight SD, Fraker PJ, et al. 1982b. 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.

9. REFERENCES

- 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.
- 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.
- 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.
- *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.

9. REFERENCES

- 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 Environ 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 decabromodiphenyl 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.

9. REFERENCES

- 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.

9. REFERENCES

- 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. EPA600/890066A.
- 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/otcqi/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/otcqi/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/otcqi/cfr/otfilter>. April 19, 2002.

9. REFERENCES

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/otcgi>. 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/otcgi>. April 19, 2002.

*EPA. 2002n. Toxic Substances Control Act. Significant new uses of chemical substances. Polybrominated biphenyls. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 721.1790. <http://ecfr.access.gpo.gov/otcgi>. 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.

9. REFERENCES

- 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.

9. REFERENCES

- 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/erullex/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'-hexabromobiphenyl and 3,3',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.

9. REFERENCES

- *FEDRIP. 2003. Federal Research in Progress. The Dialog Corporation: Cary, NC.
- *Fehring NV. 1975a. Determination of polybrominated biphenyl residues in dairy products. *J Assoc Off Anal Chem* 58(5):978-982.
- *Fehring 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.
- Fouremant 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.

9. REFERENCES

- 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 Prod* 58(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.

9. REFERENCES

- *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, Ankla 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.
- *Glinier 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 TSCA 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]

9. REFERENCES

- 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: EPA600/281/91, 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.

9. 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 lipophilic 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 organohalogenes 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.
- Hairstrom 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, Lorentzen M. 2001. A mass balance study of a commercial pentabromodiphenyl 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.
- Hakk H, Larsen GL, Orn U, et al. 2000. Association of decabromodiphenyl ether with urinary and biliary carrier proteins. *Organohalogen Compounds* 49:108-111.

9. REFERENCES

- Halbert F, Halbert S. 1978. Bitter harvest. Grand Rapids, Michigan: William B. Erdmans Publishing company.
- Hale RC, Alae 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, Strickeling 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.

9. REFERENCES

- 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.

9. REFERENCES

*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 [*Mergus 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, et al. 1997. Temporal and spatial trends in a long-term study of gas-phase PCB concentrations near the Great Lakes. *Environ Sci Technol* 31:1811-1816.

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.

9. REFERENCES

- 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. 2002. Hazardous Substances Data Bank. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search>. April 18, 2002.

9. REFERENCES

- 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 on 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.
- 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.

9. REFERENCES

- 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.
- *Imamura M, Tung TC. 1984. A trial of fasting cure for PCB-poisoned patients in Taiwan. *Am J Ind Med* 5:147-153.
- 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. OTS05222968.
- 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 oestrogen receptor α . *Organohalogen Compounds* 41:517-520.

9. REFERENCES

- *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, Olsson M. 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'-hexabromobiphenyl 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 transpeptidase 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.

9. REFERENCES

- *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 polybrominated 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, Haraguchi 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.

9. REFERENCES

- *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'-hexabromobiphenyl, 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 hexabromocyclododecane (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 polybrominated 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.

9. REFERENCES

- 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.

9. REFERENCES

- *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 CO₂ 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.
- *Krüger, C. (1988) Polybrominated biphenyl and polybrominated diphenyl ethers – detection and quantification in selected foods. Munster, University of Munster (Thesis).
- *Ku PK, Hogberg MG, Trapp AL, et al. 1978. Polybrominated biphenyl (PBB) in the growing pig diet. *Environ Health Perspect* 23:13-18.

9. 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):1071-1084.
- *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.

9. REFERENCES

- *Lambert GH, Hsu CC, Humphrey H. 1992a. Cytochrome P450IA2 *in vivo* induction: A potential biomarker 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 P450IA2 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, Destailats 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 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.

9. REFERENCES

- *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.

9. REFERENCES

- 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, Kannan 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.

9. REFERENCES

- 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 (PBDfFs) during pyrolysis of polymer blends containing brominated flame retardants. *Chemosphere* 25(3):361-374.
- Luross JM, Alae 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, Alae M, Sergeant DB, et al. 2002. Spatial distribution of polybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Laurentian 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.

9. REFERENCES

- 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.
- Mariussen 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 carcinogenicity 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.

9. 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, Cattnach 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.

9. REFERENCES

- Meerts IA, Letcher RJ, Hoving S, et al. 2001. *In vitro* estrogenicity of polybrominated diphenyl ethers, hydroxylated PDBEs and polybrominated bisphenol A compounds. *Environ Health Perspect* 109(4):399-407.
- Meerts IA, van Zanden JJ, Luijckx 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.
- Menear 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 hepatocytes. *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.

9. REFERENCES

- 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.

9. REFERENCES

- *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.

9. REFERENCES

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 decabromo 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.

9. REFERENCES

*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, Ishizuka 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.

9. REFERENCES

- 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 Latvian 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.
- *OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment. OTABA438.
- 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.

9. REFERENCES

- 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*-dioxins/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-deethylation 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.

9. REFERENCES

- 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 JJ, 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-tetrachlorodibenzo-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. Coolestipol 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-Schmiedeberg's 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.

9. 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 [³H] 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, Ikononou MG. 2002. Reconstructing source polybrominated diphenyl ether congener patterns from semipermeable membrane devices in the Fraser River, British Columbia, Canada: Comparison to commercial mixtures. *Environ Toxicol Chem* 21(11):2292-2300.
- Rayne S, Ikononou 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, Ikononou 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.

9. 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 hepatocellular 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.

9. REFERENCES

- 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.
- 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.

9. REFERENCES

- *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. 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.
- 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.

9. REFERENCES

- 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.
- Sakai 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.

9. REFERENCES

- *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 hepatocytes. *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, Kierkegaard 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 decabromodiphenyl 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, Waite 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.

9. REFERENCES

- 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, Winkler 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 568/5-81-013. PB84166495.
- Shepherd 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 ¹²⁵I-thyroxine (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.

9. REFERENCES

- *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 electronics. 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.

9. REFERENCES

- Spear PA, Higuere 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, Alae 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, Ikononou 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.

9. REFERENCES

- *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 organochlorines 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, DeVito 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.

9. REFERENCES

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 diphenylethers, 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.

9. REFERENCES

- 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* 31:325-336.
- 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 diphenyl 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.
- *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.

9. REFERENCES

- *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 hepatocarcinogens: 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* 320:337-367.
- *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, Kittl 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.
- 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.

9. REFERENCES

- 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 nicotinic 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 of 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 hexabromo-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.

9. REFERENCES

- 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. Kosshu 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 decabromobiphenyl 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 -dibenzofurans 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.

9. REFERENCES

- Weber LW, Greim H. 1997. The toxicity of brominated and mixed-halogenated dibenzo-*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 diphenyl 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/>.

9. REFERENCES

- 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, Desai 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.
- *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.

9. REFERENCES

- 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 Perspect* 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, Alaei 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, Nishikawa Y, et al. 1997. Determination of decabromodiphenyl ether in water and sediment samples by gas chromatography 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.

9. REFERENCES

- 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, Kohler 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.

9. REFERENCES

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.

9. REFERENCES

This page is intentionally blank.

10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—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 **BMD10** 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.

10. GLOSSARY

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.

10. GLOSSARY

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) (LC₅₀)—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) (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time(50) (LT₅₀)—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.

10. GLOSSARY

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.

10. GLOSSARY

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 $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ 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.

10. GLOSSARY

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

APPENDIX A

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 and Human Health Sciences, 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 and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

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 ☒ Oral
Duration: ☒ Acute ☐ Intermediate ☐ Chronic
Key to figure: 4
Species: Rat

Minimal Risk Level: 0.01 ☒ 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 T₄ 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 ¹³¹I, incorporation of ¹³¹I into monoiodotyrosine, diiodotyrosine, T₃ or T₄, 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 (T₄) 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 ¹³¹I and a significant depression (*p*<0.01) in the incorporation of ¹³¹I into monoiodotyrosine, without any apparent effect on the incorporation of ¹³¹I into diiodotyrosine, T₃ or T₄. 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: 1 mg/kg/day; NOAEL for thyroid effects.

☒ NOAEL ☐ LOAEL

Uncertainty factors used in MRL derivation:

☒ 10 for extrapolation from animals to humans
☒ 10 for human variability

APPENDIX A

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 T₃ and T₄ 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 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 3 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.

APPENDIX B

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 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology 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 3

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.

APPENDIX B

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 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "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").

APPENDIX 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/m³ 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.

APPENDIX B

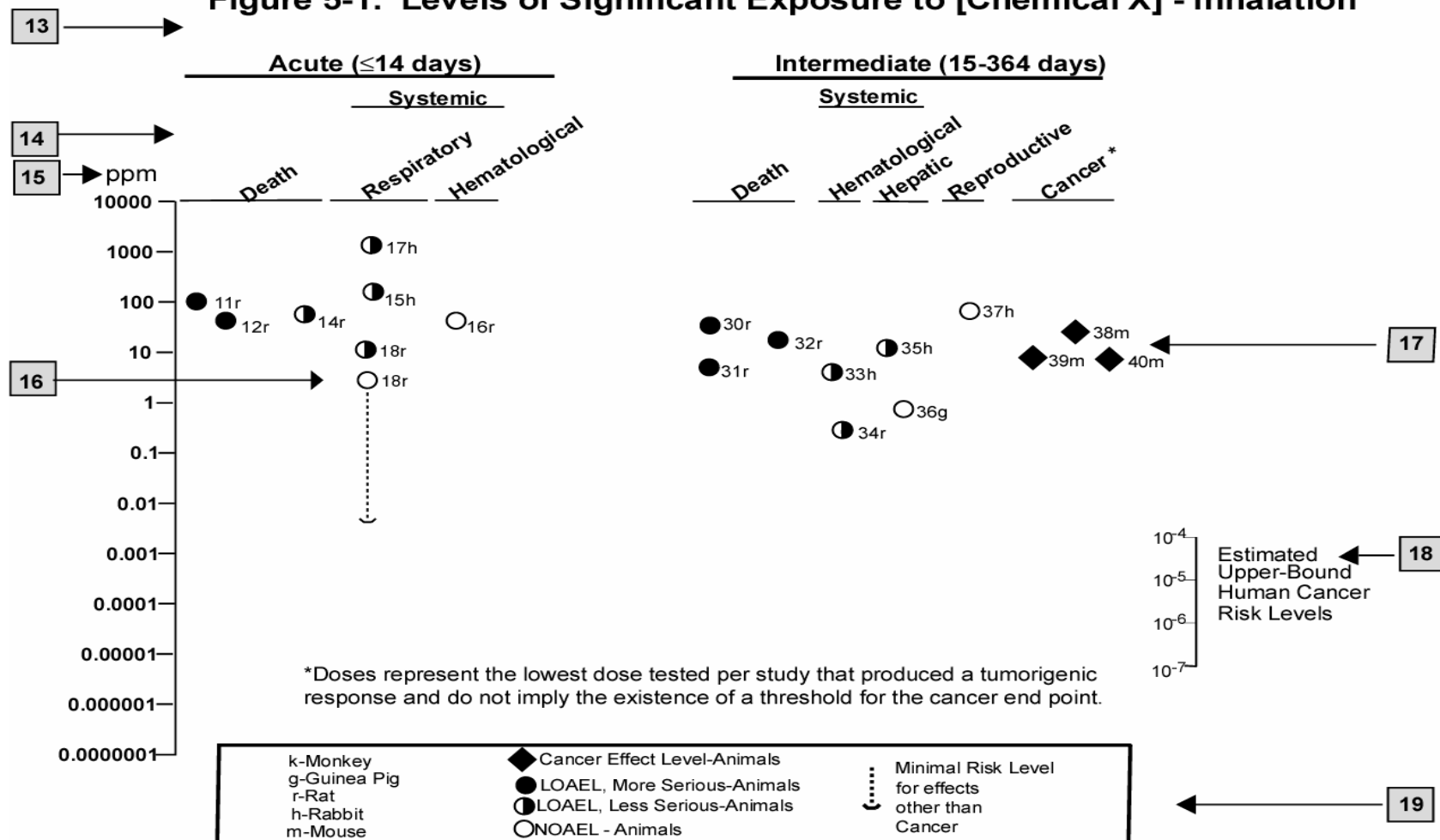
- (18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response 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) | | Reference |
| | | | | | | | Less serious (ppm) | Serious (ppm) | |
| 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 B

This page is intentionally blank.

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 |

APPENDIX C

| | |
|------------------|---|
| DOT/UN/ | Department of Transportation/United Nations/ |
| NA/IMCO | 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 |
| K _d | adsorption ratio |
| kg | kilogram |
| kgg | 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 | lutinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Levels of Significant Exposure |
| LT ₅₀ | lethal time, 50% kill |
| m | meter |
| MA | <i>trans,trans</i> -muconic acid |
| MAL | maximum allowable level |
| mCi | millicurie |
| MCL | maximum contaminant level |

APPENDIX C

| | |
|----------|--|
| 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 |

APPENDIX C

| | |
|------------------|--|
| 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 |

APPENDIX C

| | |
|---------------|--------------------------|
| $>$ | greater than |
| \geq | greater than or equal to |
| $=$ | equal to |
| $<$ | less than |
| \leq | less than or equal to |
| $\%$ | percent |
| α | alpha |
| β | beta |
| γ | gamma |
| δ | delta |
| μm | micrometer |
| μg | microgram |
| q_1^* | cancer slope factor |
| $-$ | negative |
| $+$ | positive |
| $(+)$ | weakly positive result |
| $(-)$ | weakly negative result |

