TOXICOLOGICAL PROFILE FOR POLYBROMINATED DIPHENYL ETHERS (PBDEs)

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

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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 Polybrominated Diphenyl Ethers, Draft for Public Comment was released in September 2015. 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

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FOREWORD

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

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for 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. Breysse, 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:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**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.

Publically Available Information

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.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222.

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CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Hana R. Pohl, M.D., Ph.D.
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Marc Odin, M.S., DABT
Peter McClure, Ph.D., DABT
Kimberly Zaccaria, Ph.D., DABT
Fernando Llados, Ph.D.
Mary Kawa, M.A.
Mario Citra, Ph.D.
SRC, Inc., North Syracuse, NY

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 adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

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

1. Dr. Stuart Harrad, Division of Environmental Health and Risk Management, School of Geography, Earth, and Environmental Sciences, University of Birmingham, Edgbaston, Birmingham, United Kingdom;

2. Dr. James R. Olson, Jr., Department of Chemistry, University at Buffalo, State University of New York, Buffalo, New York; and

3. Dr. Christopher Metcalfe, Metcalfe C. Environmental and Resource Studies, Trent University, 1600 West Bank Drive, Peterborough, Ontario, Canada.

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

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

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

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CONTENTS

DISCLAIMER ii
UPDATE STATEMENT iii
FOREWORD v
QUICK REFERENCE FOR HEALTH CARE PROVIDERS vii
CONTRIBUTORS xi
PEER REVIEW xiii
CONTENTS xv
LIST OF FIGURES xix
LIST OF TABLES xxi

1. PUBLIC HEALTH STATEMENT FOR POLYBROMINATED DIPHENYL ETHERS (PBDEs) 1

2. RELEVANCE TO PUBLIC HEALTH 9
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PBDEs IN THE UNITED STATES 9
2.2 SUMMARY OF HEALTH EFFECTS 11
2.3 MINIMAL RISK LEVELS (MRLs) 26

3. HEALTH EFFECTS 43
3.1 INTRODUCTION 43
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 44
3.2.1 Inhalation Exposure 45
3.2.1.1 Death 45
3.2.1.2 Systemic Effects 46
3.2.1.3 Immunological and Lymphoreticular Effects 55
3.2.1.4 Neurological Effects 56
3.2.1.5 Reproductive Effects 56
3.2.1.6 Developmental Effects 56
3.2.1.7 Cancer 57
3.2.2 Oral Exposure 57
3.2.2.1 Death 57
3.2.2.2 Systemic Effects 135
3.2.2.3 Immunological and Lymphoreticular Effects 175
3.2.2.4 Neurological Effects 181
3.2.2.5 Reproductive Effects 185
3.2.2.6 Developmental Effects 197
3.2.2.7 Cancer 236
3.2.3 Dermal Exposure 240
3.2.3.1 Death 240
3.2.3.2 Systemic Effects 240
3.2.3.3 Immunological and Lymphoreticular Effects 243
3.2.3.4 Neurological Effects 243
3.2.3.5 Reproductive Effects 243
3.2.3.6 Developmental Effects 243
3.2.3.7 Cancer 243
3.3 GENOTOXICITY 243
3.4 TOXICOKINETICS 246
3.4.1 Absorption 246
3.4.1.1 Inhalation Exposure 246

3.4.1.2 Oral Exposure 246
3.4.1.3 Dermal Exposure 252
3.4.2 Distribution 253
3.4.2.1 Inhalation Exposure 253
3.4.2.2 Oral Exposure 253
3.4.2.3 Dermal Exposure 260
3.4.3 Metabolism 260
3.4.4 Elimination and Excretion 267
3.4.4.1 Inhalation Exposure 267
3.4.4.2 Oral Exposure 268
3.4.4.3 Dermal Exposure 270
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models 270
3.5 MECHANISMS OF ACTION 273
3.5.1 Pharmacokinetic Mechanisms 273
3.5.2 Mechanisms of Toxicity 276
3.5.3 Animal-to-Human Extrapolations 296
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS 297
3.7 CHILDREN'S SUSCEPTIBILITY 299
3.8 BIOMARKERS OF EXPOSURE AND EFFECT 308
3.8.1 Biomarkers Used to Identify or Quantify Exposure to PBDEs 309
3.8.2 Biomarkers Used to Characterize Effects Caused by PBDEs 310
3.9 INTERACTIONS WITH OTHER CHEMICALS 311
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE 314
3.11 METHODS FOR REDUCING TOXIC EFFECTS 316
3.11.1 Reducing Peak Absorption Following Exposure 316
3.11.2 Reducing Body Burden 317
3.11.3 Interfering with the Mechanism of Action for Toxic Effects 318
3.12 ADEQUACY OF THE DATABASE 320
3.12.1 Existing Information on Health Effects of PBDEs 320
3.12.2 Identification of Data Needs 322
3.12.3 Ongoing Studies 336

4. CHEMICAL AND PHYSICAL INFORMATION 343
4.1 CHEMICAL IDENTITY 343
4.2 PHYSICAL AND CHEMICAL PROPERTIES 352

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL 359
5.1 PRODUCTION 359
5.2 IMPORT/EXPORT 361
5.3 USE 361
5.4 DISPOSAL 362

6. POTENTIAL FOR HUMAN EXPOSURE 365
6.1 OVERVIEW 365
6.2 RELEASES TO THE ENVIRONMENT 366
6.2.1 Air 366
6.2.2 Water 370
6.2.3 Soil 372
6.3 ENVIRONMENTAL FATE 373
6.3.1 Transport and Partitioning 373
6.3.2 Transformation and Degradation 376

6.3.2.1 Air 376
6.3.2.2 Water 377
6.3.2.3 Sediment and Soil 381
6.3.2.4 Other Media 381
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 381
6.4.1 Air 382
6.4.2 Water 385
6.4.3 Sediment and Soil 386
6.4.4 Other Environmental Media 390
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 433
6.6 EXPOSURES OF CHILDREN 437
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 439
6.8 ADEQUACY OF THE DATABASE 439
6.8.1 Identification of Data Needs 440
6.8.2 Ongoing Studies 443

7. ANALYTICAL METHODS 445
7.1 BIOLOGICAL MATERIALS 447
7.2 ENVIRONMENTAL SAMPLES 450
7.3 ADEQUACY OF THE DATABASE 455
7.3.1 Identification of Data Needs 455
7.3.2 Ongoing Studies 456

8. REGULATIONS, ADVISORIES, AND GUIDELINES 457

9. REFERENCES 463

10. GLOSSARY 527

APPENDICES
A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS A-1
B. USER'S GUIDE B-1
C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS C-1

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LIST OF FIGURES

3-1. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers – Inhalation 49

3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers – Oral 103

3-3. Levels of Significant Exposure to Decabromodiphenyl Ether – Oral 130

3-4. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE 47 Produced by Human Liver Microsomes 263

3-5. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE 99 Produced by Human Liver Microsomes 264

3-6. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE 100 Produced by Human Liver Microsomes and Human CYP2B6 265

3-7. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance 272

3-8. Existing Information on Health Effects of Polybrominated Diphenyl Ethers (PBDEs) 321

6-1. Total On- and Off-Site Releases of Decabromodiphenyl Ether, 1998–2012 369

6-2. Temporal Trends in the Concentrations (ng/g Lipid Weight) of PBDE Congeners in Lake Trout from Lake Ontario, Canada 403

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LIST OF TABLES

3-1. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers – Inhalation 46

3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers – Oral 58

3-3. Levels of Significant Exposure to Decabromodiphenyl Ether – Oral 110

3-4. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers – Dermal 241

3-5. Genotoxicity of Polybrominated Diphenyl Ethers (PBDEs) *In Vivo* 245

3-6. Genotoxicity of Polybrominated Diphenyl Ethers (PBDEs) *In Vitro* 247

3-7. Ongoing Research for PBDEs in Humans 337

4-1. Chemical Identity of Polybrominated Diphenyl Ether (PBDE) Congeners 345

4-2. Chemical Identity of Technical Polybrominated Diphenyl Ethers (PBDEs) 351

4-3. Physical and Chemical Properties of Technical Polybrominated Diphenyl Ether (PBDE) Mixtures 353

4-4. Physical and Chemical Properties of Some Polybrominated Diphenyl Ether (PBDE) Congeners 355

4-5. Typical Congener Composition of Penta-, Octa-, and Deca- Brominated Diphenyl Ether (BDE) 357

5-1. Facilities that Produce, Process, or Use Decabromodiphenyl Ether 360

6-1. Releases to the Environment from Facilities that Produce, Process, or Use Decabromodiphenyl Ether 368

6-2. Concentrations (pg/m^3) of Several Polybrominated Diphenyl Ethers (PBDEs) in Air Samples 383

6-3. Concentrations (ng/g) of Several Polybrominated Diphenyl Ethers (PBDEs) in Sediment and Suspended Particulate Samples 388

6-4. PBDE Concentrations (pg/g Wet Weight) in 18 U.S. Meat and Fish Samples 392

6-5. Concentrations (ng/g Dry Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Biosolids (Sewage Sludge) and Effluents 396

6-6. Concentrations (ng/g Lipid Weight, Except as Noted) of Several Polybrominated Diphenyl Ethers (PBDEs) in Freshwater Fish Samples from the United States 398

6-7. Concentrations (ng/g Lipid Weight Except as Noted) of Several Polybrominated Diphenyl Ethers (PBDEs) in Freshwater Fish Samples from Europe 404

6-8. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Aquatic Species 408

6-9. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Animals 413

6-10. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Human Blood Samples 422

6-11. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Human Adipose Tissue Samples 424

6-12. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Human Breast Milk Samples 425

6-13. Concentrations of PBDE Congeners in Human Milk from Nursing Mothers in the United States (2001–2004) (ng/g Lipid) 430

7-1. Analytical Methods for Determining Polybrominated Diphenyl Ethers (PBDEs) in Biological Materials 448

7-2. Analytical Methods for Determining Polybrominated Diphenyl Ethers (PBDEs) in Environmental Samples 451

8-1. Regulations, Advisories, and Guidelines Applicable to PBDEs 460

1. PUBLIC HEALTH STATEMENT FOR POLYBROMINATED DIPHENYL ETHERS (PBDEs)

This Public Health Statement summarizes the Division of Toxicology and Human Health Science's findings on PBDEs, tells you about them, the effects of exposure, and describes what you can do to limit that exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. U.S. EPA has not found PBDEs in any of the 1,832 current or former NPL sites. The total number of NPL sites evaluated for PBDEs is not known. But the possibility remains that as more sites are evaluated, sites with PBDEs may be identified. This information is important because these future sites may be sources of exposure, and exposure to PBDEs may be harmful.

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

WHAT ARE PBDEs?

PBDEs are flame-retardant chemicals that were added to a variety of consumer products to make them difficult to burn. These substances are not single chemical compounds, but rather mixtures of several brominated substances. The entire family of PBDEs consists of 209 possible substances that are referred to as congeners.

There were three important commercial PBDE mixtures (i.e., penta-, octa-, and deca- bromodiphenyl ethers [BDEs]). DecaBDE's main use was for electronic enclosures, such as television cabinets. OctaBDE was largely used in plastics for business equipment. PentaBDE was principally used in foam for cushioning in upholstery. PentaBDE and octaBDE mixtures were voluntarily withdrawn from the U.S. marketplace by their manufacturers at the end of 2004 and decaBDE was not to be manufactured or imported into the United States after December 31, 2013. In 2003, the European Union (EU) passed a Directive to ban the marketing and use of penta- and octaBDE that took effect in 2004. In 2008, the use of decaBDE was restricted by a EU's Restriction of Hazardous Substances (RoHS) Directive.

WHAT HAPPENS TO PBDEs WHEN THEY ENTER THE ENVIRONMENT?

PBDEs can be released into the air, water, and soil at places where they are produced or used. Despite the phase out of penta-, octa-, and decaBDE, vast amounts of consumer products still contain PBDEs, and these products are intended to be used for several more years. Some of these products include older televisions, computers, and furniture containing polyurethane foam.

PBDEs have very low water solubility, and when these substances are released to water, they typically bind to sediment. PBDEs in consumer items put in landfills may leach through the soil into groundwater. This is not likely to be a problem, however, because these substances generally bind strongly to soil particles, and therefore, do not move easily through soil layers.

Soils and sediments are major sinks for PBDEs. Various food items, including fish, meat, and dairy products, have been shown to contain low concentrations of PBDEs.

HOW MIGHT I BE EXPOSED TO PBDEs?

Humans can be exposed to PBDEs in a wide variety of ways, including eating contaminated foods or contaminated dusts/soils, breathing in contaminated air, or having skin contact with contaminated soil/ dust/commercial products.

The primary route of exposure to PBDEs for the general population of the United States is from ingestion of contaminated dust in indoor environments, including both personal residences and work-place environments. PBDEs have been detected in residential house dust, which you can breathe in or swallow in low concentrations. This can occur because PBDEs are physically mixed into consumer products from which they have the potential to escape into the environment when conditions are ideal. Ingestion of house dust (and to a lesser degree skin exposure to house dust) accounts for between 80 and 90% of total PBDE exposures of the general population. The remaining exposure to PBDEs in the United States is from food ingestion. You may be exposed to PBDEs through ingestion of contaminated foods, particularly those with high fat content, such as fatty fish. In breastfeeding infants, breast milk may be a major source of PBDE exposure because PBDEs can accumulate in breast milk. Due to the chemical nature of PBDEs, they have not been detected in water to any significant extent; therefore, drinking water is not expected to be a major route of exposure to PBDEs. While exposure to dust appears to be the major

exposure pathway for the general population of North American residents, PBDE exposure through dietary routes appears to be more important for European communities.

PBDEs have been detected in air samples, indicating that people can also be exposed by inhalation. Consumer products such as computer and electronic equipment (e.g., televisions) treated with PBDEs can continue to release these substances to air over time.

PBDEs can enter soil from discarded products (e.g., in landfills). Biosolids may also contain PBDEs; therefore, they may be inadvertently released to soils from the use of biosolids that are applied to add nutrients to farmlands. If you touch soil containing PBDEs, a small amount of PBDEs may pass through your skin into the bloodstream; ingestion of soil can lead to higher PBDE exposure. This route may be especially important for children who display a lot of hand to mouth activity.

HOW CAN PBDEs ENTER AND LEAVE MY BODY?

PBDEs can enter your body from food, air, water, or soil. The ways that PBDEs might enter and leave your body depend on the chemical structures of the congener components. The higher-brominated PBDEs, particularly decaBDE, act somewhat differently in the body than do lower-brominated PBDEs. If you breathe air that contains PBDEs, or swallow food, water, soil, or dust contaminated with PBDEs, the lower-brominated congeners are more likely than decaBDE to enter your body through your lungs and stomach and pass into the bloodstream.

Once PBDEs are in your body, the congeners might partially change into breakdown products called metabolites.

PBDEs and their metabolites can leave your body, mainly in the feces and a very small amount in urine. DecaBDE, with an apparent half-time of 15 days, tends to be eliminated from your body faster than lower-brominated PBDEs, with apparent half-times as high as 94 days. Lower brominated PBDEs can stay in your body for many years, stored mainly in body fat. DecaBDE also accumulates in body fat, but to a lesser degree. Both lower-brominated PBDEs and decaBDE can concentrate in breast milk fat and can enter the bodies of children through breastfeeding. Lower-brominated PBDEs and decaBDE also can enter the bodies of unborn babies through the placenta.

HOW CAN PBDEs AFFECT MY HEALTH?

Nothing definite is known about the health effects of PBDEs in people. The majority of information regarding toxicity of PBDEs and their breakdown products (metabolites) is from animal studies; however, several recent studies have evaluated associations between PBDE concentrations in human tissues (e.g., blood, breast milk) and various health effects. Due to differences in how decaBDE is absorbed and stored in your body, decaBDE is expected to be less toxic than lower-brominated PBDEs.

Rats and mice that ingested small amounts of lower-brominated PBDEs during early development had neurobehavioral changes and damage to their reproductive systems as adults. Altered neurobehavior was also observed in rats and mice that ingested decaBDE during early development, but at doses higher than observed for lower-brominated PBDEs. Adult rats and mice that ingested moderate amounts of lower-brominated PBDEs for short periods of time had mainly thyroid and liver effects. Additional findings from short-term animal studies suggest that some PBDEs might impair the immune system. Animals exposed to PBDEs by skin contact showed signs of skin irritation only if they had been scratched.

As with short-term exposure, rats and mice that ingested PBDEs for longer periods during early development also showed neurobehavioral changes; again, effects occurred at higher doses with decaBDE. Evidence from human studies is also suggestive of an association between PBDE exposure and altered neurodevelopment. Adult rats and mice that ingested small amounts of lower-brominated PBDEs over several weeks or months developed effects in the male reproductive system, thyroid, and liver. Adult animals that ingested small amounts of decaBDE over several weeks or months developed effects in the pancreas (diabetes), nervous system, immune system, and reproductive system. Evidence for PBDE-mediated effects from human studies in systems other than the developing nervous system is inconclusive or non-existent.

We don’t know if PBDEs can cause cancer in people, although liver tumors developed in rats and mice that ate extremely large amounts of decaBDE throughout their lifetime. Lower-brominated PBDEs have not yet been tested for cancer in animals.

The International Agency for Research on Cancer (IARC) has classified PBDE as a Group 3 carcinogen (*not classifiable as to its carcinogenicity to humans*) based on inadequate evidence of carcinogenicity in humans and inadequate or limited evidence in experimental animals. The EPA assigns the cancer category Group D (*not classifiable as to human carcinogenicity*) to mono-, di-, tri-, tetra-, penta-, hexa-,

octa-, and nonaBDEs and reports "*inadequate information*" to classify the specific congeners 2,2',4,4'-tetraBDE, 2,2',4,4',5-pentaBDE, and 2,2',4,4',5,5'-hexaBDE. However, EPA assigns a classification of "*suggestive evidence of carcinogenic potential*" for decaBDE. The Department of Health and Human Services has not classified PBDEs as carcinogens. The American Conference of Governmental Industrial Hygienists (ACGIH) has no data regarding cancer classifications for PBDEs.

See Chapters 2 and 3 for more information on health effects of PBDEs.

HOW CAN PBDEs AFFECT CHILDREN?

This section discusses potential health effects of PBDE exposure in humans from when they're first conceived to 18 years of age.

Studies indicate that infants and toddlers have higher exposures to PBDEs compared to older children or adults. The most likely way that infants might be exposed to PBDEs is from breast milk containing PBDEs, although fetuses in the womb could also be exposed. Toddlers and older children are exposed to PBDEs in generally the same way as are adults, mainly by ingesting contaminated household dust and food. However, soil/dust ingestion in small children (age 1−5 years) is much higher than in older children and adults. Because of their smaller weight, children's intake of PBDEs per kilogram (or pound) of body weight may be greater than that of adults. Children who live near hazardous waste sites might accidentally eat some PBDEs by putting dirty hands or other soil/dirt covered objects in their mouths, or through eating without washing their hands. Some children also eat dirt on purpose. It is also possible that children could be exposed to PBDEs following transport of the chemical on clothing from the parent's workplace to the home.

As indicated above, young children can be exposed to PBDEs both before birth and from breast milk. Both lower-brominated PBDEs and decaBDE have been found in breast milk, and they can be transferred to babies and young children. In general, however, any risks from exposures in mother's milk are outweighed by the benefits of breastfeeding. You should consult your health care provider if you have any concerns about PBDEs and breastfeeding. Since the fetus and child are still developing, effects of PBDEs might be more significant if exposure occurs during the periods before and soon after birth.

Evidence suggests that fetuses and young children are more susceptible to PBDEs than adults. Subtle behavioral changes have been observed in animals exposed to PBDEs within the first 2 weeks of life, and results from human studies are suggestive of an effect of PBDEs on neurodevelopment in children,

including impaired cognitive development (comprehension, memory), impaired motor skills, increased impulsivity, and decreased attention. One study reported that early PBDE exposure was a risk factor for the development of Attention Deficit Hyperactivity Disorder (ADHD); however, another study did not find a link between PBDE exposure and ADHD. One study investigating potential associations between early PBDE exposure and autism did not find a link between maternal PBDE serum levels and autistic behaviors in 4–5-year old children. One possible explanation for the observed behavioral effects might be related to changes in the thyroid, because development of the nervous system is dependent on thyroid hormones. Damage to developing reproductive organs and immune suppression have also been observed in animals exposed to PBDEs during development. It is unknown if these effects occur in human children.

PBDEs have not caused birth defects in animals or impaired the ability for rats or mice to become pregnant or stay pregnant.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PBDEs?

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

Ingestion and dermal contact with indoor dust containing PBDEs is the major exposure pathway to residents of the United States. Dust containing PBDEs can collect on your hands and be ingested through hand-to-mouth activities; regular hand washing may decrease PBDE exposure from this route. Additionally, PBDE exposure may be decreased by regular vacuuming and cleaning of air ducts and filters to reduce indoor dust levels.

Since many older consumer products such as televisions, computers, and furniture containing polyurethane foam contain PBDEs, replacing older products with newer ones that do not contain these substances may decrease residential PBDE exposure.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PBDEs?

PBDEs and their breakdown products (metabolites) can be measured in human blood, hair, and breast milk. However, the detection of PBDEs or their metabolites cannot predict the kind of health effects that

might develop from that exposure. Because PBDEs and their metabolites either leave the body or are distributed to body fat fairly rapidly, the tests need to be conducted within days if an acute, high-level exposure is suspected.

For more information on the different substances formed by PBDE breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

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

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

Regulations and recommendations can be expressed 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 usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

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 issued the regulation or recommendation.

EPA requires that companies that transport, store, or dispose of monobrominated diphenyl ether (monoBDE) (or diphenyl ether with one bromine attached to the structure, represented by Chemical Abstracts Service [CAS] Registry Number 101-55-3; Resource Conservation and Recovery Act [RCRA] waste number U030) follow the rules and regulations of the federal hazardous waste management program because it has been listed (U-list) as a hazardous waste due to toxicity concerns. EPA also limits the amount of monoBDE put into publicly owned waste water treatment plants. To minimize exposure of

people to monoBDE, EPA requires that industry tell the National Response Center each time 100 pounds or more of monoBDE have been released to the environment.

OSHA has not set permissible exposure limits (PELs) to protect workers against adverse health effects resulting from exposure to PBDEs. NIOSH has not recommended guidelines for worker exposure limits.

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

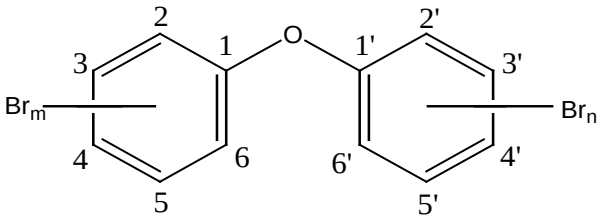
- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PBDEs IN THE UNITED STATES

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



where m + n = 1 to 10

Due to the ether linkage and the position and number of bromine atoms, there are important three-dimensional differences in the structures of PBDEs that can influence the molecules' receptor interactions and toxicological properties as discussed in Section 3.5, Mechanisms of Action. In general, PBDEs are not expected to have the same array of three-dimensional conformations as either polybrominated biphenyls (PBBs) or polychlorinated biphenyls (PCBs).

PBDEs are brominated organic compounds that were used as flame retardant additives in plastics, textiles, and other materials. As additives, they are physically mixed into product applications, rather than chemically bound. Therefore, they have the potential to migrate from the plastic matrix into the environment when conditions are ideal. Production of PBDEs began in the 1970s and has continued until recently. PentaBDE and octaBDE mixtures were voluntarily withdrawn from the U.S. marketplace by their manufacturers at the end of 2004; however, the manufacture and use of decaBDE continued past that date. In December of 2009, the two remaining U.S. producers of decaBDE and the largest U.S. importer

of this product announced commitments to phase out manufacture and importation of decaBDE for most uses in the United States by December 31, 2012, and to end manufacture and import for all uses by the end of 2013.

PBDEs are persistent in the environment and most congeners can be considered bioaccumulative. The fully brominated congener, BDE 209, has a lower tendency to bioconcentrate due to its molecular dimensions; however, numerous studies have detected this substance in tissues of birds, mammals, and fish (see Section 6.4.4).

Monitoring and body-burden data indicate that PBDEs are ubiquitous in the environment and that the general population is exposed to these substances through their past use as flame retardants. A study that examined stored blood samples from 1973 (prior to the use of PBDEs as flame retardants) showed virtually no detections of these substances in human blood; however, varying concentrations of many PBDE congeners were detected in all blood samples collected in 2003 from 39 residents in Mississippi and 10 residents in New York City, illustrating the widespread exposure to PBDEs since their inception. Body burden data have consistently shown the residents of North America have higher concentrations of PBDEs in blood than people residing in Europe, likely due to differences in past production and use of commercial formulas.

House dust was identified as a major source of exposure to PBDEs by a systematic study of American exposure routes. In the United States, concentration levels found in soil, house dust, and air tended to be greater in indoor samples compared to outdoor samples. The EPA calculated the adult intake dose of total PBDEs to be 7.1 ng/kg body weight/day. It estimated children's intakes as 47.2 ng/kg body weight/day for 1–5 year olds, 13.0 ng/kg body weight/day for 6–11 year olds, and 8.3 ng/kg body weight/day for 12–19 year olds. The much higher dose for children aged 1−5 years was largely due to higher soil/dust ingestion in this age group. Exposure to indoor dust was the predominant exposure pathway for PBDEs in these calculations. It was estimated that 90% of the intake resulted from house dust inhalation or dermal exposure. This does not include special populations such as infants that are primarily exposed through breastfeeding. PBDE concentrations were generally lower in house dust samples collected outside of the United States compared with dust samples collected within the United States. The specific PBDE congeners detected in house dust and food vary; BDE 209 is more commonly detected within indoor environments where exposure is more likely to occur through intake of contaminated dust and air. PBDE contamination of food is more likely a result of past emissions or ongoing emissions from dumpsites and older products that still contain pentaBDE, which is mainly composed of the congeners

BDE 47 and BDE 99. Ingestion of PBDEs through the diet appears to be the predominant pathway for European communities. In China, the decaBDE congener, BDE 209, was the most abundant congener detected in both maternal and cord blood samples where industrial production of BDE 209 may result in exposure.

2.2 SUMMARY OF HEALTH EFFECTS

Information is available on the potential health effects of formerly used commercial PBDE mixtures (pentaBDE, octaBDE, and decaBDE) as well as several individual PBDE congeners. As subsequently discussed, the toxicity of decaBDE is generally less pronounced than for lower-brominated PBDEs following acute and repeated-dose exposures. This difference in toxicity may be related to differences in pharmacokinetics, resulting in lower bioavailability of decaBDE (see Sections 2.3 and 3.4 for more details).

The preponderance of health effects information on PBDEs is from studies of orally exposed laboratory animals and human studies in which the main exposure route is unknown, but expected to be oral. As summarized below and detailed in Chapter 3 (Health Effects), the main targets of concern following PBDE exposure in humans are the developing nervous and reproductive systems, the developing and mature endocrine system, the liver, and the male reproductive system. Other potential targets are the female reproductive system, the adult nervous system, and the developing and adult immune system; however, evidence for these end points is limited. In other systems/organs, available data provide no consistent evidence for exposure-related effects (respiratory, cardiovascular, gastrointestinal, hematological, renal, dermal, or ocular effects); therefore, effects in these systems are considered unlikely to occur following PBDE exposure.

Developmental Effects.

Neurodevelopment. Numerous epidemiological studies have reported results suggestive of an effect of PBDE on neurodevelopment in children. PBDE concentrations in cord blood, maternal or infant serum, and/or breast milk have been correlated with cognitive score and adaptive behavior deficits in infants; mental and physical development deficits in infants/toddlers at ages 12, 24, and 36 months; language and social developmental score deficits in toddlers at 24 months; increased impulsivity in toddlers at 24–36 months; poor social competence and attention deficit hyperactivity disorder (ADHD) or increased attention problems in 4-year-old children; impaired fine motor coordination, verbal memory and

comprehension, and sustained attention in 5–7-year-old children; and poor attention and executive function deficits in 9–12-year-old children. In one birth cohort, no associations were observed between maternal serum PBDEs and neonatal behavior in 5-week-old infants or autistic behaviors at 4–5-year-old children; however, children from the same cohort showed associations between maternal serum PBDEs and decreased IQ and increased hyperactivity at 5 years of age and executive function deficits at 5–8 years of age. Pre- and perinatal studies in animals also consistently reported neurodevelopmental effects following exposure to lower-brominated PBDEs and decaBDE at doses ≥0.06 and ≥2.22 mg/kg/day, respectively, including neurobehavioral alterations, delayed ontogeny of reflexes, ultrastructural changes in the hippocampus, altered nicotinic receptor density, altered electrophysiology, and altered gene and protein expression levels.

Based on human and animal data, the developing nervous system is a target of concern for both lower-brominated PBDEs and decaBDE.

Endocrine System Development. In infants, developmental exposure to PBDEs and infant serum or cord blood thyroxine (T_4) levels were either negatively associated or not associated. Associations between developmental PBDE exposure and infant serum or cord blood triiodothyronine (T_3) and thyroid stimulating hormone (TSH) were similarly inconsistent. In animals, numerous studies have reported decreased serum T_4 and/or T_3 levels in pups after gestational and lactational exposure to penta- or tetraBDE at doses as low as 0.3 mg/kg/day in rats and 452 mg/kg/day in mice. Significant reductions in serum T_3 levels were also observed in offspring following gestational and lactational exposure to decaBDE at 146 mg/kg/day in rats and 1,500 mg/kg/day in mice, although no changes were observed in serum T_4 or TSH. A dose-related decrease in serum T_4 was observed in neonatal male mice exposed to decaBDE doses of 6–20 mg/kg/day from postnatal day (PND) 2 to 15, but no change was observed in neonatal females.

While human data are inconsistent, they suggest that PBDEs can interact with thyroid hormone homeostasis in infants and children. These data, along with available animal studies, indicate that the developing thyroid is a target of concern for PBDE exposure, especially lower-brominated PBDEs.

Reproductive System Development. Male reproductive effects significantly associated with PBDE exposure in infants included congenital cryptorchidism (undescended testes), decreased cord serum total testosterone (but not free testosterone, estradiol [E2], aromatase index, sex hormone binding globulin, or Anti-Müllerian hormone), increased serum levels of the sex hormones, E2, free E2, and inhibin B (but not

testosterone, luteinizing hormone [LH], follicle-stimulating hormone [FSH], or sex hormone binding globulin) at 3 months of age, and increased testes volume in boys at 18 months of age. In contrast, no relationships were observed between maternal PBDE exposure and hypospadias (abnormal location of the urinary tract opening) in male offspring, PBDE concentrations in children's adipose tissue and cryptorchidism, or various measures of sexual maturation in female offspring. However, serum PBDE levels in 6–8-year-old females were significantly associated with delayed onset of puberty in a longitudinal cohort of U.S. girls.

In animal studies, reproductive effects were observed in adult F1 offspring of dams exposed to a single dose of pentaBDE at 0.06 mg/kg on gestation day (GD) 6, including reductions in testicular weight, sperm/spermatid number, and daily sperm production in males and a decreased number of secondary follicles and ultrastructural changes in the ovaries in females (although F1 fertility when mated to an unexposed animal was not impaired). In animals exposed pre- or perinatally to decaBDE, reproductive effects were observed in adult male offspring of dams exposed to decaBDE doses of 10–1,500 mg/kg/day from GD 0 to 17, including testicular lesions, decreased anogenital distance (AGD), and altered sperm parameters. In contrast, no exposure-related changes in AGD, onset of puberty, or reproductive organ weight and histology were reported in offspring of dams exposed to decaBDE at doses up to 1,000 mg/kg/day during gestation and lactation or doses up to 20 mg/kg/day from PND 2 to 15. No exposure-related changes in reproductive development were reported in female offspring of dams exposed to decaBDE at doses up to 1,000 mg/kg/day during gestation and lactation or doses up to 20 mg/kg/day from PND 2 to 15.

Based on limited human and adequate animal data, it is possible that oral PBDE exposure during development may adversely affect the developing reproductive system, particularly the male reproductive system. However, data are too limited to adequately determine whether or not PBDE exposure in infants and children will lead to altered reproductive performance as adults.

Immune System Development. In offspring of rat dams exposed to pentaBDE at doses up to 25 mg/kg/day via gavage for 70 days prior to mating through PND 21, a significant dose-related trend was observed in the incidence of apoptotic lymphocytes and tingible macrophages in the thymus of PND 43 males, but not females. In PND 28 offspring of mouse dams exposed to decaBDE at doses ≥260 mg/kg/day from GD 10 to PND 21, pulmonary viral titers of respiratory syncytial virus (RSV) (measured 5 days post-infection) were significantly increased. These animal data suggest that oral PBDE

exposure during development may lead to immunosuppression; however, data are too limited to adequately assess the immunotoxic potential of PBDE exposure in infants and children.

Embryotoxicity, Fetotoxicity, and Physical Growth and Development. No human studies have evaluated associations between embryotoxicity or fetotoxicity and PBDE exposure. One study reported a significant increased risk for preterm birth in women with high serum PBDE concentrations, compared with low PBDE concentrations; however, other studies did not observe a significant association between gestational length and PBDE concentrations. Evidence for altered physical growth and development from human studies is inconsistent, with some studies reporting associations between PBDE concentrations in maternal/cord serum, breast milk, or placental tissue and decreased birth weight, length, chest circumference, head circumference, and/or body mass index (BMI), some reporting no associations, and a limited number reporting increased birth weight, length, and/or head circumference. Available data from animal studies indicate that PBDEs are not embryotoxic or fetotoxic at PBDE doses below doses that elicited maternal toxicity, although occasional observations of reduced pup weight were reported.

Based on animal studies, it is unlikely that oral PBDE exposure will cause embryotoxicity or fetotoxicity in humans; however, human and animal data indicate that PBDE exposure could potentially lead to low birth weight or other impacts on physical development.

Endocrine Effects.

Thyroid. Numerous studies have been performed to evaluate the relationship between concentrations of PBDE in body tissues and circulating thyroid hormone levels in human populations. While these studies have demonstrated that PBDE can perturb the human endocrine system and affect hormone levels, the specific findings are not consistent across studies. For example, even limiting the discussion to studies that evaluated both PBDE concentrations and thyroid hormone levels in serum samples collected only from adult men, studies have reported positive associations with T_4, negative associations with T_4, and no association with T_4. Similar inconsistencies were found in studies in pregnant women, with studies reporting a positive associations with T_4, no association with T_4, or negative associations with T_4. Results were similarly inconsistent regarding the association between PBDE concentrations and serum T_3 and TSH.

In contrast to inconsistencies observed in human studies, altered serum thyroid hormone levels have been consistently reported in laboratory animals exposed to lower-brominated PBDEs. Reduced serum T_4 has

been reported in animals following acute or intermediate exposure to lower-brominated PBDEs at doses as low as 0.8 mg/kg/day. At higher doses (≥30 mg/kg/day), some studies also report reduced serum T_3 and/or increased serum TSH; however, other studies reported no significant changes in serum T_3 and/or TSH levels in rats exposed to doses up to 300 mg/kg/day. In rat dams, reduced serum T_4 has been observed following exposure to lower-brominated PBDEs at doses as low as 0.06 mg/kg/day during gestation or gestation plus lactation. In mouse dams, no exposure-related changes were observed following exposure to pentaBDE at 452 mg/kg/day from GD 4 to PND 17. Exposure to pentaBDE at doses up to 120 mg/kg/day during gestation or gestation plus lactation did not significantly alter maternal serum T_3 and/or TSH in most studies; however, a study reported reduced maternal serum T_3 after exposure to pentaBDE at 30 mg/kg/day via dosed cookies from GD 1 to PND 21.

Histopathological changes in the thyroid (e.g., follicular cell hyperplasia, increased epithelial thickness/height, altered morphology of epithelium, cellular debris, degeneration) have been observed in intermediate-duration studies of lower-brominated BDEs at doses as low as 20 mg/kg/day in rats, 0.45 mg/kg/day in mice, and 0.06 mg/kg/day in mink. Increased thyroid weights were reported in rats exposed to doses of penta- or octaBDE as low as 50 mg/kg/day for 90 days; however, no exposure-related changes in thyroid weights were observed in rats exposed to doses of penta- or octaBDE up to 200 mg/kg/day for 15–28 days or in F0 or F1 mink exposed to dietary pentaBDE at doses up to 0.31 mg/kg/day in one-generation studies (4 weeks pre-mating through postnatal week [PNW] 6 or 33). In acute studies, no exposure-related changes in thyroid weight or histology were observed in rats exposed to penta- or tetraBDE doses up to 36 mg/kg/day for 14 days

Unlike the lower-brominated PBDEs, serum T_4 levels were not altered in rats exposed to decaBDE at doses up to 600 mg/kg/day for 4–90 days. Some studies reported reduced serum T_3 levels in rats exposed to decaBDE at doses as low as 50 mg/kg/day for 28–90 days, but another 90-day study reported no change in serum T_3 levels in rats exposed to decaBDE at doses up to 100 mg/kg/day. Serum TSH was reduced in male rats exposed to decaBDE at doses ≥300 mg/kg/day for 33 days. At higher doses (≥950 mg/kg/day), significant reductions in serum T_4 and T_3 were observed in male mice exposed for 35 days and pregnant mice exposed from GD 7 to 9.

In chronic studies of decaBDE, thyroid follicular cell hyperplasia was observed in male mice exposed to ≥3,200 mg/kg/day for 103 weeks; no histopathological changes in the thyroid were observed at doses up to 7,780 mg/kg/day in female mice, 2,240 mg/kg/day in male rats, or 2,550 mg/kg/day in female rats. In intermediate-duration studies, dose-related increases in thyroid hyperplasia were reported for male rats

exposed to a low-purity decaBDE compound at ≥80 mg/kg/day for 30 days, but hyperplasia was not observed in rats or mice exposed to high-purity decaBDE at doses up 8,000 or 9,500 mg/kg/day, respectively, for 13 weeks or in rat dams exposed to doses up to 146 mg/kg/day from GD 10 to PND 21. However, multiple areas of degenerated follicular epithelium and slight attenuation of the follicular epithelium were observed in the thyroid glands of young male rats exposed to decaBDE at doses ≥300 mg/kg/day for 33 days. No changes in thyroid weight were observed in rats exposed to decaBDE at doses up to 90 mg/kg/day for 28 days, but increased thyroid weights were reported in rat dams exposed to ≥2 mg/kg/day from GD 10 to PND 21 and young male rats exposed to 600 mg/kg/day for 33 days.

While human data are inconsistent, they suggest that PBDEs can interact with thyroid hormone homeostasis. These data, along with available animal studies, indicate that the thyroid is a target of concern for PBDE exposure, especially lower-brominated PBDEs.

Pancreas. An analysis of cross-sectional National Health and Nutrition Examination Survey (NHANES) data showed a significant increase in the risk of diabetes associated with serum concentrations of BDE 153 (but not BDE 28, BDE 47, BDE 99, or BDE 100), although the risk was higher with exposure to 50–75th percentile BDE 153 concentrations than >75th percentile BDE 153 concentrations. Serum BDE 153 concentrations (but not BDE 28, BDE 47, BDE 85, BDE 99, BDE 100, or BDE 154) were also shown to be significantly associated with increased odds of developing gestational diabetes in a cohort of 258 pregnant women. However, other cross-sectional and prospective studies found no relationship between serum PBDE concentrations and diabetes in an adult cohort from Wisconsin, an elderly cohort in Finland, or an elderly cohort in Sweden.

An intermediate-duration study evaluated insulin-regulation and pancreatic morphology in rats following exposure to decaBDE at 0, 0.05, 1, or 20 mg/kg/day daily via gavage in corn oil for 8 weeks. Serum insulin was significantly decreased by 50–60% at 1 and 20 mg/kg/day, and glucose levels were concomitantly increased by 12, 18, and 21% at 0.05, 1, and 20 mg/kg/day. Consistent with the insulin findings, morphological changes were seen in the pancreas at 1 and 20 mg/kg/day (blurred boundaries among pancreatic islet cells; quantitative data not reported). Additionally, microarray analysis indicated that type I diabetes mellitus (T1DM) canonical pathways were significantly enriched following decaBDE exposure. Subsequently, gene act network and gene coexpression network found that some major histocompatibility complex molecules and TNF-α were involved in the T1DM pathway. Only one other animal study evaluated the pancreas following decaBDE exposure. In rats exposed to decaBDE via gavage for 28 days at doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day, slight or moderate

insulitis was observed in the Langerhan's islets of the "majority of samples," but findings were not exposure-related. Similarly, no exposure-related effects were observed for serum glucose levels. The only other study evaluating serum glucose levels after decaBDE exposure instead reported reduced serum glucose levels in male rats exposed to 20 mg/kg/day of a dietary PBDE mixture containing 52.1% pentaBDE (DE-71), 44.2% decaBDE (BDE 209), and 0.4% octaBDE (DE-79) for 70 days. The observed decreased glucose levels could be due to the pentaBDE component, as male rats exposed to pentaBDE at doses of 0.27–200 mg/kg/day for 28 days also showed decreased glucose levels; the study authors did not report the lowest dose at which glucose levels were significantly lower in male rats, but they reported a BMD_{10RD} of 179.55 mg/kg/day and a $BMDL_{10RD}$ of 66.7 mg/kg/day.

Limited human evidence is inconclusive regarding potential associations between diabetes and PBDE exposure; however, considering the animal data, the pancreas may be a target of concern for oral PBDE exposure.

Hepatic Effects. Liver effects have been reported in adult, pregnant, and developing animals exposed to lower-brominated PBDEs. Histopathological effects in the liver (hepatocellular hypertrophy, necrosis, and vacuolation) were consistently observed in animals exposed to lower-brominated PBDEs for 15–90 days at doses ≥0.45 mg/kg/day, regardless of life-stage. In acute exposure studies, fatty degeneration of the liver was observed following a single pentaBDE dose of 2,000 mg/kg or repeated pentaBDE doses of 200 mg/kg/day for 7 or 14 days. Increased liver weight was also observed in animals exposed to lower-brominated PBDEs for 1–14 days at doses ≥8 mg/kg/day and 15–90 days at doses ≥1.2 mg/kg/day. In studies that evaluated hepatic enzyme induction (e.g., elevated ethoxyresorufin o-deethylase [EROD], methoxyresorufin o-deethylase [MROD], pentoxy-resorufin o-deethylase [PROD], and uridine diphosphoglucuronyl transferase [UDPGT] activity), significantly increased enzyme activities were observed in animals following acute or intermediate-duration exposure to doses ≥3 or ≥0.06 mg/kg/day, respectively, and were always observed at doses at or below the dose causing elevated liver weights in the same study. No studies evaluating liver effects following chronic exposure to lower-brominated PBDEs were located.

Evidence for hepatic toxicity following exposure to decaBDE is less consistent than evidence for lower-brominated PBDEs. There is no evidence of hepatic toxicity following acute exposure to decaBDE at doses up to 1,000 mg/kg/day for 4–14 days. In intermediate-duration studies, slight to moderate hepatocellular hypertrophy was observed in rats exposed to decaBDE at 60 mg/kg/day for 28 days, in pregnant rats exposed to 300 mg/kg/day for 21 days, and in mice exposed to 9,400 mg/kg/day for

28 days; however, other studies did not report exposure-related changes in liver histology following exposure to decaBDE at doses up to 9,500 mg/kg/day for 3–13 weeks. In an older study using an impure decaBDE compound containing lower-brominated congeners (77% decaBDE, 22% nonaBDE, 0.8% octaBDE), centrilobular cytoplasmic enlargement and vacuolation, as well as increased liver weight, were observed in male rats exposed to dietary doses of ≥80 and 800 mg/kg/day, respectively, for 30 days. Increased liver weights were also reported in rats exposed to doses ≥1 mg/kg/day for 8 weeks and mice exposed to 9,400 mg/kg/day for 28 days, but other intermediate-duration studies reported no exposure-related changes in liver weights at doses of 1,000 mg/kg/day for 21–90 days. In chronic studies, exposure to decaBDE for 103 weeks caused liver lesions that included neoplastic nodules in rats at ≥1,120 mg/kg/day, thrombosis and degeneration in rats at 2,240 mg/kg/day, and centrilobular hypertrophy and granulomas in mice at ≥3,200 mg/kg/day.

Developing animals appear to be more susceptible to liver damage following exposure to decaBDE than adult animals. Transient histopathological changes (diffuse liver cell hypertrophy with increased cytoplasmic eosinophilia) and elevated liver weights were observed in male and female rat offspring exposed to decaBDE from GD 10 to PND 21 at ≥2 and 146 mg/kg/day, respectively. Fatty degeneration, elevated liver weights, and elevated liver enzymes were observed in young male rats exposed to decaBDE at ≥300 mg/kg/day from PND 10 to 42. In mice, decaBDE exposure from GD 0 to 17 caused acute cell swelling of hepatocytes associated with pressure occlusion of hepatic sinusoids and elevated liver enzymes in PND 71 male offspring at ≥10 mg/kg/day; however, liver weight was unaltered at doses up to 600 mg/kg/day.

No studies are available on hepatic effects of PBDEs in humans. Based on the evidence in animals, PBDEs are potentially hepatotoxic in humans, especially lower-brominated PBDEs.

Male Reproductive Effects. Several studies have found results suggestive of reproductive effects in men associated with exposure to PBDE, including significant inverse correlations between serum concentrations of BDE 153 (hexaBDE) and sperm concentration and testis size in young adult Japanese males, significantly reduced sperm mobility in association with increased serum PBDE concentrations (BDE 47, BDE 100, and total) in Canadian men recruited at a fertility clinic, and altered parameters of semen quality associated with selected BDEs in men participating in a prospective cohort study in Michigan and Texas. Although a number of studies have evaluated the potential effects of PBDE exposure on male reproductive hormone levels, these studies collectively do not show consistent effects associated with PBDE exposure.

Reproductive effects have been reported in male rodents following intermediate-duration exposure to the lower-brominated PBDE congener tetraBDE, including decreased serum testosterone at ≥0.001 mg/kg/day, histopathological changes in rat or mouse testes (increased epithelial thickness, multinucleated giant cells, vacuolar spaces, apoptosis, germ cell loss) at doses ≥0.03 or ≥0.045 mg/kg/day, and decreased sperm production in rats at 1 mg/kg/day. No dose-related changes were observed in testicular weight or sperm morphology, motility, or capacitation at doses up to 30 mg/kg/day. For other lower-brominated PBDEs (pentaBDE, octaBDE), no exposure-related effects were observed in serum testosterone levels at doses up to 60 mg/kg/day for 15–70 days, sperm parameters at doses up to 20 mg/kg/day for 20 days, or male reproductive histology or organ weight at doses up to 750 mg/kg/day for 38–90 days. However, in acute studies, serum testosterone levels were significantly decreased by ~40–45% in male rats 45 days after a single gavage exposure to pentaBDE at doses ≥0.6 mg/kg and dose-related decreases in androgen-dependent tissue weights (prostate, seminal vesicle, Cowper's gland, gland penis, levator ani bulbo cavernosus) were observed in castrated rats exposed to pentaBDE at doses ≥30 mg/kg/day for 9 days (Herschberger assay).

Studies of decaBDE have been more limited. Decreased relative testes and epididymides weights, degenerative changes in the seminiferous tubules, reduced sperm count and viability, and reduced serum testosterone were reported in male mice exposed to decaBDE at 950 mg/kg/day via gavage for 35 days, compared with controls; no exposure-related effects were observed at 750 mg/kg/day. In contrast, no changes in sperm count, motility, or morphology were observed in rats or mice exposed to decaBDE at doses up to 60 or 1,500 mg/kg/day for 28–50 days; however, exposure-related decreases were observed in one sperm velocity measure (lateral head amplitude) in mice exposed to ≥500 mg/kg/day. A dose-related decrease in epididymis weight and a dose-related increase in seminal vesicle/coagulation gland weight were observed in rats exposed to 1.7–60 mg/kg/day for 28 days; however, the lowest doses at which the effects were observed were not reported. No testicular weight changes were observed at doses up to 60 mg/kg/day. In other intermediate-duration studies, no exposure-related changes in organ weight were reported for male reproductive organs in rats or mice exposed to decaBDE doses up to 800 or 1,500 mg/kg/day. Histopathological changes in male reproductive tissues have not been reported in rats or mice exposed to decaBDE at doses up to 2,550 or 7,780 mg/kg/day, respectively, for 103 weeks. Findings were negative in a one-generation study that exposed male and female rats to an impure decaBDE compound containing lower-brominated congeners (77% decaBDE, 22% nonaBDE, 0.8% octaBDE) for 60 days prior to mating through PND 21.

Based on the evidence in humans and animals, lower-brominated PBDEs are potentially toxic to the male reproductive system in humans. Available data for decaBDE provide very limited evidence of male reproductive damage.

Female Reproductive Effects. Evidence for reproductive effects in women associated with exposure to PBDEs is inconsistent. Increased length of menstrual periods (prior to pregnancy) was associated with increased breast milk concentrations of PBDEs in a study of 46 Taiwanese women, and with plasma levels of BDE 47 and BDE 153 in a study of 42 Cree women of James Bay, Canada, but not in a smaller study with 20 Taiwanese women or in 223 Californian women. Age at menarche was not associated with PBDE concentrations in breast milk; however, an analysis of cross-sectional data from a sample of 271 adolescent girls (NHANES) found that higher serum PBDE concentrations were associated with younger age of menarche. Decreased fecundability (i.e., increases in time to pregnancy between stopping contraception and becoming pregnant) was significantly associated with increased serum concentrations of BDE 47, BDE 99, BDE 100, and BDE 153 (and their sum) in 223 Californian women; however, fecundability was not significantly related to serum PBDE concentrations in a cohort of 501 Michigan and Texas couples followed prospectively for 1 year after discontinuing contraception for the purpose of becoming pregnant. A study of 65 women from Boston undergoing *in vitro* fertilization found no association between serum PBDE concentrations and risk of implantation failure, but did find a significantly increased risk of failure associated with increased (i.e., above median) concentrations of BDE 153 (but not other congeners or total PBDE) in follicular fluid. PBDEs were not associated with Polycystic Ovary Syndrome or with diagnosis of uterine fibroids.

In one-generation animal studies, no exposure-related changes were observed in reproductive end points (number of pregnancies, gestation length, number, size, or sex ratio of litters) in rats or mice exposed to lower-brominated PBDEs at doses up to 25 or 1 mg/kg/day, respectively. Similarly, in gestation plus lactation studies, no exposure-related effects on litter parameters (successful delivery of litters, gestation length, litter size, sex ratio, number of live pups) were observed in rats or mice exposed to lower-brominated PBDEs at doses up to 32 or 10 mg/kg/day, respectively, during gestation and lactation only. The number of litters surviving until PND 8 was significantly decreased following exposure to tetraBDE at 0.1 mg/kg/day from pre-mating day 28 through PND 21 in one study; however, reduced pup survival was not reported in other studies. In a one-generation study in mink, females exposed to pentaBDE at doses ≥0.25 mg/kg/day from pre-mating day 28 through PNW 6 did not whelp. It is not clear in one study whether mink exposed to 0.25 mg/kg/day never became pregnant or had complete litter loss. However, another study reported that female mink exposed to 0.31 mg/kg/day had no exposure-related changes in

mating success; rather, sows showed complete litter loss with 70% showing clear postimplantation loss. In one-generation and intermediate-duration studies, no changes in reproductive organ weight or histology were observed in female rats, mice, or mink exposed to lower-brominated PBDEs at doses up to 750, 0.45, or 0.31 mg/kg/day, respectively. One acute study reported increased paired ovary weight after exposure to tetraBDE at 0.14 mg/kg on GD 6; however, no changes in reproductive organ weight or histology were observed in female rats acutely exposed to pentaBDE at doses up to 300 mg/kg/day.

In female mice exposed to dietary tetraBDE for 28 days, serum testosterone and E2 were significantly increased at 0.45 mg/kg/day; no other study reported altered reproductive hormones in females.

Information on reproductive effects of decaBDE is limited. Findings were negative in a one-generation study that exposed male and female rats to an impure decaBDE compound contaminated with lower-brominated congeners (77% decaBDE, 22% nonaBDE, 0.8% octaBDE) for 60 days prior to mating through PND 21. In a gestational exposure study in mice (GDs 7–9), significant increases were observed in the percentage of postimplantation loss per litter and resorptions per litter in dams exposed to ≥750 and ≥1,500 mg/kg/day, respectively. Additionally, the percentage of live fetuses per litter was significantly decreased by 10% in dams exposed to 2,000 mg/kg/day. Histological changes in the ovaries (atrophic changes, decreased number of follicles, and increased fibrotic tissue) were observe in female rats exposed to decaBDE at 300 mg/kg/day from 3 weeks of age, through mating to untreated males, gestation, and lactation (~11 weeks); F0 reproductive success was not reported. In other studies, no histopathological changes in female reproductive organs were observed in rats or mice following intermediate- or chronic-duration exposure to decaBDE at doses up to 8,000 or 9,500 mg/kg/day, respectively.

Based on inconsistent data in humans and animals, it is unclear whether PBDEs affect the female reproductive system in adults.

Adult Neurological Effects. While neurobehavioral development is a potential effect of concern for PBDE exposure in humans, available human data are too limited to determine if PBDE exposure is neurotoxic in adults or adolescents. No association was found between serum PBDE concentrations and neuropsychological function assessed by 34 tests of cognitive and motor function, affective state, and olfactory function in a study population of 144 volunteers (67 males and 77 females) between the ages of 55 and 74 years who lived for at least 25 years in the upper Hudson valley of New York State. In 515 secondary students from Belgium (mean age 14.9 years), serum PBDE concentrations were not associated with most aspects of neurological performance measured in a battery of neurological tests;

however, there was a significant deterioration in performance in the finger tapping test with increasing PBDE level, suggesting an effect of PBDE on motor activity.

Evidence for neurological effects of lower-brominated PBDEs in adult animals is limited. In repeat-exposure neurobehavioral studies, impaired learning and memory were observed in male rats exposed to tetraBDE at ≥0.1 mg/kg/day for 30 days and impaired attention and inhibitory control were observed in male mice exposed to pentaBDE at 26.2 mg/kg/day for 125 days. No exposure-related neurobehavioral changes were observed in rats exposed to pentaBDE at doses ≤17.5 mg/kg/day for 90–125 days or male rats exposed once to pentaBDE doses up to 1.2 mg/kg/day. No exposure-related changes in brain weight and/or histology were observed in animals exposed to lower-brominated PBDEs at doses up to 750 mg/kg/day.

Evidence for neurological effects of decaBDE in adult animals is extremely limited. Decreased anxiety behavior in the elevated-plus maze was observed in male mice exposed to decaBDE for 15 days; however, no exposure-related changes were observed in anxiety behaviors in the light/dark test, in learning or memory in the Morris water maze, or in general neurological behaviors assessed using a functional observation battery. In another study, no changes were observed in open-field behavior of male rats exposed to decaBDE at doses up to 50 mg/kg/day via gavage for 90 days. No changes in brain weight were observed in rats or mice exposed to decaBDE at doses up to 90 or 160 mg/kg/day, respectively, for 15–60 days. No overt signs of neurotoxicity were observed in rats and mice exposed to decaBDE in estimated dietary doses as high as 16,000–19,000 mg/kg/day for 14 days, 8,000–9,000 mg/kg/day for 13 weeks, or 2,550–7,780 mg/kg/day for 103 weeks. Although the high doses and extended exposure durations provided opportunities for the induction and/or development of clinical signs, the study is limited by lack of testing for subtle behavioral changes and neurodevelopmental effects.

Based on available data in humans and animals, it is unclear whether PBDEs affect the adult nervous system.

Immunological and Lymphoreticular Effects. Limited human data regarding potential immunotoxic effects of PBDEs are available. A significant negative association was found between serum concentrations of lower-brominated PBDE and number of circulating lymphocytes in a subset of a cohort of 33 adolescent children from the Netherlands. No effects on pokeweed mitogen-stimulated DNA proliferation or IgG immunoglobulin synthesis were found in human lymphocytes exposed to lower-

brominated PBDEs *in vitro*. Studies of Swedish subjects reported a significantly negative association between serum levels of BDE 47 and levels of protein complement 3, but not with levels of multiple inflammatory markers. In a study of Chinese children, serum levels of BDE 28 and 209 were associated with an increased risk of asthma.

There is limited evidence for impaired immune function in animals following exposure to lower-brominated PBDEs; however, comprehensive immunological evaluations have not been performed on any congener or previously used commercial mixture. The plaque-forming splenic cell antibody response to injected sheep red blood cells was significantly reduced in mice exposed to 72 mg/kg/day pentaBDE for 14 days; single doses as high as 500 mg/kg had no effect. In the same study, exposure to up to 72 mg/kg/day had no effect on natural killer cell (NKC) activity. *In vitro* production of IgG immunoglobulin from pokeweed mitogen-stimulated splenocytes was reduced in mice exposed to 36 mg/kg/day pentaBDE for 14 days. Other 14-day studies in mice found no changes in NKC activity to murine YAC-1 target cells at pentaBDE doses up to 72 mg/kg/day or numbers of splenic and thymic lymphocyte subsets at pentaBDE doses up to 36 mg/kg/day, although 18 mg/kg/day of tetraBDE caused significantly reduced numbers of total lymphocytes and CD4+, CD8+, and CD45R+ subtypes in spleen. In the only intermediate-duration study evaluating immune function, no dose-related changes were observed in antibody-mediated immunity to keyhole limpet hemocyanin (KLH) or phytohemagglutinin (PHA) skin response in mink exposed to pentaBDE at doses up to 0.78 mg/kg/day for 9 weeks.

Histopathological changes in the spleen (hyperplasia, germinal center development) were reported in some studies following intermediate-duration exposure to lower-brominated PBDEs at doses as low as 0.63 mg/kg/day in mink and at 0.45 mg/kg/day in mice. In other studies, no exposure-related changes were observed in spleen, thymus, lymph node, and/or bone marrow tissue histology in rats exposed to lower-brominated PBDEs at doses up to 750 mg/kg/day for 28–90 days. Additionally, no exposure-related changes were observed in the histology of the spleen, thymus, Peyer's patches, or mesenteric lymph nodes in rat dams exposed to pentaBDE at doses up to 25 mg/kg/day via gavage for 70 days prior to mating through PND 21 (~21 weeks).

Exposure to decaBDE at 1,800 mg/kg/day for 28 days did not cause increased pulmonary viral titers of RSV (measured 5 days post-infection) in mice. In rat dams exposed to 300 mg/kg/day from 21 days prior to mating through PND 21, altered T-lymphocyte cell population distribution in the thymus and a significantly reduced response to *in vitro* PHA exposure in cultured lymphocytes were observed. In another study, no dose-related changes were reported for T-cell, B-cell, or macrophage population

distribution in the spleen of rats exposed to decaBDE at doses up to 60 mg/kg/day via gavage for 28 days. In a high-dose study, female mice exposed to decaBDE at 800 mg/kg every other day showed impaired CD4 T-cell function from 4 to 10 months of exposure, compared with controls.

Chronic ingestion of decaBDE caused splenic lesions (hematopoiesis, fibrosis, lymphoid hyperplasia) in rats exposed to ≥1,200 mg/kg/day for 103 weeks. After exposure for 13 weeks, histopathological examinations of spleen, thymus, lymph node, and/or bone marrow tissues showed no effects in rats or mice exposed to decaBDE at doses up 8,000 or 9,500 mg/kg/day. In rat dams exposed to decaBDE at 300 mg/kg/day for 21 days prior to mating through PND 21, lesions of the thymus (thickened thymus capsule, decreased lymphoid tissue in the cortex with adipose tissue replacement, increased medulla size, and obscured corticomedullary junction) and spleen (decreased size and number of lymphoid nodules, thinner lymphatic sheath around arteries, and fibrotic tissue with macrophages in the medulla) were observed.

Evidence from animals suggests that PBDE exposure may cause immune suppression, but data are limited and inconsistent. Additionally, comprehensive immunological evaluations have not been performed and human data are extremely limited. Therefore, currently available information is insufficient to adequately characterize the human immunotoxic potential of PBDEs.

Cancer. In human case-control epidemiological studies, no clear associations have been found between non-Hodgkin's lymphoma risk and exposure to BDE 47 in a group of Swedish men and women including 19 cases and 27 controls, testicular cancer risk and serum PBDE (sum of BDE 47, BDE 99, and BDE 153) in a small group of Swedish men and women including 58 cases and 58 controls, breast cancer risk and adipose concentrations of PBDE (BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and their sum) in a group of women from the San Francisco Bay area of California including 78 cases and 56 controls, breast cancer and BDE 47 in serum in native Alaskan women, thyroid cancer and serum PBDE (BDE 47, BDE 99, BDE 100, BDE 153, and their sum) in participants in a large multicenter clinical trial in the United States that included 104 cases and 208 controls, or prostate cancer and serum levels of BDE 47 in a study involving 208 prostate cancer incident cases and 268 controls in Singaporean males. In a study examining the association between exocrine pancreatic cancer risk and PBDE concentrations in adipose tissue (sum of BDE 28, BDE 47, BDE 66, BDE 100, BDE 99, BDE 85, BDE 154, BDE 153, BDE 138, and BDE 183) in a group of Swedish men and women, PBDE concentrations were significantly higher in the 21 cases compared with the 59 controls. Case-control analysis found that the risk of pancreatic cancer was not significantly increased with lipid PBDE using

median concentration in controls as a cut-off after adjustment for age, sex, and BMI at tissue sampling; however, the increase in risk was significant when the BMI adjustment was performed for the year before tissue sampling (body weight 1 year before tissue sampling obtained by questionnaire).

For most PBDEs, including pentaBDE and octaBDE, animal studies of carcinogenic effects are not available; cancer data on PBDEs in animals are limited to results of studies on commercial decaBDE products. In a bioassay conducted by the National Toxicology Program (NTP), male and female rats were exposed to high purity commercial decaBDE (lots that were 96 or 94–97% pure) in the diet in low doses of 1,120 and 1,200 mg/kg/day, respectively, and high doses of 2,240 and 2,550 mg/kg/day, respectively, for 103 weeks. Male and female mice were similarly exposed to low doses of 3,200 and 3,760 mg/kg/day, respectively, and high doses of 6,650 and 7,780 mg/kg/day, respectively. Incidences of neoplastic nodules in the liver were significantly increased in the male and female rats, although the term neoplastic nodule is poorly defined and understood, and is no longer used by NTP to characterize hepatoproliferative lesions in rats. Incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in the male mice. Slightly elevated incidences of thyroid gland follicular cell adenoma or carcinoma (combined) were additionally observed in exposed male mice, although the increases were not statistically significant. Carcinogenicity was also evaluated in rats that were exposed to 0.01, 0.1, or 1.0 mg/kg/day dietary doses of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for approximately 2 years. No exposure-related neoplastic changes were found, but the power of this study to detect carcinogenic effects is limited by the very low dose levels in comparison to those tested in the NTP bioassay.

The EPA hazard descriptor for decaBDE is “suggestive evidence of carcinogenic potential” based on: (1) no studies of cancer in humans exposed to decaBDE; (2) a statistically significant increase in incidence of neoplastic nodules and a slight increase in incidence of carcinomas (not statistically significant) in the liver of low- and high-dose male rats and high-dose female rats; (3) a significantly increased incidence of hepatocellular adenoma or carcinoma (combined) in male mice at the low dose and marginally increased incidence at the high dose; (4) a nonsignificantly increased incidence of hepatocellular adenoma or carcinoma (combined) in female mice; (5) a slightly greater (but statistically not significant) incidence of thyroid gland adenomas or carcinomas (combined) in dosed male and female mice; (6) a significantly increased incidence in male mice, at both doses, of follicular cell hyperplasia, considered by many as a precursor to thyroid tumors; and (7) an apparent absence of genotoxic potential. DecaBDE has been classified as a Group 3 carcinogen (*not classifiable as to its carcinogenicity to humans*) by the International Agency for Research on Cancer (IARC) based on inadequate evidence of

carcinogenicity in humans and inadequate or limited evidence in experimental animals. The EPA assigns the cancer category Group D (*not classifiable as to human carcinogenicity*) to mono-, di-, tri-, tetra-, penta-, hexa-, octa-, and nonaBDEs and reports "*inadequate information*" to classify the specific congeners 2,2',4,4'-tetraBDE, 2,2',4,4',5-pentaBDE, and 2,2',4,4',5,5'-hexaBDE. The Department of Health and Human Services has not evaluated PBDEs for carcinogenicity. ACGIH has no data regarding cancer classifications for PBDEs.

2.3 MINIMAL RISK LEVELS (MRLs)

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

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

People are environmentally exposed to PBDE mixtures of different congeneric composition than previously used commercial PBDE products. Although the toxicity or potency of environmental mixtures of congeners consequently may be greater or less than that of the commercial PBDE mixtures or individual congeners, there are insufficient mixture toxicity data on which to directly base MRLs for environmental PBDEs. Due to the likelihoods that (1) multiple mechanisms (aryl hydrocarbon receptor [AhR]-receptor-dependent mechanisms, AhR-independent mechanisms, or both) may be involved in health effects induced by PBDEs, (2) different PBDE congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PBDEs with differing

biological activities, as well as to the lack of a suitable approach for quantitatively evaluating joint toxic action from concurrent exposures to PBDEs, PBBs, PCBs, chlorinated dibenzo-p-dioxins (CDDs), and/or chlorinated dibenzofurans (CDFs) in the environment, data from previously used commercial PBDE mixtures and individual congeners were reviewed to develop MRLs for assessing health risks from environmental exposures to PBDEs.

Separate MRLs were derived for lower-brominated PBDEs and decaBDE based on important differences in pharmacokinetics and toxicity of decaBDE compared to lower-brominated PBDEs. The most recent and best available estimates of oral absorption efficiencies for PBDE congeners indicate a range of 10–26% for decaBDE (BDE 209) and 70–85% for tetraBDE (BDE 47), pentaBDE (BDE 99, BDE 100), and hexaBDE (BDE 153, BDE 154) (Chen et al. 2006; Hakk et al. 2002a, 2002b, 2009; Morck and Klasson Wehler 2001; Morck et al. 2003; Örn and Klasson-Wehler 1998; Riu et al. 2008; Sandholm et al. 2003; Sanders et al. 2006a, 2006b; Staskal et al. 2005). Consistent with the higher absorption efficiencies of the lower-brominated congers, the animal toxicity database indicates that toxic effects occur at lower doses following exposure to lower-brominated PBDEs than following exposure to decaBDE. For example, the acute exposure levels required to cause neurobehavioral effects in mice are higher for decaBDE (≥2.22 mg/kg) than penta-, tetra-, and hexaBDE (≥0.8, ≥1, and ≥0.45 mg/kg, respectively) (Eriksson et al. 2001; Gee and Moser 2008; Johansson et al. 2008; Sand et al. 2004; Viberg et al. 2003a, 2003b, 2004a, 2004b).

Inhalation MRLs

Lower-brominated BDEs. Derivation of an acute-duration MRL for lower-brominated BDEs is not recommended at this time due to insufficient information. The inhalation database for acute-duration exposure to PBDEs is essentially limited to a single 14-day unpublished industry-sponsored study of octaBDE in rats (Great Lakes Chemical Corporation 1978). In this study, groups of five male and five female Charles River CD rats were whole-body exposed to dust of an unspecified commercial octaBDE mixture in mean analytical concentrations of 0, 0.6, 3.7, 23.9, or 165.2 mg/m^3 for 8 hours/day for 14 consecutive days. The average mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particles were 3.5 µm and 2, respectively. Study end points included clinical signs (including observations for respiratory distress and nasal and ocular irritation), body weight and food consumption, hematology (5 indices), blood chemistry (5 indices, thyroid hormones not assessed), urinalysis (10 indices), organ weights (5 organs including thyroid/parathyroid), gross pathology, and histology (21 tissues including nasal turbinates, trachea, lungs, and thyroid). The clinical laboratory tests

were limited to rats in the control and two highest dose groups. The histological exams were limited to the control and highest dose groups, except for the liver, which was examined in all groups. Signs of increased respiration rate (rapid breathing) were observed by the end of each exposure period in rats exposed to ≥24 mg/m^3; this effect always disappeared by the following morning. Liver weight was significantly increased and hepatic lesions occurred in rats exposed to ≥3.7 mg/m^3. At 3.7 mg/m^3, the liver lesions consisted of very slight to slight, focal to multifocal cytoplasmic enlargement of the hepatocytes, accompanied by focal acidophilic degeneration of individual to small groups of cells. The liver lesions were similar in the higher dose groups except that the hepatocyte enlargement was multifocal to diffuse in distribution, and there were focal, small to large areas of hepatocellular necrosis present to a very slight to marked degree. There were no exposure-related histological changes in other tissues.

As detailed above, hepatocellular hypertrophy accompanied by some degenerative hepatocellular changes was found following exposure to octaBDE at concentrations ≥3.7 mg/m^3 for 14 days (Great Lakes Chemical Corporation 1978). However, this study is limited by small animal numbers and incomplete evaluation of other end points at lower doses. Additionally, a well-designed 13-week study (Great Lakes Chemical Corporation 2000) found hepatocellular hypertrophy at a higher minimum effect level (16 mg/m^3) than the 14-day study, but no degenerative liver changes. The available information indicates that there is insufficient evidence for considering the hepatic changes as adverse acute effects. More importantly, exposure to ≥16 mg/m^3 caused changes in serum levels of thyroid hormones (decreased T_3, increased TSH) in the 13-week study. Thyroid hormone levels were not determined in the 14-day study. Therefore, due to the lack thyroid hormone data in the 14-day study, as well as the lack of any clear lowest-observed-adverse-effect levels (LOAELs) for the other end points in the 14-day study, particularly at exposures levels below the LOAEL for thyroid effects in the 13-week study, the data are inadequate to derive an MRL for acute-duration exposure.

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

The intermediate-duration inhalation MRL is based on a no-observed-adverse-effect level (NOAEL) of 1.1 mg/m^3 for changes in thyroid hormones in rats that were intermittently exposed to octaBDE for 13 weeks (Great Lakes Chemical Corporation 2000). Calculation of the MRL is detailed below.

The inhalation database for intermediate-duration exposure to PBDEs consists of one well-conducted 13-week study (Great Lakes Chemical Corporation 2000). This is an unpublished industry-sponsored study in which a commercial octaBDE product (bromine content 78.7%) was administered to groups of

10 male and 10 female Crl:CD(SD)IGS BR rats, via nose-only inhalation as a dust aerosol, in measured concentrations of 0 (air only), 1.1, 16, or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks. The mean MMADs in the low to high exposure groups were 2.0, 2.7, and 2.8 μm, and the corresponding mean GSDs were 3.37, 3.72, and 3.01. Clinical and physical signs, body weight, food consumption, and survival were evaluated throughout the study. Ophthalmic, hematology (11 indices), serum chemistry (18 indices), and serum thyroid hormone (TSH, total T_3, and total T_4) evaluations were performed near the end of the exposure period. Urine analyses were not conducted. Comprehensive necropsies, organ weight measurements, and histological examinations (including respiratory tract and thyroid) were performed following exposure termination.

Hepatic, nasal, lung, thyroid, and ovarian effects were observed (Great Lakes Chemical Corporation 2000). The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at ≥16 mg/m^3 and liver weight (absolute and relative) at 202 mg/m^3. Total incidences of centrilobular hepatocellular hypertrophy in the 0, 1.1, 16, and 202 mg/m^3 groups were 1/10, 0/10, 3/10, and 10/10, respectively, in males and 0/10, 0/10, 3/10, and 6/10, respectively, in females; severity was predominantly minimal in affected animals from all groups. The incidence of nasal goblet cell lesions was increased at 202 mg/m^3, but showed no clear dose-related trends for increasing incidence or severity. Total incidences of nasal goblet cell hypertrophy were slightly increased in nasal level II of both sexes at ≥1.1 mg/m^3; respective incidences in the 0, 1.1, 16, and 202 mg/m^3 exposure groups were 4/10 (all minimal), 9/10 (7 minimal, 2 mild), 6/10 (all minimal), and 10/10 (9 minimal, 1 mild) in males, and 2/10 (all minimal), 6/10 (all minimal), 4/10 (all minimal), and 8/10 (all minimal) in females. Nasal goblet cell hypertrophy was also slightly increased in nasal level IV in males at 202 mg/m^3 (4/10, 0/10, 1/10, and 8/10, all minimal severity, not increased in females). Histological changes in the lungs included alveolar histiocytosis and chronic active inflammation that were only clearly increased in incidence at 202 mg/m^3. Total incidences of alveolar histiocytosis at 0, 1.1, 16, and 202 mg/m^3 were 3/10, 5/10, 5/10, and 10/10, respectively, in males, and 0/10, 5/10, 2/10, and 10/10, respectively, in females. Corresponding total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10, and 10/10 in males, and 0/10, 1/10, 1/10, and 10/10 in females. The severity of both lesion types tended to increase from minimal at lower doses to mild/moderate at 202 mg/m^3. Gross lung changes also occurred in both sexes at 202 mg/m^3; these included lung firmness and white discoloration and/or enlargement in the bronchial and/or mediastinal lymph nodes. The lymph node effects correlated with the histological finding of granulomatous inflammation. There were no exposure-related gross or histopathological changes in the spleen, bone marrow, thymus, or other tissues, including thyroid. Thyroid hormone assessments, however, showed exposure-related decreases in mean thyroxine (total T_4) at ≥16 mg/m^3 in

both sexes, and increases in TSH at ≥16 mg/m^3 in males and 202 mg/m^3 in females. The changes were usually statistically significant ($p<0.05$ or $p<0.01$) compared to controls and were considered to be consistent with chemical-induced hypothyroidism. There were no serum T_3 changes. Qualitative histological evaluations of step sections of ovaries showed an absence of corpora lutea in 3/10 females exposed to 202 mg/m^3, compared to 0/10 in the control and lower exposure groups. This 30% incidence was interpreted to be a treatment-related effect because an absence of corpora lutea was considered unusual in rats at 20 weeks of age.

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

$$NOAEL_{ADJ} = 1.1 \text{ mg/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.196 \text{ mg/m}^3$$
$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.196 \text{ mg/m}^3 \times 2.7 = 0.53 \text{ mg/m}^3$$

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

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

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

Oral MRLs

Lower-brominated Diphenyl Ethers

- An MRL of 0.00006 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to lower-brominated diphenyl ethers.

The acute oral MRL is based on a LOAEL of 0.06 mg/kg/day for endocrine effects in rat dams and reproductive and neurobehavioral effects in F1 offspring exposed to 2,2',4,4',5-pentaBDE (BDE 99) on GD 6 via gavage (Kuriyama et al. 2005, 2007; Talsness et al. 2005). The MRL was estimated by dividing the 0.06 mg/kg LOAEL by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability).

In a series of reports, pregnant rats were exposed to BDE 99 at 0, 0.06, or 0.3 mg/kg via gavage on GD 6 (Kuriyama et al. 2005, 2007; Talsness et al. 2005). Serum thyroid hormones levels (T_3, free-T_3, T_4, free-T_4) were analyzed in dams and pups on PNDs 1, 14, and 22 (Kuriyama et al. 2007). Male and female offspring were evaluated for emergence of physical landmarks and reflexes and for open-field behavior on PNDs 36 and 71 (Kuriyama et al. 2005). Twelve male offspring per dose group were sacrificed at PND 140, and the thymus, spleen, liver, testis, epididymis, seminal vesicle, and ventral prostate were weighed. The right testis and caudal epididymis were retained for spermatid and sperm counts and morphology, respectively. Additionally, blood was collected for analysis of testosterone and LH levels (Kuriyama et al. 2005). Similarly, 10 F1 females per group were sacrificed ~PND 90 for histological evaluation of the ovary, uterus, and vagina. Ovarian follicles were counted in 10 ovaries from each group, and 1 ovary from 1 female offspring in each group was analyzed by transmission electron microscopy (Talsness et al. 2005). Fertility was assessed in F1 males and females (20/group) mated to unexposed partners. The uterine and F2 fetal weights and the number of implantations, resorptions, and fetuses were determined. The F2 fetuses were examined for external anomalies and when present, the fetuses were stained and examined for skeletal anomalies (Kuriyama et al. 2005; Talsness et al. 2005). In a separate group of F1 males, male sexual behavior was assessed in 20 males/group at ~PND 160 (Kuriyama et al. 2005).

Serum T4 levels were significantly decreased by 23–33% in the 0.06 and 0.3 mg/kg dams, sacrificed on PND 1. No changes were observed in T_3, free-T_3, or free-T_4 at PND 1 or any thyroid hormone levels at PND 22 in dams. In pups, no dose-related changes were observed at PND 1 or 14. At PND 22, serum T_4 was significantly decreased by 19–22% in F1 males and females and serum free-T_4 was significantly

decreased by 24% in F1 females exposed to 0.3 mg/kg (Kuriyama et al. 2007). For F1 development of physical landmarks and reflexes, no exposure-related effects were observed for the age at fur development or eye opening, testes descent, or the ability to master the rotating rod test. However, significant delays in the eruption of incisors in F1 pups and the development of the cliff-drop aversion reflex were observed in F1 males in the 0.3 mg/kg group, compared with controls. During a 24-hour observation of open-field activity, total activity, time spent active, duration of activity per active phase, and total activity per active phase were all significantly increased in F1 offspring on PND 36 in the 0.3 mg/kg group, compared with controls. On PND 71, the increased total activity and time spent active persisted in the 0.3 mg/kg group, and was also significantly increased in the 0.06 mg/kg group.

In F1 males sacrificed on ~PND 140, no exposure-related changes were observed in body weight, liver weight, or thymus weight; however, absolute spleen weight was significantly increased by 9% in the 0.06 and 0.3 mg/kg groups, and relative spleen weight was significantly increased by 12% in the 0.06 mg/kg group. Compared with controls, significantly altered male reproductive organ weights at PND 140 included a 10 and 11% decrease in relative testes and epididymis weight, respectively, in the 0.3 mg/kg group and a 5% decrease in relative epididymis weight in the 0.06 mg/kg group; no significant changes were observed in absolute organ weights. In both dose groups, the number of spermatids and sperm and daily sperm production were significantly decreased, compared with controls. No exposure-related effects were observed for sperm morphology. No changes were observed in serum testosterone or LH levels. Despite sperm alterations, no significant exposure-related effects were observed in male reproductive function or the majority of male sexual behaviors. The only significantly altered male sexual behavior was a 32% decrease in the percent of males with two or more ejaculations.

In F1 females sacrificed on ~PND 90, no statistically significant, exposure-related histological changes were observed at the light microscopic level in the ovary, uterus, or vagina of female offspring, and no exposure-related effects were observed in the number of ovarian follicles. However, multiple ultrastructural changes were noted in the ovaries of PND 90 female offspring from dams exposed to 0.06 or 0.3 mg/kg, including destruction of the surface of the serosal epithelial cells, necrosis, and numerous vesicular structures with dense granular material within the cytoplasm. Additional changes observed in the 0.3 mg/kg group included degenerative changes and aggregates of small and large vesicles filled with homogeneously dense granular material in the cytoplasm and clumped chromatin within the condensed nucleus. No exposure-related changes were found for F1 female pregnancy rate, total implantation sites, implantation sites/dam, F2 fetuses/gravid dam, or total number of live F2 fetuses. However, the resorption rates were 12 and 15% in the 0.06 and 0.03 mg/kg groups, respectively,

compared with the control rate of 9%. Statistics were not reported; however, the resorption rates in the exposed rats were also reportedly increased compared with historical controls (average control resorption rate=5.4%, with rates up to 10% considered to be within normal limits). In addition, the percentage of litters with resorptions was higher in the exposed females, being 47% in the control group and 69% and 72% in the 0.06 and 0.3 mg/kg groups, respectively. In F2 pups, mean fetal weight was significantly increased (by 5%) in the 0.06 mg/kg group, but not in the 0.3 mg/kg group, compared with controls. Three fetuses from different litters in the 0.3 mg/kg/day group showed skeletal anomalies (tail, skull, vertebrae); however, this incidence of anomalies in 3/18 litters is not significantly elevated compared with the control incidence of 0/19 (Fisher's exact test, performed for this review).

Collectively, these studies indicate a LOAEL of 0.06 mg/kg, the lowest dose tested, for endocrine effects in F0 dams (decreased serum T_4), reproductive effects in F1 adult offspring (impaired spermatogenesis, ultrastructural changes in ovaries, increased resorptions in F1 females mated to unexposed males) and neurobehavioral effects in F1 adult offspring (increased activity in open field). No NOAEL was identified.

Data from other several acute-duration studies of PBDEs support the selection of the co-critical effects observed at the LOAEL of 0.06 mg/kg:

- Numerous studies reported reduced serum T_4 levels in adult, nonpregnant mice and rats following acute exposure to commercial pentaBDE mixtures (Bromkal 70, Bromkal 70-5 DE, DE-71), the commercial octaBDE mixture DE-79, or 2,2',4,4'-tetraBDE (BDE 47). Significant reductions of 19–92% have been reported following gavage exposure at doses ≥10 and ≥0.8 mg/kg/day in rats and mice, respectively, for 1–14 days (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998, 2002; Hallgren et al. 2001; Hoppe and Carey 2007; Richardson et al. 2008; Stoker et al. 2004, 2005; Zhou et al. 2001).

- In a companion study to the critical studies described above, pregnant rats (8/group) were administered BDE 47 (98% purity) at 0, 0.14, or 0.7 mg/kg via gavage in peanut oil vehicle on GD 6 (Talsness et al. 2008). As observed in pentaBDE-exposed F1 females, ultrastructural changes (accumulation of vesicular structures with homogeneously dense granular material in the cytoplasm of the stromal cells, large vacuoles) were observed in the ovaries of F1 females from both dose groups on PND 100. No exposure-related changes were observed in F1 female fertility or F2 litter parameters. F1 males were not evaluated for developmental reproductive effects following tetraBDE exposure.

- Alterations in open-field activity have been consistently reported in mice exposed to pentaBDE (BDE 99) at doses ≥0.8 mg/kg on PND 3 or 10 and evaluated at 2–8 months of age, characterized by decreased activity during the first 20-minute period of a 1-hour session, followed by increased activity during the third 20-minute period (Eriksson et al. 2002b, 2006; Fischer et al. 2008; Sand et al. 2004; Viberg et al. 2002, 2004a, 2004b). Several other 1-day exposure studies reported

similar findings in rats and mice following exposure to various lower-brominated PBDEs. Decreased spontaneous activity and/or impaired habituation were observed in rats exposed to BDE 99 at 8 mg/kg on PND 10, mice exposed to 2',4,4',5,5'-hexaBDE (BDE 153) at ≥0.45 mg/kg on PND 10, mice exposed to BDE 47 at 10.5 mg/kg on PND 10, mice exposed to 2,2',3,4,4',5',6-heptaBDE (BDE 183) at 15.2 mg/kg on PND 3, and mice exposed 2,2',3,4,4',5,5',6-octaBDE (BDE 203) at 16.8 mg/kg on PND 3 or 10 (Eriksson et al. 2001; Viberg et al. 2003a, 2005, 2006). Increased vertical activity was significantly increased at 4 months, but not at 2 months, in mice exposed to BDE 47 at ≥1 mg/kg on PND 10; no changes were observed in horizontal activity or habituation (Gee and Moser 2008).

Additional information on the derivation of the acute-duration oral MRL for lower-brominated BDEs is provided in Appendix A.

- An MRL of 0.000003 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to lower-brominated BDEs.

The intermediate oral MRL is based on a minimal LOAEL of 0.001 mg/kg/day for a 34% reduction in serum testosterone in male rats exposed to 2,2',4,4'-tetraBDE (BDE 47) for 8 weeks via gavage (Zhang et al. 2013b). The MRL was estimated by dividing the 0.001 mg/kg/day minimal LOAEL by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability).

Groups of 20 male rats were exposed to BDE 47 (≥98.7%) at 0, 0.001, 0.03, or 1 mg/kg/day via gavage in corn oil 6 days/week for 8 weeks (Zhang et al. 2013b). Twenty-four hours after the final treatment, rats were sacrificed. Testes were fixed for histological analysis and labeling of apoptotic cells or prepared for analysis of sperm production. Daily sperm production was estimated by dividing the total number of mature spermatids per testis by 6.1 (i.e., the days of the seminiferous cycle that the spermatids are present in the seminiferous epithelium). Testicular samples were examined for reactive oxygen species (ROS) and mRNA expression of apoptosis related proteins (ser15, ser473, p53, PTEN, AKT, BAD, caspase 3, FAS, FASL). Serum levels of E2, FSH, LH, and testosterone were measured. Histological examination of the testes showed a significant increase in the number of multinucleated giant cells (arising from spermatocytes that aborted meiosis) at ≥0.03 mg/kg/day and abundant vacuolar spaces in the seminiferous epithelium at 1 mg/kg/day (quantitative data not reported). Additionally, the number of apoptotic cells was significantly increased by 1.9- and 3-fold in the testes of rats from the 0.03 and 1 mg/kg/day groups, respectively, and the mRNA levels of several apoptosis genes were elevated in a dose-related manner. Daily sperm production was significantly decreased by 23% in the 1 mg/kg/day group, compared with controls. Serum testosterone was significantly decreased by ~34, 53, and 62% in the 0.001, 0.03, and 1 mg/kg/day groups, respectively, compared with controls. No exposure-related changes were observed

in serum E2, FSH, or LH levels. Testicular ROS levels were significantly elevated at 1 mg/kg/day, compared with controls. A minimal LOAEL of 0.001 mg/kg/day was determined for this study based on the 34% decrease in serum testosterone. The change in testosterone is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, this statistically significant reduction in serum testosterone is considered an early indication of damage to the male reproductive system, considering the additional effects observed at ≥0.03 mg/kg/day (histological lesions in testes, sperm effects).

One additional rat study and a mouse study report histopathological changes in the testes following intermediate-duration exposure to tetraBDE at ≥0.03 mg/kg/day; neither study evaluated serum testosterone levels (Huang et al. 2015; Wang et al. 2013). In the rat study, a NOAEL of 0.001 mg/kg/day and a LOAEL of 0.03 mg/kg/day were identified for increased epithelial thickness and spermatocyte apoptosis in the testes of males exposed to BDE 47 for 8 weeks via gavage (Huang et al. 2015). In the mouse study, a NOAEL of 0.0015 mg/kg/day and a LOAEL of 0.045 mg/kg/day were identified for germ cell loss and increased apoptosis in the testes of males exposed to BDE 47 for 30 days via gavage (Wang et al. 2013).

No other study evaluated testicular histopathology following exposure to BDE 47. Following intermediate exposure to other congeners, no changes in testicular histology were observed in rats exposed to commercial pentaBDE mixtures (Bromkal 70-5 DE, DE-71) at gavage doses up to 250 mg/kg/day for 15–28 days (Becker et al. 2012; Oberg et al. 2010), commercial penta- or octaBDE mixtures (DE-71, unspecified octa mixture) at dietary doses up to 750 mg/kg/day for 28–90 days (IRDC 1976, 1977; WIL Research Laboratories 1984), or a pentaBDE mixture (52.1% pentBDE, 44.2% decaBDE, 0.4% octaBDE) at dietary doses up to 20 mg/kg/day for 70 days (Ernest et al. 2012). However, testicular apoptosis was not evaluated in any of these studies.

No other study evaluated serum testosterone levels following exposure to BDE 47. However, as observed with exposure to BDE 47, acute exposure to 0.06 or 1.2 mg/kg of 2,2',4,4',5-pentaBDE (BDE 99) also led to a significant 40–45% decrease in serum testosterone levels in rats (Alonso et al. 2010). No other studies evaluated this end point following exposure to single congeners. Other studies evaluating serum testosterone levels after intermediate-duration exposure to lower-brominated PBDEs mixtures (DE-71, dietary PBDE mixture described above) did not report exposure-related decreases (Becker et al. 2012; Ernest et al. 2012; Stoker et al. 2005). These data suggest that the individual congeners, BDE 47 and BDE 99, which have been identified as two of the most abundant congeners for human exposure (Harrad

et al. 2004; Lorber 2008; Wong et al. 2013), may have a greater capacity to alter serum testosterone levels than PBDE mixtures.

One-generation studies of BDE 47 reported developmental effects at ≥0.03 mg/kg/day, including:

- Impaired spatial learning in the Barnes maze in PNW 8 offspring of mouse dams fed tetraBDE-dosed cornflakes from pre-mating day 28 through PND 21 (Koenig et al. 2012).
- Decreased center-field activity in an open field (indicating increased anxiety) in PND 60 female offspring from mouse dams fed tetraBDE-dosed cornflakes from pre-mating day 28 through PND 21 (Ta et al. 2011).
- Decreased pre-weaning weight, decreased pup vocalizations on PNDs 8–10, and decreased sociability on PND 72 in female offspring of mouse dams exposed to tetraBDE via gavage from pre-mating day 28 through PND 21 (Woods et al. 2012).

Additional information on the derivation of the intermediate-duration oral MRL for PBDEs is provided in Appendix A.

A chronic-duration oral MRL was not derived for lower-brominated PBDEs due to insufficient data. Only one chronic study of PBDEs other than high-purity decaBDE has been conducted (Kociba et al. 1975; Norris et al. 1975a). In this study, Sprague-Dawley rats (25/sex/dose level) were fed a 77.4% pure commercial decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for approximately 2 years. Evaluations that included clinical signs, body weight, food consumption, hematology, clinical chemistry, urine indices, and comprehensive histological examinations showed no exposure-related effects. The highest NOAEL is 1 mg/kg/day (highest tested dose), but this NOAEL is not appropriate for MRL estimation due to insufficient sensitivity of the study. In particular, using the NOAEL of 1 mg/kg/day and an uncertainty factor of 100, a chronic oral MRL based on this study would be 5 times higher than the 0.002 mg/kg/day intermediate MRL. A similar pattern was observed for thyroid effects in the study used to derive the acute-duration oral MRL (Zhou et al. 2001) as summarized above. Due to the insufficiencies of the chronic data for MRL derivation, the intermediate oral MRL could be used as a value for chronic exposure.

Decabromodiphenyl Ether

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

The MRL was derived based on a NOAEL of 1.34 mg/kg for neurobehavioral effects in 2–4-month-old mice following a single exposure to 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209) on PND 3 (Buratovic et al. 2014; Johansson et al. 2008). The MRL was estimated by dividing the 1.34 mg/kg NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

In the first study (Johansson et al. 2008), neonatal male mice (3–4 litters/group) were exposed to a single dose of BDE 209 (98% purity) at 0, 1.34, 2.22, 13.4, or 20.1 mg/kg via gavage in a 20% fat emulsion vehicle (1:10 mixture egg lecithin and peanut oil) on PND 3 (Johansson et al. 2008). Mice were observed for clinical signs of toxicity and body weight was measured at PND 3 and PNW 4. Spontaneous motor behavior (locomotion, rearing, total activity) was evaluated in an open field test at 2 months (10 mice/group) and at 4 months (16 mice/group). Motor activity was measured during a 60-minute period, divided into three 20-minute intervals. Nicotine-induced behavior was evaluated at 4 months following single subcutaneous injections of 80 µg nicotine/kg (8/group) or 10 mL 0.9% NaCl/kg (8/group). Anxiety was assessed at 4 months using the elevated plus maze. No clinical signs of toxicity or body weight effects were observed. At 2 months, significantly decreased locomotion, rearing, and total activity were observed during the first 20-minute interval of the open field assessment in mice exposed to ≥2.22 mg/kg, compared with controls. However, during the third 20-minute interval, when activity should decrease due to habituation, locomotion, rearing, and total activity were significantly increased in mice exposed to ≥13.4 mg/kg. None of the end points measured were significantly altered in mice exposed to 1.34 mg/kg. At 4 months, significantly decreased locomotion, rearing, and total activity were observed during the first interval of the open field assessment in mice exposed to ≥2.22 mg/kg, compared with controls. During the third interval, significantly increased locomotion, rearing, and total activity were observed in mice exposed to ≥2.22 mg/kg. Additionally, total activity, but not rearing or locomotion, was significantly decreased during the first 20-minute interval in the 1.34 mg/kg group; no significant changes were observed during the third interval in the 1.34 mg/kg group. Statistical analysis shows that habituation ability declined in mice exposed to ≥2.22 mg/kg/day when tested at 4 months of age, compared with 2 months of age. At 4 months, nicotine exposure caused significantly decreased activity during the first interval in mice exposed to ≥13.4 mg/kg, compared with saline-injected mice from the same decaBDE exposure group. This finding is the opposite of the expected increase in activity due to nicotine exposure, which was observed in controls and lower dose decaBDE groups. During the third interval, mice exposed to ≥13.4 mg/kg and nicotine showed impaired habituation. No exposure-related effects were observed in the elevated plus maze assessment. A NOAEL of 1.34 mg/kg and a LOAEL of 2.22 mg/kg were determined for the nonhabituating profile (i.e., decreased activity early in the test period and increased activity late in the test period). The singular finding of decreased total activity

during the first 20-minute interval at 4 months in the 1.34 mg/kg group was not considered sufficient to establish a LOAEL of 1.34 mg/kg. The nonhabituating profile, which is a common effect observed with developmental PBDE exposure (Eriksson et al. 2002b, 2006; Fischer et al. 2008; Sand et al. 2004; Viberg et al. 2002, 2003a, 2004a, 2004b), was considered to be a stronger basis for a NOAEL/LOAEL determination.

In the second study (Buratovic et al. 2014), neonatal male mice (6 litters/group; 31–40 males and 23–34 females per group) were administered 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209, >95% purity) at doses of 0, 1.34, 5.76, or 13.4 mg/kg via gavage in a 20% fat emulsion vehicle (1:10 mixture egg lecithin and peanut oil) on PND 3. Mice were observed for clinical signs of toxicity and body weight changes throughout the study (no further details were provided). Spontaneous motor behavior (locomotion, rearing, total activity) was evaluated in an open field at 2 months (18/sex/group). Motor activity was measured during a 60-minute period, divided into three 20-minute intervals. Directly after spontaneous motor evaluation, 9/sex/group were injected with a cholinergic agent (0.25 mg/kg paraoxon in males, 80 µg/kg nicotine in females), while the other 9/sex/group were injected with 0.9% saline, for evaluation of cholinergic-induced locomotion. At 4 months, spontaneous behavior was assessed again in the saline-injected animals only (9 males/group at all doses and 9 females/group in the control and high-dose group only). Learning and memory was assessed using the Morris water maze at 5 and 7 months in 13–15 males from the 0, 5.76, and 13.4 mg/kg groups only (the same mice were evaluated at each time point). In the spontaneous activity assessment, a dose-related decrease in locomotion, rearing, and total activity was observed during the first 20 minutes of open field testing in a novel environment at 2 months. Decreases were significant at all doses tested in both sexes; however, findings were only dose-related for total activity. However, during the third 20-minute interval, when activity should decrease due to habituation, locomotion, rearing, and total activity were significantly increased in males and females at ≥5.76 mg/kg. At 2 months, cholinergic agents caused decreased activity during the first interval in mice exposed to ≥5.76 mg/kg, compared with saline-injected mice from the same decaBDE exposure group. This finding is the opposite of the expected increase in activity due to paraoxon or nicotine exposure, which was observed in controls and low-dose decaBDE groups. During the third interval, mice exposed to ≥5.76 mg/kg and cholinergic agent showed impaired habituation. At 4 months, total activity during the first 20 minutes was still significantly decreased at all doses in males, and locomotion and rearing were significantly decreased in males in the mid- and high-dose groups only; all three parameters were significantly decreased in high-dose females (other doses not evaluated). All three parameters were significantly increased in high-dose males and females during the third 20-minute period, indicating decreased habituation; locomotion and rearing were also slightly, but significantly, increased in mid-dose

males. In the Morris water maze, initial learning was comparable between exposed and control mice at 5 and 7 months. However, latencies to find the escape platform during the reversal learning phase (learning to find the escape platform in a new location after initial training) were significantly longer in mid- and high-dose males at 5 and 7 months (other exposure groups not assessed). A NOAEL of 1.34 mg/kg and a LOAEL of 5.76 mg/kg were determined for the nonhabituating profile (i.e., decreased activity early in the test period and increased activity late in the test period). Similar to the Johansson et al. (2008) study, the finding of decreased total activity during the first 20-minute interval at 2 and 4 months in the 1.34 mg/kg group was not considered sufficient to establish a LOAEL of 1.34 mg/kg. The nonhabituating profile was considered to be a stronger basis for a NOAEL/LOAEL determination, and additional neurological effects (impaired learning, altered response to cholinergic agents) support a LOAEL of 5.76 mg/kg.

A similar study supports the LOAEL of 2.22 mg/kg for altered neurobehavior in developmentally exposed mice. Decreased spontaneous activity and impaired habituation were observed in 2- and 6-month-old mice exposed to BDE 209 at doses ≥2.22 mg/kg on PND 3, which was the lowest dose tested (Viberg et al. 2003b). These effects were not observed if exposure was on PND 10 or 19 at doses up to 20.1 mg/kg (Viberg et al. 2003b). Additionally, decreased spontaneous activity was observed in 2-month-old rats following exposure to BDE 209 doses ≥6.7 mg/kg on PND 3 (lowest dose tested) (Viberg et al. 2007). At 20.1 mg/kg, impaired habituation and decreased nicotine-induced behavior were also observed. This nonhabituating behavior profile (i.e., decreased activity early in the test period and increased activity late in the test period) is consistent with neurobehavioral alterations observed following early postnatal exposure to lower-brominated PBDEs and has been reported in adult mice neonatally exposed to certain PCB congeners (see the Acute MRL Worksheet for lower-brominated PBDEs for more details).

Additional neurodevelopmental effects observed in mice following acute exposure to BDE 209 from PND 2 to 15 at 20 mg/kg/day via micropipette include delayed ontogeny of reflexes, increased locomotion in males at PND 70, and learning impairment and impulsivity at 16 months, but not at 3 months (Rice et al. 2007, 2009). In rats, impaired learning was observed in Morris water maze in PND 25 rat offspring of dams exposed to BDE 209 from GD 1 to 14 at doses ≥30 mg/kg/day via gavage (Chen et al. 2014).

Additional information on the derivation of the acute-duration oral MRL for BDE 209 is provided in Appendix A.

- An MRL of 0.0002 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to decabromodiphenyl ether.

The MRL was derived based on a minimal LOAEL of 0.05 mg/kg/day for a 12% increase in serum glucose in adult rats exposed to 2,2′,3,3′,4,4′,5,5′,6,6′-decabromodiphenyl ether (BDE 209) for 8 weeks via gavage (Zhang et al. 2013a). The MRL was estimated by dividing the 0.05 mg/kg/day LOAEL by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability).

Groups of 10 male rats were exposed to BDE 209 at 0, 0.05, 1, or 20 mg/kg/day daily via gavage in corn oil for 8 weeks (Zhang et al. 2013a). Rats were observed for clinical signs of toxicity and body weights were measured every 3 days. Rats were fasted for 24 hours after the final gavage treatment, and then sacrificed. Body weights and heart, spleen, lung, kidney, and liver weights were recorded. Blood was collected for clinical chemistry analysis (serum total cholesterol, triglycerides, glucose, insulin, and TNF-α) and determination of plasma markers of oxidative stress (malondialdehyde [MDE], reduced glutathione [GSH], and superoxidase dismutatase [SOD]). Liver samples from three rats in the control and low-dose (0.05 mg/kg/day) groups were collected for microarray analysis (Affymetrix GeneChip), and gene ontogeny category, pathway, gene-act-network, and gene co-expression analyses were conducted. Quantitative real-time-polymerase chain reaction (qPCR) was performed to quantitate gene expression to validate the gene expression data obtained from microarray analysis. No clinical signs of toxicity or body weight effects were observed. The relative liver weight was significantly decreased at 1 and 20 mg/kg/day by 9% (absolute liver weights were not reported). No changes were observed in relative weights of heart, spleen, lung, or kidney. No exposure-related changes were reported in serum cholesterol or triglyceride levels. Serum glucose levels were significantly increased by 12, 18, and 21% in the 0.05, 1, and 20 mg/kg/day groups, compared with controls. Serum insulin was significantly decreased by 50–60% at 1 and 20 mg/kg/day. Subsequent to this finding, the pancreas was evaluated histologically. Consistent with the insulin findings, morphological changes were seen at 1 and 20 mg/kg/day, including blurred boundaries among pancreatic islet cells (quantitative data not reported). Plasma SOD activity was significantly decreased in all exposed groups and plasma GSH was significantly decreased at 1 and 20 mg/kg/day. Serum TNF-α was significantly increased at 1 and 20 mg/kg/day. Additionally, decaBDE induced 1,257 liver gene transcript changes, and 18 canonical pathways were significantly enriched. Four of them were involved in immune diseases, including autoimmune thyroid disease, graft-versus-host disease, allograft rejection, and T1DM. Subsequently, gene act network and gene coexpression network found that some major histocompatibility complex molecules and TNF-α

were involved in the T1DM pathway. A minimal LOAEL of 0.05 mg/kg/day was determined for this study based on the 12% increase in serum glucose levels. The change in glucose is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, the increase in serum glucose is considered to be part of a spectrum of effects indicative of altered insulin homeostasis and toxicity to the pancreas, including decreased serum insulin and morphological changes in pancreatic islet cells observed at ≥1 mg/kg/day following decaBDE exposure.

The relevance of these findings to human health is uncertain. An analysis of cross-sectional NHANES data showed a significant increase in risk of diabetes associated with serum concentrations of BDE 153 (but not other congeners), although the risk was higher with exposure to 50–75th percentile BDE 153 concentrations than >75th percentile BDE 153 concentrations (Lim et al. 2008). Serum BDE 153 concentrations (but not BDE 28, BDE 47, BDE 85, BDE 99, BDE 100, or BDE 154) were also shown to be significantly associated with increased odds of developing gestational diabetes in a cohort of 258 pregnant women (Smarr et al. 2016). However, other cross-sectional and prospective studies found no relationship between serum PBDE concentrations and diabetes in an adult cohort from Wisconsin (Turyk et al. 2015), an elderly cohort in Finland (Airaksinen et al. 2011), or an elderly cohort in Sweden (Lee et al. 2011).

Only one other animal study evaluated the pancreas following decaBDE exposure. In rats exposed to BDE 209 via gavage for 28 days at doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day, slight or moderate insulitis was observed in the Langerhan's islets of the "majority of samples," but findings were not exposure-related (Van der ven et al. 2008a). Similarly, no exposure-related effects were observed for serum glucose levels (Van der ven et al. 2008a). The only other study evaluating serum glucose levels after decaBDE exposure instead reported reduced serum glucose levels in male rats exposed to 20 mg/kg/day of a dietary PBDE mixture containing 52.1% pentaBDE (DE-71), 44.2% decaBDE (BDE 209), and 0.4% octaBDE (DE-79) for 70 days (Ernest et al. 2012). The observed decreased glucose levels could be due to the pentaBDE component, as male rats exposed to pentaBDE at doses of 0.27–200 mg/kg/day for 28 days also showed decreased glucose levels; the study authors did not report the lowest dose at which glucose levels were significantly lower in male rats, but they reported a BMD_{10RD} of 179.55 mg/kg/day and a $BMDL_{10RD}$ of 66.7 mg/kg/day (Van der ven et al. 2008b). Other effects occurred at doses 4–40-fold higher than the observed pancreatic and related effects:

- A LOAEL of 2 mg/kg/day was identified for transient histopathological effects in the liver of male offspring and kidney of female offspring of rat dams exposed to BDE 209 from GD 10 to PND 21 (no NOAEL identified) (Fujimoto et al. 2011).

- A LOAEL of 10 mg/kg/day was identified for hepatocytic swelling in the liver, vacuolization in the interstitial cells of testes, and sperm damage in PND 71 male offspring of mouse dams exposed to BDE 209 from GD 0 to 17 (no NOAEL identified) (Tseng et al. 2008, 2013).

- A LOAEL of 20 mg/kg-day was identified for decreased anxiety in mice treated with BDE 209 by daily gavage for 15 days (no NOAEL identified) (Heredia et al. 2012).

- A LOAEL of 20.1 mg/kg/day was identified for altered hippocampal electrophysiology in rats exposed to BDE 209 on GD 1 to PND 41, PNDs 1–21, or PNDs 22–41 (no NOAEL identified) (Xing et al. 2009).

Additional information on the derivation of the intermediate-duration oral MRL for decaBDE is provided in Appendix A.

No MRL was derived for chronic-duration oral exposure to decaBDE. Only one chronic study of high-purity decaBDE has been conducted. In this study, F344 rats and B6C3F1 mice (50/sex/group per species) were administered a commercial decaBDE product (94–97% pure) in the diet for 103 weeks (NTP 1986). Calculated dietary doses based on body weight and food intake were 0, 1,120, or 2,240 mg/kg/day for male rats; 0, 1,200, or 2,550 mg/kg/day for female rats; 0, 3,200, or 6,650 mg/kg/day for male mice; and 0, 3,760, or 7,780 mg/kg/day for female mice. Animals were examined daily for clinical signs. Body weights and food consumption were measured throughout the study, and comprehensive gross and histological examinations were performed on all animals in all dose groups, including those that were moribund or died during the study. No hematology, clinical chemistry, or urine indices or thyroid hormone levels were evaluated. Liver degeneration and thrombosis were significantly ($p<0.05$) increased in male rats at 2,240 mg/kg/day; respective incidences in the control, low, and high dose groups were 13/50, 19/50, and 22/50 for degeneration and 1/50, 0/50, and 9/50 for thrombosis. The thrombosis was characterized by a near total occlusion of a major hepatic blood vessel by a dense fibrin coagulum. Neoplastic nodules in the liver were significantly increased in a dose-related manner in males exposed to doses ≥1,120 mg/kg/day and in females exposed to 2,550 mg/kg/day. However, no treatment-related increases were observed in the incidence of hepatocellular carcinomas. Other effects in exposed rats included fibrosis of the spleen, lymphoid hyperplasia of the mandibular lymph nodes, and acanthosis of the forestomach at 2,240 mg/kg/day. In mice, histopathological changes occurred in males exposed to 3,200 mg/kg/day, including centrilobular hypertrophy and granulomas in the liver and follicular cell hyperplasia in the thyroid. An MRL was not derived because the lowest tested dose, 1,120 mg/kg/day in male rats, is a LOAEL for a liver lesion (neoplastic nodules) that is precancerous and associated with thrombosis in the same tissue.

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 PBDEs. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

PBDEs are classes of brominated hydrocarbons that were previously used as flame retardant additives in plastics, textiles, and other materials. Production of PBDEs began in the 1970s and has continued until recently. PentaBDE and octaBDE mixtures were voluntarily withdrawn from the U.S. marketplace by their manufacturers at the end of 2004; however, the manufacture and use of decaBDE continued past that date (EPA 2010). In December of 2009, the two remaining U.S. producers of decaBDE and the largest U.S. importer of this product announced commitments to phase out manufacture and importation of decaBDE for most uses in the United States by December 31, 2012, and to end manufacture and import for all uses by the end of 2013 (EPA 2013j). Although PBDEs are no longer produced or used, concern continues to exist for health effects of PBDEs due to evidence that PBDE congeners have become ubiquitously distributed in the environment and are present in tissues and breast milk of the general population (EPA 2010; Meijer et al. 2008; Park et al. 2011; Rawn et al. 2014; Schecter et al. 2010). PBDEs comprise 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 PBDEs (monobrominated through decabrominated), each containing one or more isomers. PBDEs are structurally similar when viewed in one dimension, differing only in the ether linkage between the two phenyl rings in PBDEs, but the oxygen bridge confers three-dimensional conformational differences that can influence toxicological properties. Consequently, on the basis of chemical structure, it cannot be assumed that the health effects of PBDE congeners are necessarily similar. Reviews on the health effects and other aspects of PBDEs include those by Bellinger (2013), Darnerud et al. (2001), de Boer et al. (2000a), de Wit (2002), Dingemans et al. (2011), EPA (2008a, 2008b, 2008c, 2008d), Gill et al. (2004), Hardy (1999, 2002a, 2002b), Hardy et al. (2009), Markowski (2007), McDonald (2002), Rahman et al. (2001), Silberhorn et al. (1990), and WHO (2006). Discussions of health effects are divided into lower-brominated congeners and decaBDE due to important differences in pharmacokinetics and toxicity of decaBDE compared to lower-brominated PBDEs. Toxicity data for previously used

PBDE mixtures as well as individual PBDE congeners are included in this profile, with mixtures being categorized by their most prominent congener (see Table 4-3, Physical and Chemical Properties of Technical PBDE Mixtures). Using current health effects evaluation procedures, toxicity data for individual congeners may over- or underestimate the actual health risk of PBDE mixtures because congeners vary in toxic potency and may be influenced by other congeners in an additive, less-than-additive, or more-than-additive way. It is also important to recognize that the PBDEs to which people may be exposed may be different from the original PBDE source because of possible changes in congener composition resulting from differential partitioning and transformation in the environment and/or differential biological metabolism and retention.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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 PBDEs (Bahn et al. 1980; Brown et al. 1981; Chanda et al. 1982; Landrigan et al. 1979; Rosenman et al. 1979; Stross et al. 1981). These people are believed to have been exposed predominantly 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. The highest NOAEL and all LOAEL values from each reliable inhalation study of health effects end points in each species and duration category for PBDEs are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.1 Death

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

No deaths occurred in groups of five male and five female rats that were chamber-exposed to pentaBDE aerosol (compound dissolved in corn oil), octaBDE dust, or decaBDE dust in concentrations as high as 200,000, 60,000, or 48,200 mg/m^3, respectively, for 1 hour and observed for the following 14 days (IRDC 1974, 1975a, 1975b). Confidence in these studies is limited by a lack of control data. There was no mortality in rats that were exposed to dusts of commercial octaBDE products at concentrations of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978) or $\leq$202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000).

Table 3-1 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation

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

Table 3-1 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
2	Rat (CD)	13 wk 5 d/wk 6 hr/d	Resp	16	202 (alveolar histiocytosis, chronic active lung inflammation)		Great Lakes Chemical Corporation 2000 OctaBDE (technical)	
			Cardio	202				
			Gastro	202				
			Hemato	202				
			Musc/skel	202				
			Hepatic	1.1	16 (centrilobular hepatocellular hypertrophy)			
			Renal	202				
			Endocr	1.1[b]	16 (decreased serum T4, increased serum TSH)			
			Dermal	202				
			Ocular	202				
			Bd Wt	202				
Immuno/ Lymphoret								
3	Rat (CD)	13 wk 5 d/wk 6 hr/d		16	202 (grossly discolored and enlarged bronchial and mediastinal lymph nodes associated with chronic active lung inflammation and alveolar histiocytosis)		Great Lakes Chemical Corporation 2000 OctaBDE (technical)	

Table 3-1 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
Reproductive								
4	Rat (CD)	13 wk 5 d/wk 6 hr/d		16 F	202 F (absence of corpora lutea in ovaries)		Great Lakes Chemical Corporation 2000 OctaBDE (technical)	

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

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

Note on chemical form: The chemical form in all studies was a technical octaBDE mixture (exact composition was not reported).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest observed adverse effect level; Musc/skel = muscular/skeletal; NOAEL = no observed adverse effect level; Resp = respiratory; T4 = thyroxine; TSH = thyroid stimulating hormone; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation

Acute (≤14 days)

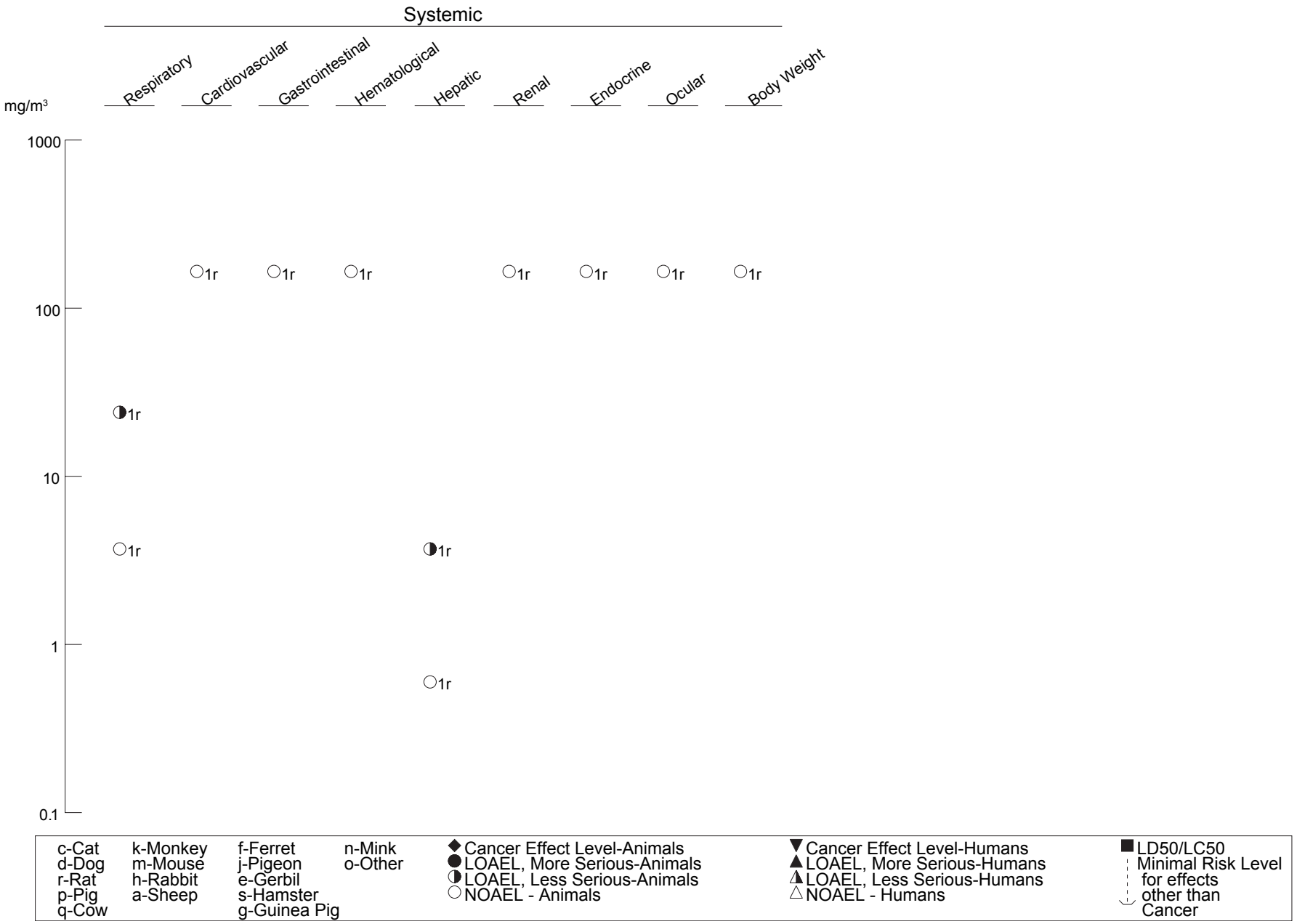
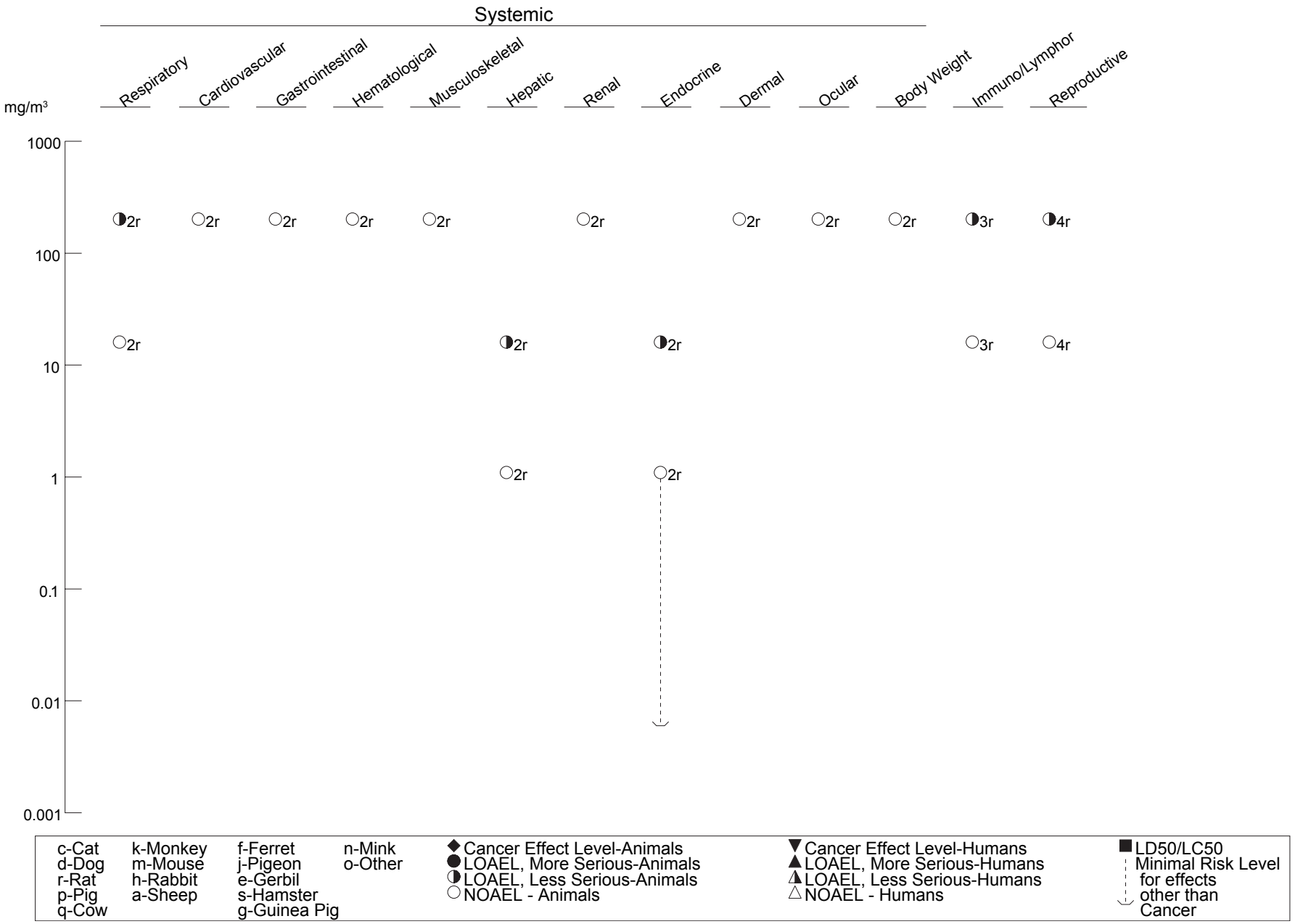


Figure 3-1. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Inhalation *(Continued)*

Intermediate (15-364 days)



3.2.1.2 Systemic Effects

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

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

Transient signs of respiratory distress that included tachypnea or dyspnea developed in rats that were chamber-exposed to pentaBDE aerosol (compound dissolved in corn oil), octaBDE dust, or decaBDE dust in very high concentrations of 200,000, 60,000, and 48,200 mg/m^3, respectively, for 1 hour (IRDC 1974, 1975a, 1975b). Confidence in these effect levels is low due to a small number of tested animals and lack of control data.

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

Histological changes in the lungs, but no clearly observed changes in the nasal cavity, were found in a study of rats that were nose-only exposed to 0, 1.1, 16, or 202 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000). The pulmonary effects included alveolar histiocytosis and chronic active inflammation, which occurred in both sexes, and were only clearly induced at 202 mg/m^3. Total incidences of alveolar histiocytosis in the 0, 1.1, 16, and 202 mg/m^3 exposure groups were 3/10, 5/10, 5/10, and 10/10 in males, respectively, and 0/10, 5/10, 2/10, and 10/10 in females, respectively. Respective total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10, and 10/10 in males, and 0/10, 1/10, 1/10, and 10/10 in females. Both lesions were predominantly minimal or mild in severity, with moderate severity occurring in a few high-dose animals. Additional effects included gross pulmonary changes in both sexes at 202 mg/m^3; these included lung firmness and white discoloration and/or enlargement in the bronchial and/or mediastinal lymph nodes. The gross lymph node changes correlated with the histological granulomatous inflammation. Effects in

nasal tissues were equivocal. Incidences of nasal goblet cell hypertrophy were slightly increased in nasal level II of both sexes at ≥1.1 mg/m^3, but changes in incidence were not clearly dose-related and there was essentially no increase in severity from minimal levels with increasing dose. Total incidences of goblet cell hypertrophy in nasal level II in the 0, 1.1, 16, and 202 mg/m^3 exposure groups were 4/10, 9/10, 6/10, and 10/10 respectively, in males, and 2/10, 6/10, 4/10, and 8/10, respectively, in females. Minimal severity goblet cell hypertrophy was also slightly increased in nasal level IV in males at 202 mg/m^3 (4/10, 0/10, 1/10, and 8/10), but not in females.

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

No histopathological changes were observed in the heart of rats that were exposed to dusts of commercial octaBDE products at concentrations of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000).

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

No histopathological changes were observed in the stomach and lower gastrointestinal tract of rats that were exposed to dusts of commercial octaBDE products at concentrations of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978), or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000).

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to PBDEs.

No adverse hematological changes occurred in rats that were exposed to 24.4 or 174 mg/m^3 of commercial octaBDE dust aerosol for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Evaluation of a limited number of indices (hemoglobin, hematocrit, total erythrocyte count, and total and differential leukocyte counts) showed no unusual responses except for an elevation in leukocyte numbers. The observed increase in leukocyte counts was considered to be an unusual response by the investigators, although it was within the normal range for control rats in their laboratory. Comprehensive hematological assessments showed no unusual changes in rats exposed to commercial

octaBDE as dust aerosol at concentrations of ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to PBDEs.

Hepatic effects were observed in a 14-day inhalation study of dusts of commercial octaBDE mixtures. In this study, rats were chamber-exposed to concentrations of 0, 0.6, 3.7, 23.9, or 165.2 mg/m^3 as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Increased liver weight and hepatic histological changes occurred in rats exposed to concentrations ≥3.7 mg/m^3. At 3.7 mg/m^3, the liver lesions consisted of very slight to slight severity focal to multifocal cytoplasmic enlargement of the hepatocytes, accompanied by focal acidophilic degeneration of individual to small groups of cells. The liver lesions were similar in rats exposed to concentrations ≥24.4 mg/m^3, except that the hepatocyte enlargement was multifocal to diffuse in distribution and accompanied by focal, small to large areas of hepatocellular necrosis of very slight to marked degree.

Similar hepatic changes were found in a study of rats that were nose-only exposed to 0, 1.1, 16, or 202 mg/m^3 commercial octaBDE as dust aerosol for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000). The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at ≥16 mg/m^3 and increased liver weight (absolute and relative) at 202 mg/m^3. Respective total incidences of centrilobular hepatocellular hypertrophy (predominantly minimal to mild) in the 0, 1.1, 16, and 202 mg/m^3 groups were 1/10, 0/10, 3/10, and 10/10 in males, and 0/10, 0/10, 3/10, and 6/10 in females. Serum chemistry evaluations showed no clear effects of exposure. Serum cholesterol was significantly increased (66.2% more than controls, $p<0.01$) in 202 mg/m^3 females, but the magnitude of the elevation was not considered toxicologically significant. Some other statistically significant serum chemistry alterations (increased mean globulin and total protein, decreased albumin/globulin ratio) also occurred in females exposed to 202 mg/m^3, but these changes were not considered exposure-related due to small magnitudes of changes and lack of similar changes in the males.

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

No histopathological changes were observed in the kidneys or urinary bladder of rats that were exposed to dusts of commercial octaBDE products at concentrations of 174 mg/m^3 for 8 hours/day for 14 consecutive

days (Great Lakes Chemical Corporation 1978) or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000). Urinalyses were not performed in any of these studies.

Endocrine Effects. There is evidence suggestive of hypothyroidism in a small group of workers who were occupationally exposed to decaBDE (Bahn et al. 1980). In another study, plasma levels of thyroid hormones (T_3 and free T_4) and eight PBDE congeners (tetra- to heptaBDEs) were monitored for 198–221 days in three electronic dismantling workers (Pettersson et al. 2002). The hormones remained within normal ranges and there were no correlations between levels of hormones and the plasma concentrations of congeners.

An acute inhalation study of commercial octaBDE dust in rats showed no histopathological changes in the thyroids, parathyroids, adrenals, or pituitary following chamber exposure to 174 mg/m^3 as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Rats that were nose-only exposed to commercial octaBDE at concentrations of 1.1, 16, or 202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks similarly showed no histological changes in the adrenals, pancreas, parathyroids, pituitary, or thyroids (Great Lakes Chemical Corporation 2000). Measurements of serum levels of thyroid hormones in the 13-week rat study, however, showed exposure-related decreases in mean thyroxine (total T_4) in both sexes exposed at ≥16 mg/m^3, and increases in TSH in males exposed at ≥16 mg/m^3 and in females exposed at 202 mg/m^3. The changes were usually statistically significant ($p<0.05$ or $p<0.01$) compared to controls and were considered by the investigators to be consistent with chemical-induced hypothyroidism. There were no serum T_3 changes, thyroid-attributable clinical signs or body weight effects, or gross or histopathological changes in the thyroid. The 1.1 mg/m^3 LOAEL for thyroid effects was used as the basis for the intermediate-duration MRL for inhalation exposure to octaBDE, as indicated in the footnote to Table 3-1 and discussed in Chapter 2 and Appendix A.

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to PBDEs.

No gross or histological changes in the skin were observed in rats that were nose-only exposed to commercial octaBDE as dust aerosol at concentrations of ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000).

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

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

No histopathological changes were observed in eyes of rats that were chamber-exposed to ≤174 mg/m^3 of commercial octaBDE as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Opthalmoscopic and histological examinations showed no ocular effects in rats following nose-only exposure to ≤202 mg/m^3 of commercial octaBDE dust aerosol for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000).

3.2.1.3 Immunological and Lymphoreticular Effects

A study conducted in China examined the association between serum levels of four BDEs (28, 47, 66, and 209), as well as PCBs and organochlorine pesticides, and the prevalence of asthma in children (3–6 years old) living in a heavily populated area (Meng et al. 2016). The study involved 620 cases and 218 controls. Serum analyses showed significantly higher levels of BDEs in cases than in controls. BDE 209 had the highest mean concentration in cases, 4.02 ng/g lipid, compared to 1.73 ng/g lipid in controls. In multivariable-adjusted analyses, the odds ratio (OR) for risk of asthma associated with 1 ng/g increase was statistically significant only for BDE 28 (OR 3.63; 95% confidence interval [CI] 1.23–10.70). Strafication of children based on asthma severity showed that BDE 209 was positively correlated with the severity of the condition (OR 1.40; 95% CI 1.14–1.72). PCBs and organochlorine pesticide also were associated with increased risk of asthma.

No histopathological changes were observed in the spleen, mesenteric or mediastinal lymph nodes, or bone marrow from rats that were exposed to 174 mg/m^3 of octaBDE dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). Rats that were nose-only exposed to commercial octaBDE at concentrations of 1.1, 16, or 202 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 13 weeks similarly showed no effects in bone marrow, spleen, or thymus, although gross changes in pulmonary lymph nodes were observed at 202 mg/m^3 (Great Lakes Chemical Corporation

2000). The effects included discolored and/or enlarged bronchial and mediastinal lymph nodes, and appeared to be associated with concurrent granulomatous inflammation of the lungs.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to PBDEs.

No clinical signs of neurotoxicity were observed in rats that were exposed to dusts of commercial octaBDE products at concentrations of 174 mg/m^3 for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978) or ≤202 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000). Histological examinations of nervous system tissues, performed only in the 13-week study, showed no effects in the brain (forebrain, midbrain, hindbrain), optic nerve, or a peripheral nerve (sciatic).

3.2.1.5 Reproductive Effects

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

No histopathological changes were observed in testes or ovaries from rats that were exposed to commercial octaBDE at concentrations ≤174 mg/m^3 as powdered dust for 8 hours/day for 14 consecutive days (Great Lakes Chemical Corporation 1978). A histological effect in the ovaries was found in a study of rats that were nose-only exposed to 0, 1.1, 16, or 202 mg/m^3 as dust aerosol for 6 hours/day, 5 days/week for 13 weeks (Great Lakes Chemical Corporation 2000). Absence of corpora lutea, based on qualitative evaluation of step sections of the ovary, was found in 3/10 females at 202 mg/m^3, compared to 0/10 incidences in the control and both lower exposure groups. The investigators interpreted this 30% increase in incidence be treatment-related because an absence of corpora lutea was considered unusual in rats at 20 weeks of age. No gross or histopathological changes were observed in the oviduct, uterus, or vagina, or in male reproductive tissues (testes with epididymides and vas deferens).

3.2.1.6 Developmental Effects

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

3.2.1.7 Cancer

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

3.2.2 Oral Exposure

Human data presented below are primarily from studies that attempted to identify relationships between concentrations of PBDE in serum or other tissues and various health outcomes. Details of PBDE exposure in these study populations are typically unknown. However, exposure is presumed to have been primarily by the oral route for those studies presented below.

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

3.2.2.1 Death

Single-dose gavage LD_{50} values of 5,000 and 6,200 mg/kg were determined for pentaBDE (Saytex 115 and DE-71, respectively) in rats that were observed for 14 days (British Industrial Biological Research Association 1977; Pharmakon Research International Inc. 1984). Another study found that a single 5,000 mg/kg dose of pentaBDE caused deaths in four of five rats in the 14 days following treatment, whereas doses ≤500 mg/kg caused no mortality (IRDC 1975b). No deaths occurred in rats exposed to pentaBDE in estimated dietary doses of ≤90 mg/kg/day for 28 days (IRDC 1976) or ≤100 mg/kg/day for 90 days (WIL Research Laboratories 1984).

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

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

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	once (GO)				6200 (44-day LD50)	British Industrial Biological Research Association 1977 PentaBDE (DE-71)	
2	Rat Spartan	once (GO)				5000 (4/5 died)	IRDC 1975b PentaBDE (technical)	
3	Rat (Sprague-Dawley)	once (GO)				5000 (14-day LD50)	Pharmakon Research International Inc. 1984 PentaBDE (Saytex 115)	
Systemic								
4	Rat (Sprague-Dawley)	once (GO)	Hepatic	1.2 M			Albina et al. 2010 PentaBDE (BDE99)	
			Renal		0.6 M (phagolysosomes in renal tubules)			
5	Rat (Sprague-Dawley)	once (GO)	Hepatic	1.2 M			Alonso et al. 2010 PentaBDE (BDE99)	No biologically relevant changes in hepatic serum chemistry.
			Renal	0.6 M	1.2 M (increased total protein in urine)			
			Endocr		0.6 M (reduced serum testosterone)			
6	Rat (CD)	10 d Gd 6-15 (GO)	Bd Wt	10	100 (20% reduction in maternal body weight gain)		Argus Research Laboratories 1985a PentaBDE (Saytex 115)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Rat (Sprague-Dawley)	14 d Gd 6-19 (GO)	Bd Wt	2 F			Blanco et al. 2012 PentaBDE (BDE99)	
8	Rat (Wistar)	7 d 1 x/d (GO)	Hepatic	8 F	40 F (porphyria)		Bruchajzer 2011 PentaBDE (technical)	
			Bd Wt	200 F				
9	Rat (Wistar)	14 d 1 x/d (GO)	Hepatic		8 F (porphyria)		Bruchajzer 2011 PentaBDE (technical)	
			Bd Wt	200 F				
10	Rat (Wistar)	7 d 1 x/d	Hepatic	40 F	200 F (fatty degeneration)		Bruchajzer et al. 2010 PentaBDE (technical)	
			Bd Wt	40 F	200 F (7% decrease in body weight gain)			
11	Rat (Wistar)	14 d 1 x/d	Hepatic	40 F	200 F (fatty degeneration)		Bruchajzer et al. 2010 PentaBDE (technical)	
			Bd Wt	40 F	200 F (10% decrease in body weight gain)			

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
12	Rat (Wistar)	once 5 d observation (GO)	Hepatic	200 F	2000 F (fatty degeneration)		Bruchajzer et al. 2011 PentaBDE (technical)	
			Bd Wt	200 F	2000 F (11% decrease in body weight gain)			
				200 F	2000 F (11% decrease in body weight gain)			
13	Rat (Wistar)	7 d 1 x/d (GO)	Hepatic	2 F	8 F (porphyria)		Bruchajzer et al. 2012 OctaBDE (technical)	
			Bd Wt	8 F	40 F (9% decrease in body weight gain)			
14	Rat (Wistar)	14 d 1 x/d (GO)	Hepatic	8 F	40 F (porphyria)		Bruchajzer et al. 2012 OctaBDE (technical)	
			Bd Wt	8 F	40 F (5% decrease in body weight gain)			
15	Rat (Sprague-Dawley)	14 d 1 x/d (GO)	Hepatic	76.6 M			Carlson, 1980b OctaBDE (technical)	
16	Rat (Sprague-Dawley)	14 d 1 x/d (GO)	Hepatic	56.4 M			Carlson, 1980b PentaBDE (technical)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
17	Rat (Sprague-Dawley)	14 d 1 x/d (GO)	Endocr		18 (reduced serum T4)		Darnerud and Sinjari 1996 PentaBDE (Bromkal 70)	
18	Rat (Sprague-Dawley)	6 d Gd 6.5-11.5 (GO)	Endocr	120 F			Ellis-Hutchings et al. 2009 PentaBDE (DE-71)	No exposure-related changes in serum thyroid hormone levels.
			Bd Wt	120 F				
19	Rat (Sprague-Dawley)	14 d 1 x/d (G)	Endocr	6 F	18 F (reduced serum T4, reduced T4 protein binding)		Hallgren and Darnerud 2002 TetraBDE (BDE47)	
			Bd Wt	18 F				
20	Rat (Sprague-Dawley)	14 d 1 x/d (GO)	Hepatic		18 F (reduced liver vitamin A)		Hallgren et al. 2001 PentaBDE (Bromkal 70-5DE)	
			Endocr		18 F (reduced serum T4)			
			Bd Wt	36 F				
21	Rat (Sprague-Dawley)	2 wk 1 x/d (GO)	Endocr		14 M (reduced serum T4)		Hoppe and Carey 2007 PentaBDE (technical)	No exposure-related changes in fat pad weight, adipocyte number, size, viability, lipolysis or glucose oxidation.
			Bd Wt	14 M				
			Metab	14 M				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
22	Rat Spartan	once (GO)	Bd Wt	5000			IRDC 1975a OctaBDE (technical)	
23	Rat Spartan	once (GO)	Bd Wt	500			IRDC 1975b PentaBDE (technical)	
24	Rat (Wistar)	once Gd 6 (GO)	Endocr		0.06[b] F (reduced serum T4)		Kuriyama et al. 2007 PentaBDE (BDE99)	
25	Rat (CD)	10 d Gd 6-15 (GO)	Bd Wt	25			Life Science Research Israel Ltd. (1987) OctaBDE (FR-1208)	
26	Rat (Wistar)	5 d Pnd 22-26 (GO)	Endocr	3 F	30 F (reduced serum T4)		Stoker et al. 2004 PentaBDE (DE-71)	
			Bd Wt	60 F				
27	Rat (Wistar)	5 d Pnd 23-27 (GO)	Endocr	3 M	30 M (reduced serum T4)		Stoker et al. 2004 PentaBDE (DE-71)	
			Bd Wt	60 M				
28	Rat (Wistar)	3 d 1 x/d (GO)	Endocr	30 M	60 M (increased serum LH)		Stoker et al. 2005 PentaBDE (DE-71)	
			Bd Wt	60 M				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Rat (Wistar)	9 d 1 x/d (GO)	Bd Wt	240 M			Stoker et al. 2005 PentaBDE (DE-71)	Hershberger Assay (castrated rats, supplemented with s.c. testosterone)
30	Rat (Wistar)	once Gd 6 (GO)	Bd Wt	0.7 F			Talsness et al. 2008 TetraBDE (BDE47)	
31	Rat (CD)	10 d Gd 6-15 (GO)	Bd Wt	25	50 (40% reduced maternal body weight gain)		WIL Research Laboratories 1986 OctaBDE (DE-79)	
32	Rat (Long-Evans)	4 d 1 x/d (GO)	Endocr	10 F	30 F (reduced serum T4)		Zhou et al. 2001 PentaBDE (DE-71)	
			Bd Wt	300 F				
33	Rat (Long-Evans)	4 d 1 x/d (GO)	Endocr	3 F	10 F (reduced serum T4)		Zhou et al. 2001 OctaBDE (DE-79)	
			Bd Wt	300 F				
34	Mouse (C57BL/6N)	14 d 1 x/d (GO)	Endocr		18 (reduced serum T4)		Darnerud and Sinjari 1996 PentaBDE (Bromkal 70)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
35	Mouse C57BL/6J	once (GO)	Hepatic	500 F			Fowles et al. 1994 PentaBDE (DE-71)	
			Endocr	100 F	500 F (reduced serum T4)			
			Bd Wt	500 F				
36	Mouse (C57BL/6N)	14 d 1 x/d (GO)	Hepatic	72 F			Fowles et al. 1994 PentaBDE (DE-71)	
			Endocr		18 F (reduced serum T4)			
			Bd Wt	72 F				
37	Mouse (C57BL/6N)	14 d 1 x/d (GO)	Hepatic	18 F	36 F (reduced liver vitamin A)		Hallgren et al. 2001 PentaBDE (Bromkal 70-5DE)	
			Endocr		18 F (reduced serum T4)			
			Bd Wt	36 F				
38	Mouse (C57BL/6N)	14 d 1 x/d (GO)	Endocr		18 F (reduced serum T4)		Hallgren et al. 2001 TetraBDE (BDE47)	
			Bd Wt	18 F				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
39	Mouse (C57BL/6)	4 d 1 x/d (GO)	Endocr	10 F	100 F (reduced serum T4)		Richardson et al. 2008 TetraBDE (BDE47)	
			Bd Wt	100 F				
Immuno/ Lymphoret								
40	Rat (Sprague-Dawley)	14 d 1 x/d (GO)		36			Darnerud and Thuvander 1998 PentaBDE (Bromkal 70-5DE)	No exposure-related changes in spleen or thymus weight, number or distribution of lymphocyte subpopulations, or in vitro IgG production.
41	Mouse (C57BL/6N)	14 d 1 x/d (GO)		18	36 (reduced in vitro production of IgG in mitogen- stimulated splenocytes)		Darnerud and Thuvander 1998 PentaBDE (DE-71)	
42	Mouse (C57BL/6N)	once (GO)		500 F			Fowles et al. 1994 PentaBDE (DE-71)	No exposure-related change in spleen or thymus weights or antibody respose to sheep red blood cells.
43	Mouse (C57BL/6N)	14 d 1 x/d (GO)		36 F	72 F (reduced antibody response to sheep red blood cells, decreased thymus weight)		Fowles et al. 1994 PentaBDE (DE-71)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
44	Mouse (C57BL/6N)	14 d 1 x/d (GO)		18 F			Hallgren et al. 2001 TetraBDE (BDE47)	No exposure-related changes in spleen or thymus weight
Neurological								
45	Rat (Sprague-Dawley)	once (GO)		1.2 M			Belles et al. 2010 PentaBDE (BDE99)	No changes in brain histology or in functional observation battery, open-field testing, passive avoidance test, or Morris water maze.
Reproductive								
46	Rat (Sprague-Dawley)	once (GO)			0.6 F (decreased serum testosterone)		Alonso et al. 2010 PentaBDE (BDE99)	
47	Rat (Sprague-Dawley)	14 d Gd 6-19 (GO)		2 F			Blanco et al. 2012 PentaBDE (BDE99)	No treatment-related changes in gravid uterine weight or number of implantation or resorptions.
48	Rat (Wistar)	3 d 1 x/d (GO)		30 M	60 M (increased serum LH)		Stoker et al. 2005 PentaBDE (DE-71)	
49	Rat (Wistar)	9 d 1 x/d (GO)			30 M (20% decrease in ventral prostate weight)		Stoker et al. 2005 PentaBDE (DE-71)	Hershberger Assay (castrated rats, supplemented with s.c. testosterone)

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
50	Rat (Wistar)	once Gd 6 (GO)		0.7 F			Talsness et al. 2008 TetraBDE (BDE47)	No dose-related changes in ovary weight or histology.
51	Mouse (BALB/c)	3 d 1 x/d (GO)		300 F			Mercado-Feliciano and Bigsby 2008a PentaBDE (DE-71)	Mice were ovariectomized 3 weeks prior to exposure; no change in uterus weight or uterus/vaginal histology.
Developmental								
52	Rat (CD)	10 d Gd 6-15 (GO)		200			Argus Research Laboratories 1985a PentaBDE (Saytex 115)	No changes in number, sex, and weight of fetuses, fetal death, early and late resorptions, gross malformations, or skeletal or visceral abnormalities.
53	Rat (CD)	10 d Gd 6-15 (GO)		10	25 (increased resorptions and reduced fetal body weight)		Argus Research Laboratories 1985b OctaBDE (Saytex 115)	
54	Rat (Sprague-Dawley)	14 d Gd 6-19 (GO)		1	2 (delayed ossification, liver and heart hypertrophy)		Blanco et al. 2012 PentaBDE (BDE99)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
55	Rat (Long- Evans)	7 d Pnd 6-12 (GO)			30 M (impaired learning in visual discrimination task at Pnd 30-83)		Dufault et al. 2005 PentaBDE (DE-71)	
56	Rat (Sprague-Dawley)	6 d Gd 6.5-11.5 (GO)		120			Ellis-Hutchings et al. 2009 PentaBDE (DE-71)	No exposure-related changes in embryo viability, growth, or morphology.
57	Rat (Sprague-Dawley)	14 d Gd 6.5-19.5 (GO)		120			Ellis-Hutchings et al. 2009 PentaBDE (DE-71)	No exposure-related effects on fetal survival, growth, or malformations.
58	Rat (Sprague-Dawley)	once Pnd 10 (GO)			1 (impaired learning and memory at 2 months)		He et al. 2009 TetraBDE (BDE47)	
59	Rat (Sprague-Dawley)	once Pnd 10 (GO)			1 (impaired learning and memory and 23% decrease in relative uterine weight at 2 months)		He et al. 2011 TetraBDE (BDE47)	
60	Rat (Wistar)	once Gd 6 (GO)			0.06[b] (increased activity and impaired spermatogenesis in adult offspring)		Kuriyama et al. 2005 PentaBDE (BDE99)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
61	Rat (Wistar)	once Gd 6 (GO)		0.06	0.3 (reduced serum T4 in Pnd 22 offspring)		Kuriyama et al. 2007 PentaBDE (BDE99)	
62	Rat (CD)	10 d Gd 6-15 (GO)		2.5	10 (minimal increased post-implantation loss)		Life Science Research Israel Ltd. (1987) OctaBDE (FR-1208)	
63	Rat (Wistar)	once Gd 6 (GO)			0.06[b] F (ultrastructural changes in ovaries in F1 females at Pnd 90, increased resorptions in F1 females mated to unexposed males)		Talsness et al. 2005 PentaBDE (BDE99)	
64	Rat (Wistar)	once Gd 6 (GO)			0.14 F (reduced number of secondary ovarian follicles at Pnd 38 and ultrastructural changes in the ovary at Pnd 100 in offspring)		Talsness et al. 2008 TetraBDE (BDE47)	
65	Rat (Sprague-Dawley)	once Pnd 10 (G)		0.8 M	8 M (decreased spontaneous activity, impaired habituation)		Viberg et al. 2005 PentaBDE (BDE99)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
66	Rat (CD)	10 d Gd 6-15 (GO)		25	50 (reduced fetal weight and increased skeletal variations associated with maternal tox)		WIL Research Laboratories 1986 OctaBDE (DE-79)	
67	Rat (Long-Evans)	14 d Gd 6-20 (GO)		1	10 (reduced serum T4 in fetuses)		Zhou et al. 2002 PentaBDE (DE-71)	
68	Mouse (C57BL/6)	once Pnd 10 (GO)		10 M			Costa et al. 2015 TetraBDE (BDE47)	No exposure-related changes in serum T3 or T4.
69	Mouse (C57BL/6N)	once Pnd 10 (G)			6.8 M (decreased post-tetanic and long term potential in hippocampal slices at Pnd 17-19)		Dingemans et al. 2007 TetraBDE (BDE47)	
70	Mouse (NMRI)	once Pnd 10 (G)			0.8 M (altered spontaneous activity and habituation at 2-4 months)		Eriksson et al. 2001 PentaBDE (BDE99)	
71	Mouse (NMRI)	once Pnd 10 (G)		0.7 M	10.5 M (altered spontaneous activity and habituation at 2-4 months)		Eriksson et al. 2001 TetraBDE (BDE47)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
72	Mouse (NMRI)	once Pnd 3 (G)			8 M (altered spontaneous activity and habituation at 4 months)		Eriksson et al. 2002b PentaBDE (BDE99)	
73	Mouse (NMRI)	once Pnd 10 (G)			8 M (altered spontaneous activity and habituation at 4 months)		Eriksson et al. 2002b PentaBDE (BDE99)	
74	Mouse (NMRI)	once Pnd 19 (G)		8 M			Eriksson et al. 2002b PentaBDE (BDE99)	No exposure-related alterations in spontaneous activity at 4 months.
75	Mouse (NMRI)	once Pnd 10 (G)		0.8 M	12 M (altered spontaneous activity and habituation at 4-6 months)		Eriksson et al. 2006 PentaBDE (BDE99)	
76	Mouse (NMRI)	once Pnd 10 (G)			0.8 M (decreased activity and impaired learning and memory during at 2-6 months)		Fischer et al. 2008 PentaBDE (BDE99)	
77	Mouse (C57BL/6N)	once Pnd 10 (GO)			1 M (increased motor activity at 4 months)		Gee and Moser 2008 TetraBDE (BDE47)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
78	Mouse (C57BL/6N)	once Pnd 10 (GO)		30 M			Gee et al. 2008 TetraBDE (BDE47)	No exposure-related changes in offspring body weight or serum T3 or T4 levels.
79	Mouse (NMRI)	once Pnd 10 (GO)			12 M (decreased spontaneous activity and impaired habituation at 2 months)		Hallgren et al. 2015 PentaBDE (BDE99)	
80	Mouse (C57BL/6)	once Pnd 10 (G)		0.4	0.8 (decreased total activity at 2 months)		Sand et al. 2004 PentaBDE (BDE99)	
81	Mouse (NMRI)	once Pnd 10 (G)			8 M (decreased spontaneous activity, altered habituation, and altered response to cholinergic agent at 2 months)		Viberg et al. 2002 PentaBDE (BDE99)	
82	Mouse (NMRI)	once Pnd 10 (G)			0.45 M (decreased spontaneous activity at 6 months)		Viberg et al. 2003a HexaBDE (BDE153)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
83	Mouse (C57/BL)	once Pnd 10 (G)		0.4	0.8 (decreased spontaneous activity and impaired habituation at 2-8 months)		Viberg et al. 2004a PentaBDE (BDE99)	
84	Mouse (NMRI)	once Pnd 10 (G)		0.4 M	12 M (decreased spontaneous activity, impaired habituation, and decreased density of cholinergic nicotinic receptors in hippocampus at 4 months)		Viberg et al. 2004b PentaBDE (BDE99)	
85	Mouse (NMRI)	once Pnd 3 (G)			16.8 M (decreased spontaneous activity and impaired habituation at 2 months)		Viberg et al. 2006 OctaBDE (BDE203)	
86	Mouse (NMRI)	once Pnd 10 (G)			16.8 M (decreased spontaneous activity, impaired habituation, and impaired learning and memory at 2-3 months)		Viberg et al. 2006 OctaBDE (BDE203)	
87	Mouse (NMRI)	once Pnd 3 (G)			15.2 M (decreased spontaneous activity at 2 months)		Viberg et al. 2006 HeptaBDE (BDE183)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
88	Mouse (NMRI)	once Pnd 10 (G)		15.2 M			Viberg et al. 2006 HeptaBDE (BDE183)	No change in spontaneous activity or habituation at 2 months.
89	Mouse (NMRI)	once Pnd 3 (G)		18.5 M			Viberg et al. 2006 NonaBDE (BDE206)	No changes in spontaneous motor behavior or habituation at 2 months.
90	Mouse (NMRI)	once Pnd 10 (G)			18.5 M (decreased spontaneous activity and impaired habituation at 2 months)		Viberg et al. 2006 NonaBDE (BDE206)	
91	Rabbit (New Zealand)	13 d Gd 7-19 (GO)		5 F	15 F (delayed ossification of sternebrae with decreased maternal weight gain)		Breslin et al. 1989 OctaBDE (technical)	
INTERMEDIATE EXPOSURE								
Systemic								
92	Rat (Sprague-Dawley)	5 wk Gd 6 - Pnd 21 (IN)	Endocr	1 F	10 F (reduced serum T4 levels)		Bansal et al. 2014 PentaBDE (DE-71)	Dams were given DE-71-dosed vanilla wafers.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
93	Rat (Sprague-Dawley)	15 d 1 x/d (GO)	Endocr	3 M	30 M (follicular cell hypertrophy and hyperplasia in thyroid, reduced serum T3 and T4, increased serum TSH)		Becker et al. 2012 PentaBDE (DE-71)	Study 1 (conducted at ILS)
			Bd Wt	60 M				
94	Rat (Sprague-Dawley)	15 d 1 x/d (GO)	Hepatic		3 M (centrilobular hepatocyte hypertrophy)		Becker et al. 2012 PentaBDE (DE-71)	Study 2 (conducted at RTI)
			Endocr	3 M	30 M (decreased serum T3 and T4, increased serum TSH)			
			Bd Wt	60 M				
95	Rat (Sprague-Dawley)	21 wk Pmd 70 - Pnd 42 (GO)	Hepatic	0.5 M	5 M (hepatocellular hypertrophy)		Bondy et al. 2011, 2013 PentaBDE (DE-71)	
			Renal	25				
			Endocr	0.5 M	5 M (reduced serum T4)			
			Bd Wt	25				
96	Rat (Sprague-Dawley)	6 wk Gd 1 - Pnd 21 (IN)	Endocr	3 F	30 F (reduced serum T3 and T4)		Bowers et al. 2015 PentaBDE (DE-71)	Dams were given DE-71-dosed cookies.
			Bd Wt	30 F				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
97	Rat (Wistar)	21 d 1 x/d (GO)	Hepatic		8 F (porphyria)		Bruchajzer 2011 PentaBDE (technical)	
			Bd Wt		8 F (decreased body weight gain)			
98	Rat (Wistar)	28 d 1 x/d (GO)	Hepatic	2 F	8 F (porphyria)		Bruchajzer 2011 PentaBDE (technical)	
			Bd Wt	2 F	8 F (8% decrease in body weight gain)			
99	Rat (Wistar)	21 d 1 x/d	Bd Wt	40 F	200 F (12% decrease in body weight gain)		Bruchajzer et al. 2010 PentaBDE (technical)	
100	Rat (Wistar)	28 d 1 x/d	Bd Wt	40 F	200 F (14% decrease in body weight gain)		Bruchajzer et al. 2010 PentaBDE (technical)	
101	Rat (Wistar)	21 d 1 x/d (GO)	Hepatic	2 F	8 F (porphyria)		Bruchajzer et al. 2012 OctaBDE (technical)	
			Bd Wt	8 F	40 F (9% decrease in body weight gain)			

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
102	Rat (Wistar)	28 d 1 x/d (GO)	Bd Wt	8 F	40 F (8% decrease in body weight gain)		Bruchajzer et al. 2012 OctaBDE (technical)	
103	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	1.77 M			Carlson 1980a PentaBDE (technical)	
104	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	14.1 M			Carlson 1980a PentaBDE (technical)	
105	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	2.4 M			Carlson, 1980a OctaBDE (technical)	
106	Rat (Sprague-Dawley)	90 d (GO)	Hepatic	19.2 M			Carlson, 1980a OctaBDE (technical)	
107	Rat (Sprague-Dawley)	90 d 1 x/d (GO)	Hepatic	0.015 M			Daubie et al. 2011 PentaBDE (BDE99)	No exposure-related changes in hepatic clinical chemistry
			Bd Wt	0.015 M				
108	Rat (Long- Evans)	125 d Pnd 1-125 (F)	Endocr		17.5 M (reduced serum T4)		Driscoll et al. 2009 PentaBDE (DE-71)	
			Bd Wt	26.2 M				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
109	Rat (Wistar)	18 wk Gd 6 - Pnw 16 5-7 d/wk (GO)	Hepatic		50 (hepatocellular hypertrophy and vacuolization)		Dunnick et al. 2012 PentaBDE (DE-71)	
			Endocr		50 (thyroid gland follicular hypertrophy)			
			Bd Wt	50 M	50 F (14% decrease in body weight)			
110	Rat (Sprague-Dawley)	33 d Gd 6 - Pnd 18 (GO)	Hepatic		18 F (reduced liver vitamin A)		Ellis-Hutchings et al. 2006 PentaBDE (DE-71)	
			Endocr		18 F (reduced serum T4)			
			Bd Wt	18 F				
111	Rat (Sprague-Dawley)	70 d (F)	Hepatic	20 M			Ernest et al. 2012 52.1% penta-, 44.2% deca-, 0.4% octa-BDE	No exposure-related changes in hepatic clinical chemistry.
			Endocr	2 M	20 M (reduced serum T4; increased epithelial thickness of inner follicles and vacuolation of the luminal apices of epithelial cells in thyroid)			
			Bd Wt	20 M				
			Metab	2 M	20 M (reduced serum glucose level)			

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
112	Rat (Sprague-Dawley)	28 d (G)	Hepatic	2.5	25 (decreased hepatic vitamin A content)		Fattore et al. 2001 PentaBDE (Bromkal 70-5DE)	
113	Rat (Sprague-Dawley)	4 wk 1 x/d (GO)	Endocr		14 M (reduced serum T4)		Hoppe and Carey 2007 PentaBDE (technical)	
			Bd Wt	14 M				
			Metab		14 M (increased adipocyte lipolysis, decreased adipocyte glucose oxidation)			
114	Rat (CD)	28 d (F)	Hepatic		9 (increased liver weight and enlarged parenchymal cells)		IRDC 1976 PentaBDE (technical)	
			Renal	90				
			Endocr	90				
			Bd Wt	90				
115	Rat (CD)	28 d (F)	Hepatic		9 (increased liver weight and enlarged parenchymal cells)		IRDC 1976 OctaBDE (technical)	
			Renal	90				
			Endocr	90				
			Bd Wt	90				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
116	Rat (CD)	13 wk (F)	Resp	750 F			IRDC 1977 OctaBDE (technical)	
			Cardio	750 F				
			Gastro	750 F				
			Hemato	70 F	750 F (reduced erythrocytes, hematocrit and hemoglobin)			
			Hepatic		5 M (cytomegaly with vacuolation and necrosis at higher doses)			
			Renal	50 M	600 M (minimal increase in tubular degenerative changes)			
			Endocr	7 F	50 M (increased thyroid weight with follicular epithelial changes at higher doses)			
			Dermal	750 F				
			Ocular	750 F				
			Bd Wt	70 F	600 M (12% reduced body weight gain)			
117	Rat (Long- Evans)	36 d Gd 6 - Pnd 21 (GO)	Endocr	1.7 F	10.2 F (reduced serum T4)		Kodavanti et al. 2010 PentaBDE (DE-71)	
			Bd Wt	30.6 F				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
118	Rat (Sprague-Dawley)	28 d 1 x/d (GO)	Resp	250			Oberg et al. 2010 PentaBDE (Bromkal 70-5DE)	
			Cardio	250				
			Hemato	250				
			Hepatic	2.5	25 (centrilobular hypertrophy, reduced vitamin A content in liver)			
			Renal	250				
			Bd Wt	250				
			Metab	25	250 (hypercalcemia, magnesemia, and phosphatemia in males; hyperatremia and hypokalemia in females)			
119	Rat (Long- Evans)	~11 wk Pmd 28 - Pnd 21 (IN)	Bd Wt	11.4 F			Poon et al. 2011 PentaBDE (DE-71)	Rats were given pentaBDE-dosed vanilla wafers.
120	Rat (Wistar)	20 d Pnd 22-41 (GO)	Endocr	3 F	30 F (reduced serum T4)		Stoker et al. 2004 PentaBDE (DE-71)	
			Bd Wt	60 F				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
121	Rat (Wistar)	31 d Pnd 23-53 (GO)	Endocr		3 M (reduced serum T4)		Stoker et al. 2004 PentaBDE (DE-71)	
			Bd Wt	60 M				
122	Rat (Wistar)	31 d Pnd 23-53 (GO)	Endocr		60 M (reduced serum T4)		Stoker et al. 2005 PentaBDE (DE-71)	
			Bd Wt	120 M				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
123	Rat (Wistar)	28 d (G)	Resp	200			Van der Ven et al. 2008b PentaBDE (DE-71)	NOAEL values for Bd Wt, Hepatic, Endocr, and Metab effects are BMDL(RD10%) values for decreased Bd Wt, vitamin A in liver, serum T4 and glucose.
			Cardio	200				
			Gastro	200				
			Musc/skel	200				
			Hepatic	0.05 M				
			Renal	200				
			Endocr	1.1 M				
			Dermal	200				
			Bd Wt	9.7 M				
			Metab	66.7 M				
124	Rat (Wistar)	34 d Gd 1 - Pnd 14 (F)	Endocr		3.2 F (reduced serum T4)		Wang et al. 2011a TetraBDE (BDE47)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
125	Rat (Sprague-Dawley)	90 d (F)	Resp	100			WIL Research Laboratories 1984 PentaBDE (DE-71)	
			Cardio	100				
			Gastro	100				
			Hemato	100				
			Musc/skel	100				
			Hepatic		2	(hypertrophy, mild degeneration, and slight necrosis)		
			Renal	100				
			Endocr	2	10	(reduced serum T4)		
			Dermal	100				
			Ocular	100				
			Bd Wt	10	100	(reduced weight gain)		
126	Rat (Sprague-Dawley)	30 d 1 x/d (GO)	Bd Wt	1 M			Yan et al. 2012 TetraBDE (BDE47)	
127	Rat (Sprague-Dawley)	6 wk Gd 1 - Pnd 21 (GO)	Bd Wt	0.2 F			Zhao et al. 2014 PentaBDE (BDE99)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
128	Rat (Long-Evans)	36 d Gd 6 - Pnd 21 (GO)	Endocr	10 F	30 F (reduced maternal serum T4)		Zhou et al. 2002 PentaBDE (DE-71)	
			Bd Wt	30 F				
129	Mouse (CD-1)	36 d Gd 6 - Pnd 21	Bd Wt	18 F			Branchi et al. 2005 PentaBDE (BDE99)	Administered via "self-administration" from a modified syringe or gavage.
130	Mouse (C57BL/6J)	70-80 d Pmd 28 - Pnd 21 (IN)	Bd Wt	1 F			Koenig et al. 2012 TetraBDE (BDE47)	Mice were fed 1-2 tetraBDE dosed cornflakes.
131	Mouse (BALB/c)	28 d (F)	Hepatic		0.45 F (hepatocyte vacuolation, pyknotic nuclei in the hepatocytes, periportal lymphocytic infiltration)		Maranghi et al. 2013 TetraBDE (BDE47)	
			Endocr		0.45 F (cellular debris in the follicular lumen of thyroid; increased serum testosterone and E2)			
			Bd Wt	0.45 F				

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
132	Mouse (NS)	6 wk 5 d/wk (GO)	Hepatic	1 M			McIntyre et al. 2015 TetraBDE (BDE47)	No exposure-related changes in glucose tolerance, insulin resistance, lipogenesis, or liver weight or histology.
			Bd Wt	1 M				
			Metab	1 M				
133	Mouse (NMRI)	29 d Gd 4 - Pnd 17 ~every 3 d (GO)	Endocr	452 F			Skarman et al. 2005 PentaBDE (BDE99)	BDE-99; No change in maternal serum T4 levels.
			Bd Wt	452 F				
134	Mouse (NMRI)	29 d Gd 4 - Pnd 17 ~every 3 d (GO)	Endocr	452 F			Skarman et al. 2005 PentaBDE (Bromkal 70-5DE)	Bromkal 70-5DE; no change in maternal serum T4 levels.
			Bd Wt	452 F				
135	Mouse (C57BL/6J)	70-80 d Pmd 28 - Pnd 21 (IN)	Bd Wt	1 F			Ta et al. 2011 TetraBDE (BDE47)	Dams were fed tetraBDE-dosed cornflakes.
136	Mouse (C56BL/6)	30 d (GO)	Bd Wt	30 M			Wang et al. 2013 TetraBDE (BDE47)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
137	Mouse (ICR)	28 d 1 x/d (GO)	Hepatic		1.2 M (swollen hepatic cells)		Zhang et al. 2014 DiBDE (BDE15)	
			Renal		1.2 M (10% decrease in relative kidney weight)			
			Bd Wt	1.2 M				
138	Mouse (ICR)	12 wk 7 d/wk (GO)	Hepatic		150 M (increased relative liver weight, increased serum ALT, hepatocyte hypertrophy and vacuolization and inflammatory cell infiltration)		Zhang et al. 2015b TetraBDE (BDE47)	
			Bd Wt	150 M				
139	Mouse (ICR)	12 wk 7 d/wk (GO)	Hepatic		150 M (increased relative liver weight, increased serum ALT, hepatocyte hypertrophy and vacuolization and inflammatory cell infiltration)		Zhang et al. 2015a TetraBDE (BDE47)	
			Bd Wt	150 M				
140	Mink (NS)	9 wk (F)	Bd Wt	0.08 M	0.63 M (21% decrease in body weight)		Martin et al. 2007 PentaBDE (DE-71)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
141	Mink (NS)	16-17 wk Pmw 4 - Pnw 6 (F)	Bd Wt	0.31 F			Zhang et al. 2009 PentaBDE (DE-71)	
142	Mink (NS)	43-44 wk Pmw 4 - Pnw 33 (F)	Bd Wt	0.06			Zhang et al. 2009 PentaBDE (DE-71)	
Immuno/ Lymphoret								
143	Rat (Sprague-Dawley)	21 wk Pmd 70 - Pnd 42 (GO)		25			Bondy et al. 2011, 2013 PentaBDE (DE-71)	No exposure-related changes in spleen or thymus weight or histology.
144	Rat (CD)	28 d (F)		90			IRDC 1976 PentaBDE (technical)	No exposure-related changes in spleen weight or spleen or thymus histology.
145	Rat (CD)	28 d (F)		90			IRDC 1976 OctaBDE (technical)	No exposure-related changes in spleen weight or spleen or thymus histology.
146	Rat (CD)	28 d (F)		90			IRDC 1976 PentaBDE (technical)	No exposure-related changes in spleen weight or spleen or thymus histology.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
147	Rat (CD)	13 wk (F)		750 F			IRDC 1977 OctaBDE (technical)	No exposure-related changes in spleen weight or spleen or thymus histology.
148	Rat (Sprague-Dawley)	28 d 1 x/d (GO)		250			Oberg et al. 2010 PentaBDE (Bromkal 70-5DE)	No exposure-related changes in spleen or thymus weight or histology.
149	Rat (Sprague-Dawley)	90 d (F)		100			WIL Research Laboratories 1984 PentaBDE (DE-71)	No exposure-related changes in thymus weight or spleen or thymus histology.
150	Mouse (BALB/c)	28 d (F)			0.45 F (follicular hyperplasia and lymphocytic infiltration in spleen; lymphocytic apoptosis and Hassal's bodies in thymus)		Maranghi et al. 2013 TetraBDE (BDE47)	
151	Mink (NS)	9 wk (F)		0.08 M	0.63 M (spleen hyperplasia)		Martin et al. 2007 PentaBDE (DE-71)	Immune function was not altered (KLH antibody induction, PHA skin challenge).

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
152	Rat (Sprague-Dawley)	90 d 1 x/d (GO)		0.015 M			Daubie et al. 2011 PentaBDE (BDE99)	No exposure-related changes in elevated plus-maze, open-field, or Morris water maze test.
153	Rat (Long- Evans)	125 d Pnd 1-125 (F)		17.5 M	26.2 M (impaired attention and inhibitory control)		Driscoll et al. 2009 PentaBDE (DE-71)	
154	Rat (Sprague-Dawley)	28 d 1 x/d (GO)		250			Oberg et al. 2010 PentaBDE (Bromkal 70-5DE)	No exposure-related changes in brain weight or histology.
155	Rat (Wistar)	28 d (G)		200			Van der Ven et al. 2008b PentaBDE (DE-71)	No exposure-related changes in brain weight or histology.
156	Rat (Sprague-Dawley)	30 d 1 x/d (GO)			0.1 M (impaired learning and memory; decreased glutamate and receptor density in hippocampus)		Yan et al. 2012 TetraBDE (BDE47)	
157	Mink (NS)	19 wk Pmd 28 - Pnw 6 (F)		0.25 F			Bull et al. 2007 PentaBDE (DE-71)	No maternal cholinergic effects were observed.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
158	Rat (Sprague-Dawley)	15 d 1 x/d (GO)		30 M	60 M (67% increase in serum prolactin; dose-related increase in serum testosterone and FSH)		Becker et al. 2012 PentaBDE (DE-71)	Study 1 (conducted at ILS)
159	Rat (Sprague-Dawley)	15 d 1 x/d (GO)		60 M			Becker et al. 2012 PentaBDE (DE-71)	Study 2 (conducted at RTI); no dose-related changes in reproductive organ weight, histopathology, or serum reproductive hormone levels.
160	Rat (Sprague-Dawley)	21 wk Pmd 70 - Pnd 42 (GO)		25			Bondy et al. 2011, 2013 PentaBDE (DE-71)	No treatment-related changes in the number of pregnant females, litters, or litter size.
161	Rat (Sprague-Dawley)	6 wk Gd 1 - Pnd 21 (IN)		30 F			Bowers et al. 2015 PentaBDE (DE-71)	Dams were given DE-71-dosed cookies. No treatment-related changes in no. of implants, no. of litters, litter size, or sex ratio.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
162	Rat (Sprague-Dawley)	36 d Gd 6 - Pnd 21 (GO)		2 F			Cheng et al. 2009 PentaBDE (BDE99)	No exposure-related changes in number of litters, litter size, or sex ratio.
163	Rat (Sprague-Dawley)	70 d (F)		20 M			Ernest et al. 2012 52.1% penta-, 44.2% deca-, 0.4% octa-BDE	No exposure-related changes in reproductive organ weight, testicular histology, or sperm parameters.
164	Rat (Sprague-Dawley)	8 wk (GO)		0.001 M	0.03 M (increased epithelial thickness in testes, spermatocyte apoptosis)		Huang et al. 2015 TetraBDE (BDE47)	
165	Rat (CD)	28 d (F)		90			IRDC 1976 PentaBDE (technical)	No exposure-related changes in reproductive organ weight or histology.
166	Rat (CD)	28 d (F)		90			IRDC 1976 OctaBDE (technical)	No exposure-related changes in reproductive organ weight or histology.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
167	Rat (CD)	13 wk (F)		600 M 750 F			IRDC 1977 OctaBDE (technical)	No exposure-related changes in reproductive organ weight or histology
168	Rat (Sprague-Dawley)	28 d 1 x/d (GO)		250			Oberg et al. 2010 PentaBDE (Bromkal 70-5DE)	No exposure-related changes in reproductive organ weight or histology.
169	Rat (Long- Evans)	~11 wk Pmd 28 - Pnd 21 (IN)		11.4 F			Poon et al. 2011 PentaBDE (DE-71)	Rats were given pentaBDE-dosed vanilla wafers; no change in number of pregnancies, implantation sites, or live pups, litter size, or sex ratio.
170	Rat (Wistar)	20 d Pnd 22-41 (GO)		30 F	60 F (delayed vaginal opening)		Stoker et al. 2004 PentaBDE (DE-71)	
171	Rat (Wistar)	31 d Pnd 23-53 (GO)		3 M	30 M (delayed preputial separation)		Stoker et al. 2004 PentaBDE (DE-71)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
172	Rat (Wistar)	31 d Pnd 23-53 (GO)			60 M (delayed PPS, 22-28% decrease in prostate and seminal vesicle weights)		Stoker et al. 2005 PentaBDE (DE-71)	
173	Rat (Wistar)	28 d (G)		9.6 M 200 F			Van der Ven et al. 2008b PentaBDE (DE-71)	Male NOAEL is a BMDL(RD10%) for increased % of deformed sperm heads; no exposure-related changes in female reproductive organ weights or histology.
174	Rat (Sprague-Dawley)	90 d (F)		100			WIL Research Laboratories 1984 PentaBDE (DE-71)	No exposure-related changes in reproductive organ weight or histology.
175	Rat (Sprague-Dawley)	8 wk 6 d/wk (GO)			0.001[c] M (34% reduction in serum testosterone)		Zhang et al. 2013b TetraBDE (BDE47)	
176	Rat (Sprague-Dawley)	6 wk Gd 1 - Pnd 21 (GO)		0.2 M			Zhao et al. 2014 PentaBDE (BDE99)	No exposure-related changes in gestational lengths, litter sizes, sex ratio, or live births.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
177	Rat (Long-Evans)	36 d Gd 6 - Pnd 21 (GO)		30 F			Zhou et al. 2002 PentaBDE (DE-71)	No change in the gestation length, litter size, or sex ratio
178	Mouse (CD-1)	36 d Gd 6 - Pnd 21		18 F			Branchi et al. 2005 PentaBDE (BDE99)	Administered via "self-administration" from a modified syringe or gavage; No change in gestation length, litter size, # live pups, or sex ratio.
179	Mouse (C57BL/6J)	70-80 d Pmd 28 - Pnd 21 (IN)		1 F			Koenig et al. 2012 TetraBDE (BDE47)	Mice were fed 1-2 tetraBDE dosed cornflakes; no change in the number of pregnancies, size of litter, or sex ratio of pups.
180	Mouse (BALB/c)	28 d (F)			0.45 F (increased serum testosterone and E2)		Maranghi et al. 2013 TetraBDE (BDE47)	
181	Mouse (BALB/c)	34 d 1 x/d (GO)		50 F			Mercado-Feliciano and Bigsby 2008a PentaBDE (DE-71)	Mice were ovariectomized 3 weeks prior to exposure; no change in uterus weight or uterus/vaginal histology.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
182	Mouse (NMRI)	29 d Gd 4 - Pnd 17 ~every 3 d (GO)		452 F			Skarman et al. 2005 PentaBDE (BDE99)	BDE-99; no change in maternal serum T4 levels.
183	Mouse (NMRI)	29 d Gd 4 - Pnd 17 ~every 3 d (GO)		452 F			Skarman et al. 2005 PentaBDE (Bromkal 70-5DE)	Bromkal 70-5DE; no changes in pregnancy rate, gestation length, or litter size.
184	Mouse (C57BL/6J)	70-80 d Pmd 28 - Pnd 21 (IN)		1 F			Ta et al. 2011 TetraBDE (BDE47)	Dams were fed tetraBDE-dosed cornflakes; no change in gestation length, litter size, or sex ratio.
185	Mouse (C56BL/6)	30 d (GO)		0.0015 M	0.045 M (germ cell loss and apoptosis in testes)		Wang et al. 2013 TetraBDE (BDE47)	
186	Mouse (C57BL/6)	10 wk Pmd 28 - Pnd 21 (GO)		0.03 F	0.1 F (58% decrease in litters surviving until Pnd 8)		Woods et al. 2012 TetraBDE (BDE47)	Females carrying on copy of a truncated Mecp2 gene were mated to unexposed wild-type males; LSE values are based on the wild-type offspring only.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
187	Mink (NS)	19 wk Pmd 28 - Pnw 6 (F)		0.05 F	0.25 F (no litters produced)		Bull et al. 2007 PentaBDE (DE-71)	
188	Mink (NS)	16-17 wk Pmw 4 - Pnw 6 (F)		0.06 F		0.31 F (complete litter loss)	Zhang et al. 2009 PentaBDE (DE-71)	
Developmental								
189	Rat (Sprague-Dawley)	5 wk Gd 6 - Pnd 21 (IN)		1 M	10 M (reduced serum T4 in Pnd 21 offspring)		Bansal et al. 2014 PentaBDE (DE-71)	Dams were given DE-71-dosed vanilla wafers.
190	Rat (Sprague-Dawley)	36 d Gd 6 - Pnd 21 (GO)		1	2 (altered neurobehavior, decreased hippocampal BDNF, and decreased serum T3, T4, and free T4 in offspring at Pnd 21-23)		Blanco et al. 2013 PentaBDE (BDE99)	
191	Rat (Sprague-Dawley)	21 wk Pmd 70 - Pnd 42 (GO)		0.5 M	5 M (decreased serum T4 in male offspring on Pnd 43)		Bondy et al. 2011, 2013 PentaBDE (DE-71)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
192	Rat (Sprague-Dawley)	6 wk Gd 1 - Pnd 21 (IN)		0.3	3 (reduced serum T3 and T4 in Pnd 21 offspring)		Bowers et al. 2015 PentaBDE (DE-71)	Dams were given DE-71-dosed cookies.
193	Rat (Sprague-Dawley)	36 d Gd 6 - Pnd 21 (GO)			2 M (delayed appearance of reflexes, impaired learning/memory at Pnd 36-37, and oxidative stress in the hippocampus at Pnd 37)		Cheng et al. 2009 PentaBDE (BDE99)	
194	Rat (Long- Evans)	7 d Pnd 6-12 (GO)		15 M			Driscoll et al. 2012 PentaBDE (DE-71)	No learning or attention deficits at Pnd 40-95.
195	Rat (Sprague-Dawley)	33 d Gd 6 - Pnd 18 (GO)			18 (decreased serum T4 in offspring)		Ellis-Hutchings et al. 2006 PentaBDE (DE-71)	Half of the dams in each group were maintained on a vitamin A deficient diet.
196	Rat (Long- Evans)	36 d Gd 6 - Pnd 21 (GO)		1.7	10.2 (reduced serum T4 in offspring at Pnd 7 and 14, reduced mammary gland development at Pnd 21, reduced female body weight from Pnd 29-58)		Kodavanti et al. 2010 PentaBDE (DE-71)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
197	Rat (Long- Evans)	36 d Gd 6 - Pnd 21 (GO)		0.96 M	2.85 M (reduced serum T4 in male offspring at Pnd 7-21)		Miller et al. 2012 PentaBDE (DE-71)	
198	Rat (Long- Evans)	36 d Gd 6 - Pnd 21 (GO)			11.2 (reduced serum T4 in offspring at Pnd 7-21)		Miller et al. 2012 PentaBDE (DE-71)	
199	Rat (Long- Evans)	~11 wk Pmd 28 - Pnd 21 (IN)			5.7 (reduced serum T4)		Poon et al. 2011 PentaBDE (DE-71)	Rats were given pentaBDE-dosed vanilla wafers.
200	Rat (Long- Evans)	36 d Gd 6 - Pnd 21 (GO)			1.7 M (hypertensive reaction to hyperosmotic stress in adult male offspring)		Shah et al. 2011 PentaBDE (DE-71)	
201	Rat (Long- Evans)	36 d Gd 6 - Pnd 21 (GO)		1.7	10.2 (transient reduction in serum T4 in offspring at Pnd 4 and 21)		Szabo et al. 2009 PentaBDE (DE-71)	
202	Rat (Wistar)	34 d Gd 1 - Pnd 14 (F)			3.2 (reduced serum T4 in offspring at Pnd 7 and 14)		Wang et al. 2011a TetraBDE (BDE47)	

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
203	Rat (Sprague-Dawley)	6 wk Gd 1 - Pnd 21 (GO)		0.2 M			Zhao et al. 2014 PentaBDE (BDE99)	No exposure-related changes in reflex maturation, motor coordination, or spatial learning of Pnd 3-36 offspring; no offspring body weight effects.
204	Rat (Long-Evans)	36 d Gd 6 - Pnd 21 (GO)		1	10 (reduced serum T4 in offspring on Pnd 4 and 14)		Zhou et al. 2002 PentaBDE (DE-71)	
205	Mouse (CD-1)	36 d Gd 6 - Pnd 21			18 M (transient alterations in open-field behavior of offspring at Pnd 34)		Branchi et al. 2005 PentaBDE (BDE99)	Administered via "self-administration" from a modified syringe or gavage; data from both groups were pooled for neurodevelopmental endpoints.
206	Mouse (CD-1)	5 wk Gd 8 - Pnd 21 (GO)		0.2 M			Kim et al. 2015 TetraBDE (BDE47)	No exposure-related changes in offspring body weight, motor activity at Pnd 21, or social interaction at Pnd 70.
207	Mouse (C57BL/6J)	70-80 d Pmd 28 - Pnd 21 (IN)			0.03 (impaired learning in offspring at Pnw 8)		Koenig et al. 2012 TetraBDE (BDE47)	Mice were fed 1-2 tetraBDE dosed cornflakes.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
208	Mouse (NMRI)	29 d Gd 4 - Pnd 17 ~every 3 d (GO)		452			Skarman et al. 2005 PentaBDE (BDE99)	BDE-99; no changes in offspring body weight or serum T4 levels
209	Mouse (NMRI)	29 d Gd 4 - Pnd 17 ~every 3 d (GO)			452 (reduced serum T4 in offspring at Pnd 11)		Skarman et al. 2005 PentaBDE (Bromkal 70-5DE)	Bromkal 70-5DE
210	Mouse (C57BL/6J)	70-80 d Pmd 28 - Pnd 21 (IN)			0.03 F (decreased center-field activity in open field in female offspring at Pnd 60)		Ta et al. 2011 TetraBDE (BDE47)	Dams were fed tetraBDE-dosed cornflakes.
211	Mouse (C57BL/6)	10 wk Pmd 28 - Pnd 21 (GO)			0.03 F (decreased pre-weaning weight; decreased pup vocalizations on Pnd 8-10, decreased sociability on Pnd 72)		Woods et al. 2012 TetraBDE (BDE47)	Females carrying on copy of a truncated Mecp2 gene were mated to unexposed wild-type males; LSE values are based on the wild-type offspring only.
212	Mink (NS)	19 wk Pmd 28 - Pnw 6 (F)		0.05			Bull et al. 2007 PentaBDE (DE-71)	No cholinergic effects in 6-week-old offspring.

Table 3-2 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
213	Mink (NS)	40 wk Pmd 28 - Pnw 27 (F)		0.05			Bull et al. 2007 PentaBDE (DE-71)	No cholinergic effects in 45-week-old offspring.
214	Mink (NS)	16-17 wk Pmw 4 - Pnw 6 (F)		0.06			Zhang et al. 2009 PentaBDE (DE-71)	No change in body weight, organ weights, plasma T3/T4, hepatic enzyme activity, or thyroid histology in offspring at weaning (Pnw 6).

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

b Three studies were used to derive an acute oral minimal risk level (MRL); concentration divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for animal to human, and 10 for human variability), resulting in an MRL of 0.00006 mg/kg/day.

c Used to derive an intermediate oral minimal risk level (MRL); concentration divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human, 10 for human variability), resulting in an MRL of 0.000003 mg/kg/day.

Note on chemical form: Mixtures are identified by composition or trade name (if reported); otherwise, they are reported as "technical". Trade names include Bromkal 70, Bromakal 70-5 DE, DE-71, and Saytex 115 for pentaBDE mixtures and DE-79, FR-1208, and Saytex 111 for octaBDE mixtures. For the studies by Bruchajzer (2011) and Bruchajzer et al. (2010, 2011, 2012), the mixtures were made to resemble formerly used commercial mixtures. The pentaBDE mixture was composed of 63.2% pentaBDE, 21.4% tetraBDE, 15.4% hexaBDE, and 0.04% heptaBDE; the octaBDE mixture was composed of 65.7% octaBDE, 14.8% heptaBDE, 1.7% hexaBDE, and 17.8% nona- and deca-BDE. Individual congeners are identified by IUPAC number: BDE 15 = 4,4'-diBDE; BDE 47 = 2,2',4,4'-tetraBDE; BDE 99 = 2,2',4,4',5-pentaBDE; BDE 153 = 2,2',4,4',5,5'-hexaBDE; BDE 183 = 2,2',3,4,4',5',6-heptaBDE; BDE 203 = 2,2',3,4,4',5,5',6-octaBDE; BDE 206 = 2,2',3,3',4,4',5,5',6-nonaBDE

BDNF = brain derived neurotrophic factor; Bd Wt = body weight; BMDL = benchmark dose lower confidence limit; Cardio = cardiovascular; d = day(s); E2 = estradiol; Endocr = endocrine; (F) = feed; F = Female; FSH = follicle stimulating hormone; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; Hemato = hematological; IgG = immunoglobulin G; Immuno/Lymphoret = immunological/lymphoreticular; IN = ingestion; LH = luteinizing hormone; KLH = keyhole limpet hemocyanin; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; PHA = phytohemagglutinin; Pmd = pre-mating day; Pmw = pre-mating week; Pnd = post-natal day; Pnw = post-natal week; PPS = preputial separation; Resp = respiratory; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; x = time(s); wk = week(s)

Figure 3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral

Acute (≤14 days)

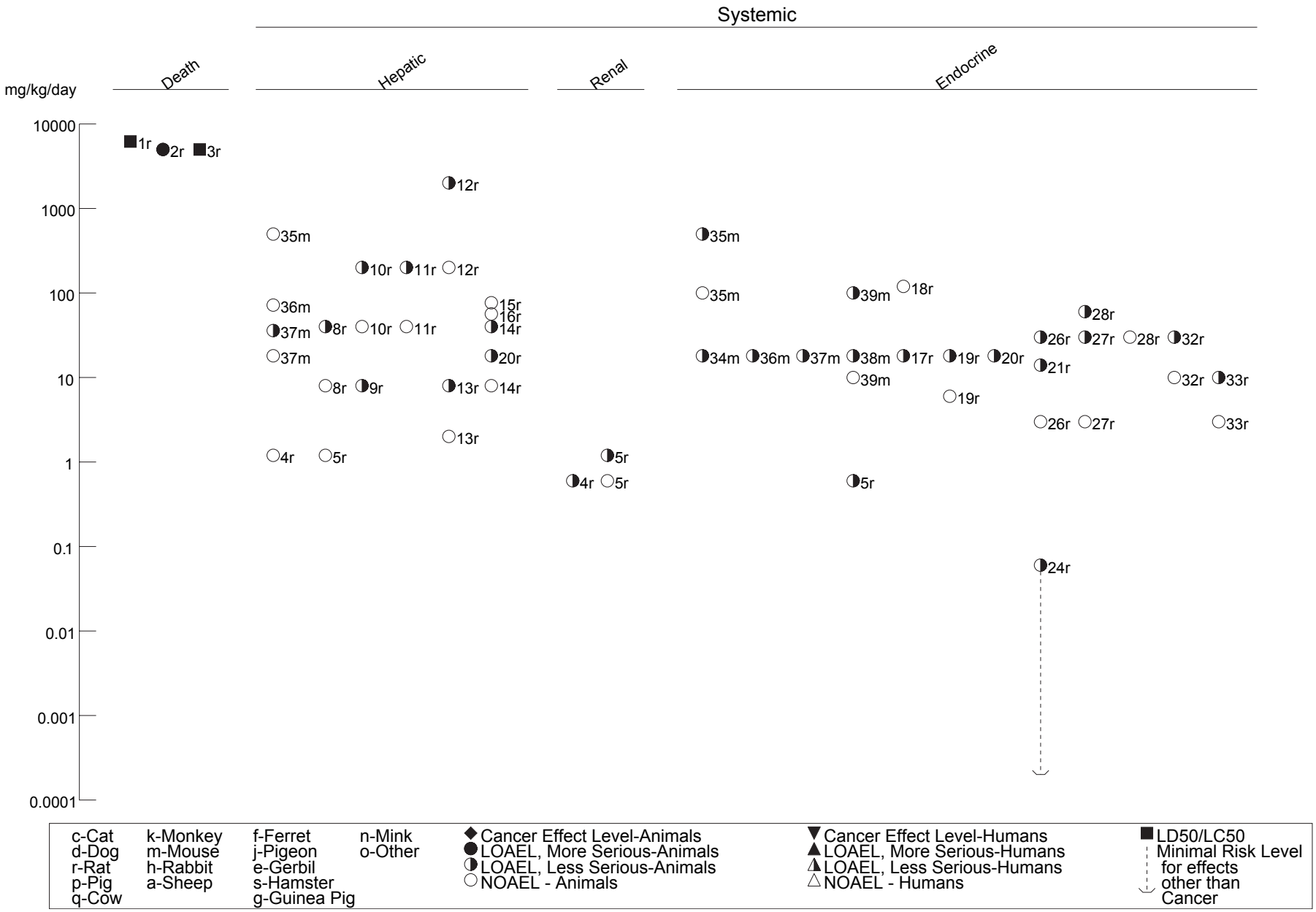


Figure 3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral *(Continued)*

Acute (≥14 days)

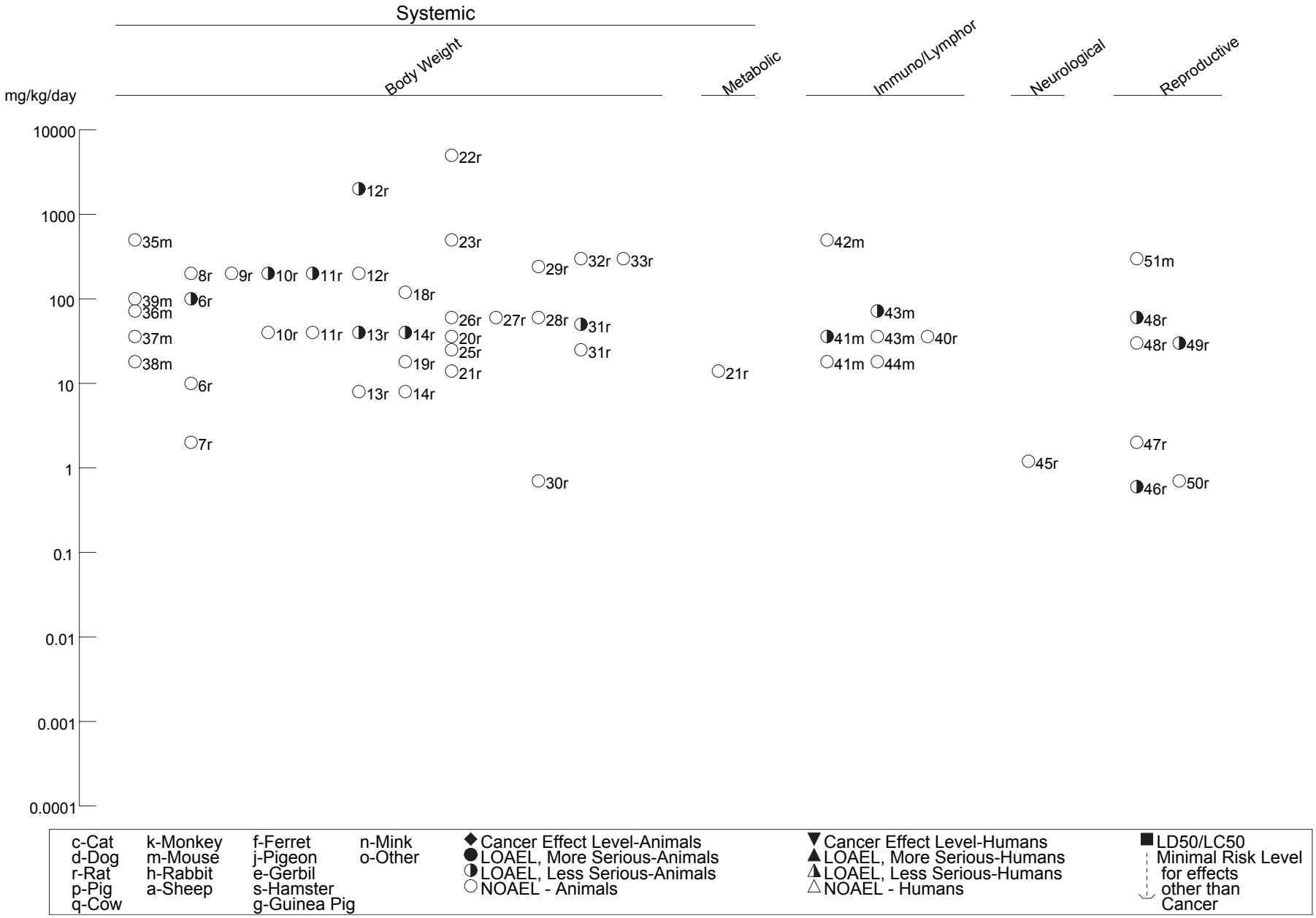


Figure 3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral *(Continued)*

Acute (≤14 days)

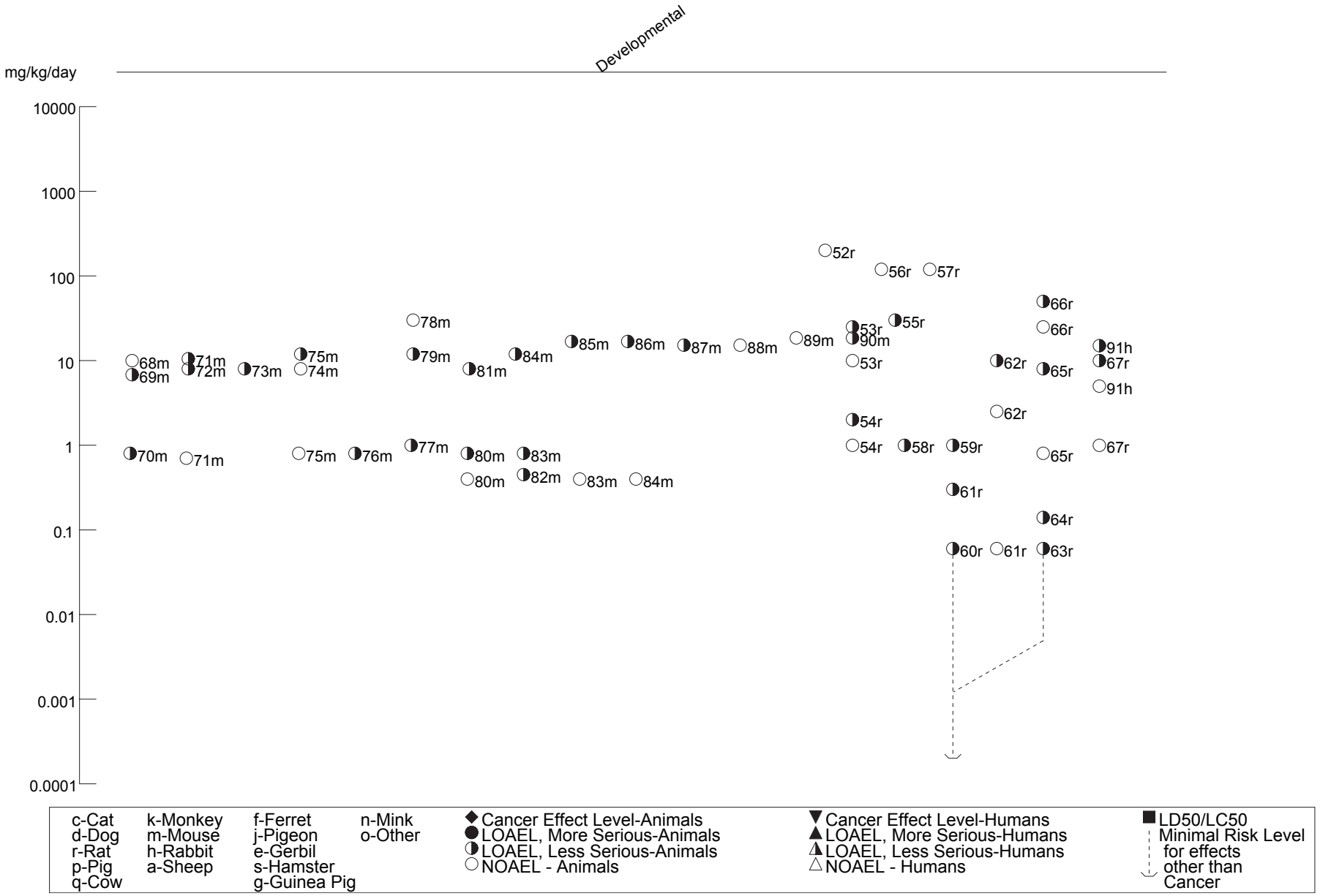


Figure 3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral *(Continued)*

Intermediate (15-364 days)

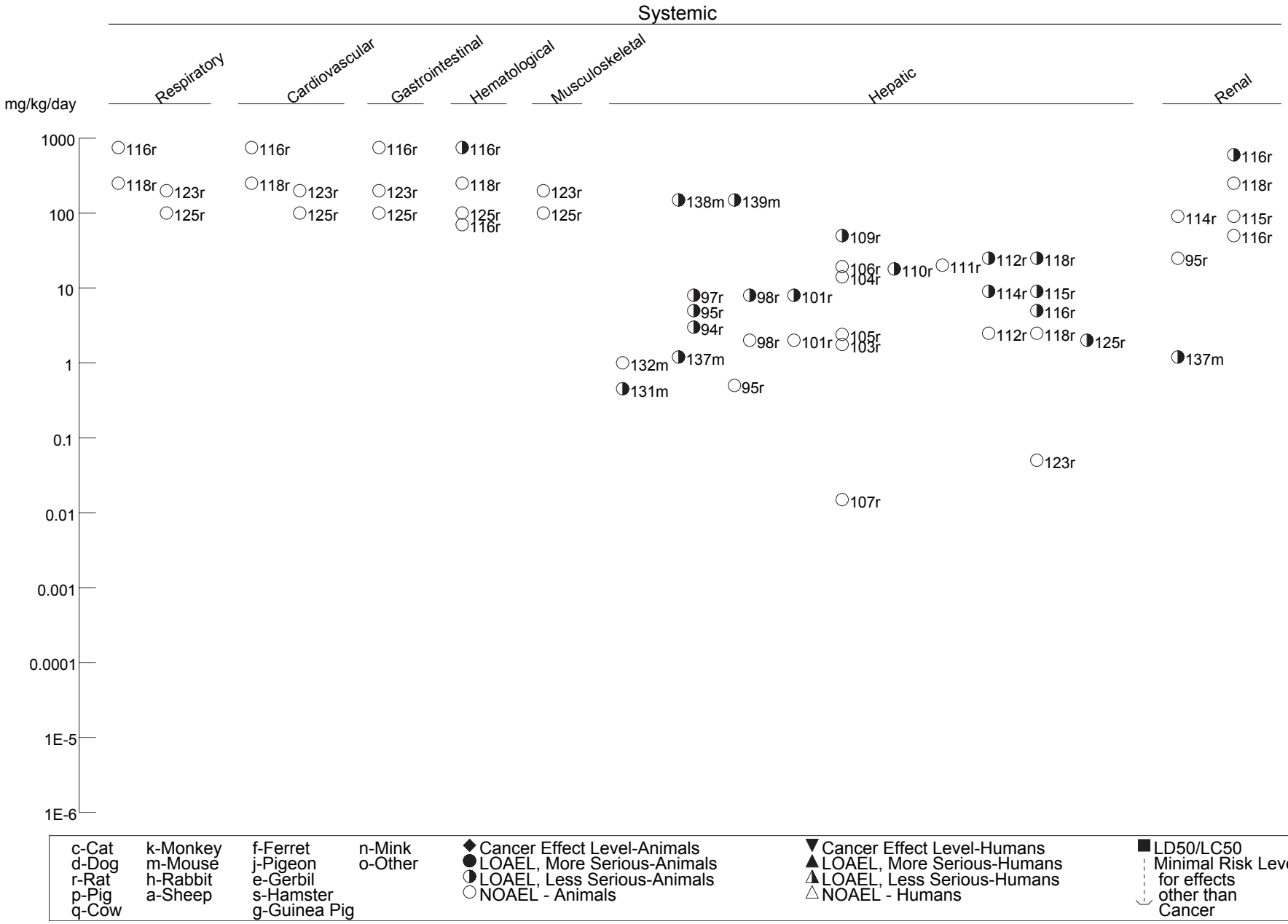


Figure 3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral *(Continued)*

Intermediate (15-364 days)

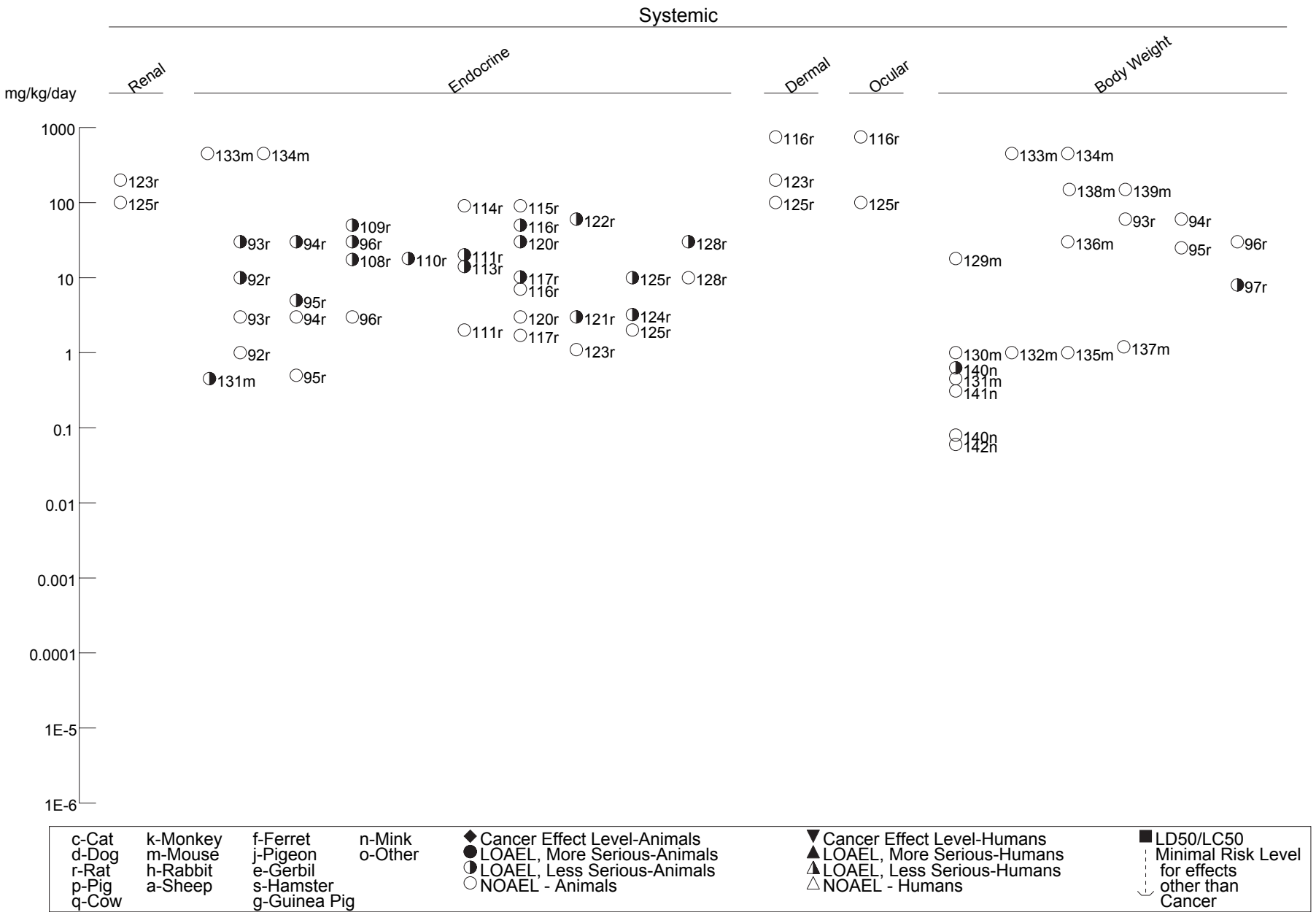


Figure 3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral *(Continued)*

Intermediate (15-364 days)

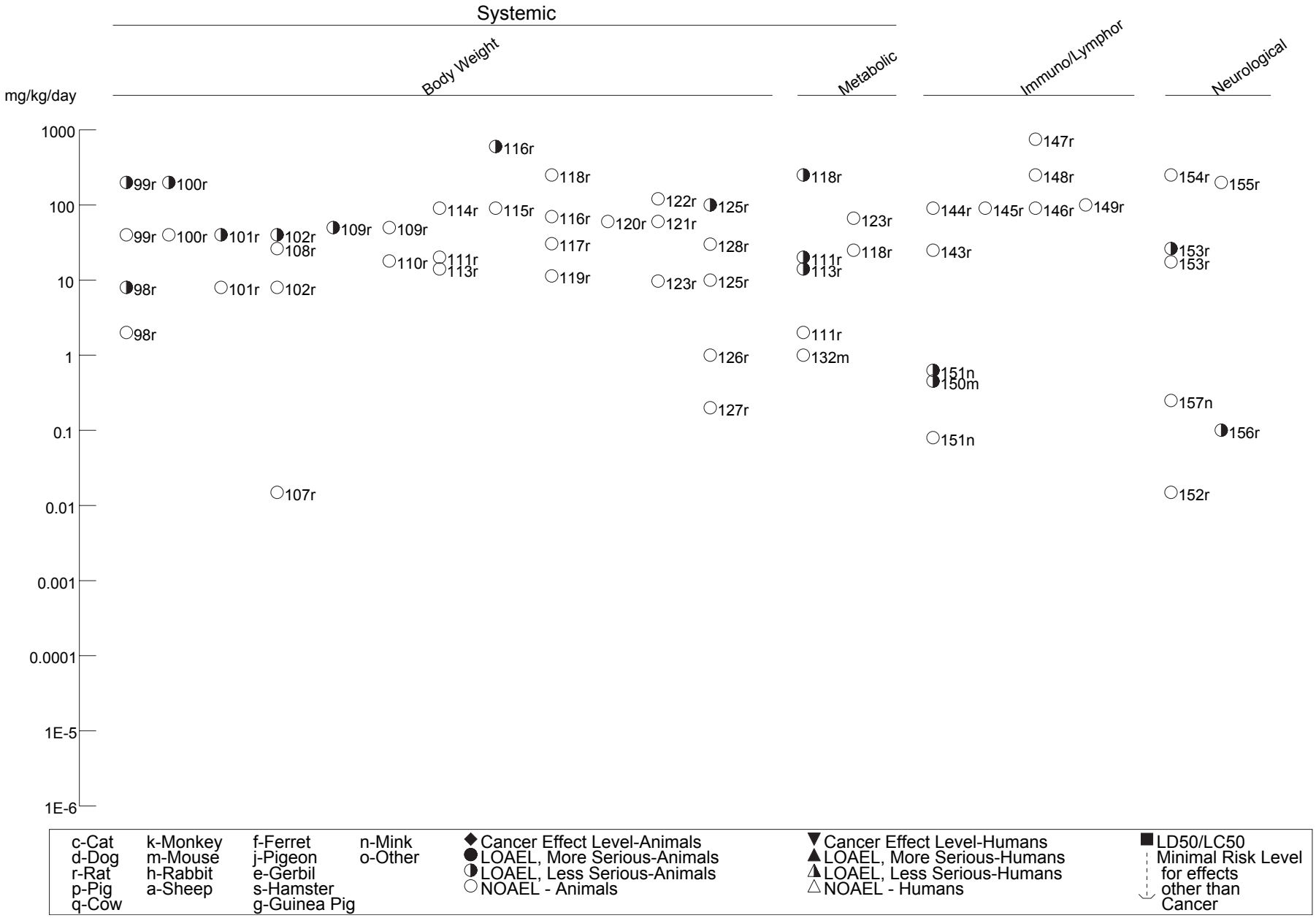


Figure 3-2. Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Oral *(Continued)*

Intermediate (15-364 days)

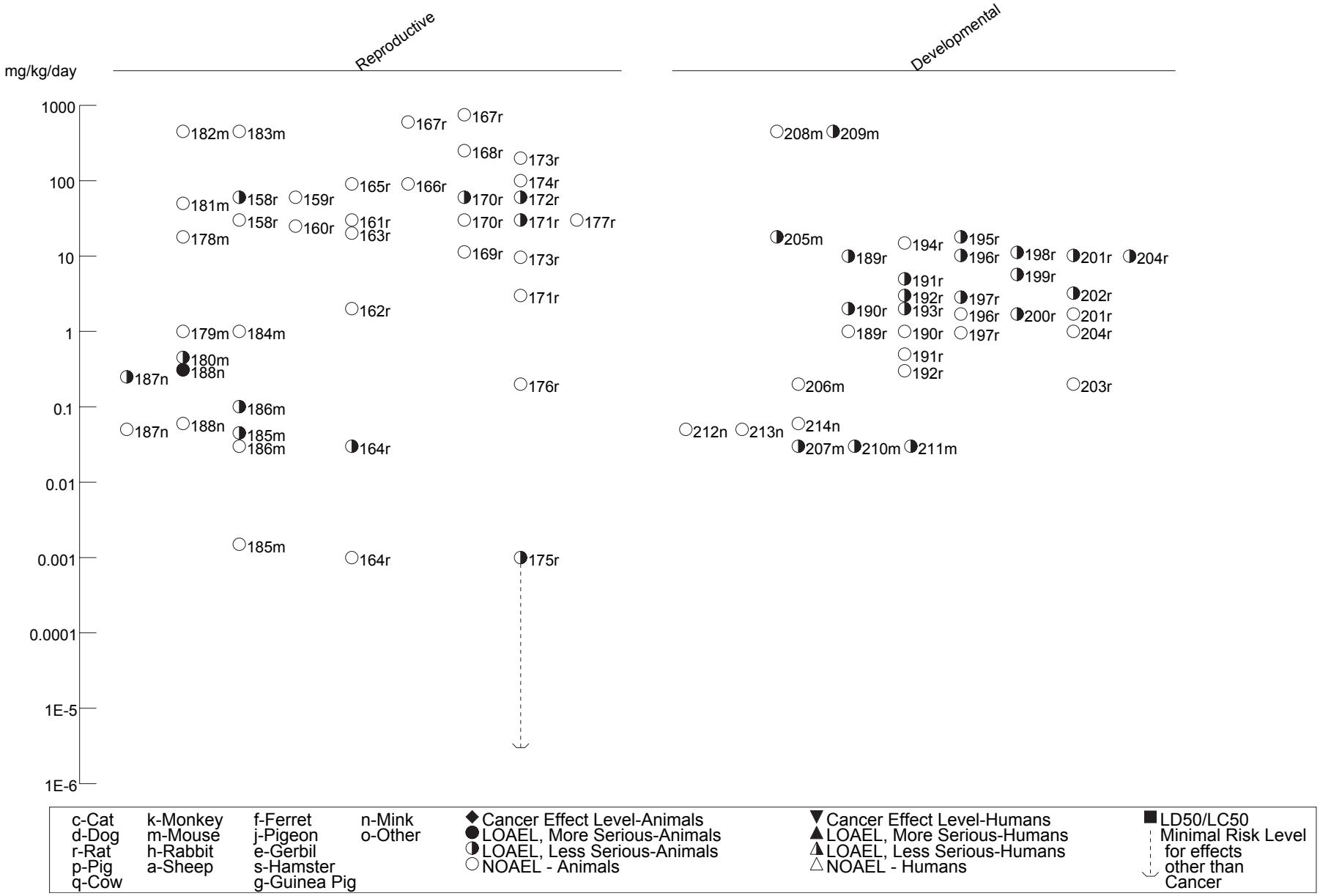


Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Wistar)	7 d 1 x/d	Hepatic	1000 F			Bruchajzer et al. 2010 DecaBDE (BDE209)	
			Bd Wt	1000 F				
2	Rat (Wistar)	14 d 1 x/d	Hepatic	1000 F			Bruchajzer et al. 2010 DecaBDE (BDE209)	
			Bd Wt	1000 F				
3	Rat (Sprague-Dawley)	14 d 1 x/d (GO)	Hepatic	95.9 M			Carlson 1980b DecaBDE (technical)	
4	Rat Spartan	once (GO)	Bd Wt	5000			IRDC 1974 DecaBDE (technical)	
5	Rat (Fischer- 344)	14 d 1 x/d (F)	Bd Wt	16000			NTP 1986 DecaBDE (technical, 94-97% pure)	
6	Rat (Long-Evans)	4 d 1 x/d (GO)	Endocr	100 F			Zhou et al. 2001 DecaBDE (DE-83R)	No exposure-related changes in serum thyroid hormone levels.
			Bd Wt		300 F			
7	Mouse (C57)	3 d Gd 7-9 (G)	Endocr	750 F	1500 F	(reduced maternal serum T4)	Chi et al. 2011 DecaBDE (BDE209)	
8	Mouse (B6C3F1)	14 d 1 x/d (F)	Bd Wt	19000			NTP 1986 DecaBDE (technical, 94-97% pure)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
9	Mouse (C3H/HeNCrlC(F)	1 wk	Bd Wt	9800 M			Sakamoto et al. 2013 DecaBDE (BDE209)	No change in liver weights were observed.
Developmental								
10	Rat (Sprague-Dawley)	2 wk Gd 1-14 (GO)		10 M	30 M (impaired learning in Pnd 25 offspring)		Chen et al. 2014 DecaBDE (BDE209)	
11	Rat (Sprague-Dawley)	once Pnd 3 (G)			6.7 M (decreased spontaneous activity at 2 months)		Viberg et al. 2007 DecaBDE (BDE209)	
12	Mouse (NMRI)	once Pnd 3 (GO)		1.34[b]	5.76 (decreased activity and impaired habituation at 2-4 months; impaired learning at 5-7 months)		Buratovic et al. 2014 DecaBDE	
13	Mouse (C57)	3 d Gd 7-9 (G)		150	750 (10% decrease in fetal weight, 3% increase in post-implantation loss)		Chi et al. 2011 DecaBDE (BDE209)	
14	Mouse (NMRI)	once Pnd 3 (G)		1.34[b] M	2.22 M (decreased activity and impaired habituation at 2 and 4 months)		Johansson et al. 2008 DecaBDE (BDE209)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Mouse (C57BL/6J)	14 d Pnd 2-15 (IN)		6	20 (delayed ontogeny of reflexes in males and females, increased locomotion in Pnd 70 males, reduced serum T4 in Pnd 21 males)		Rice et al. 2007 DecaBDE (BDE209)	Compound administered via micropipette.
16	Mouse (C57BL/6J)	14 d Pnd 2-15 (IN)		6	20 (learning impairment and impulsivity at 16 months of age)		Rice et al. 2009 DecaBDE (BDE209)	Compound administered via micropipette.
17	Mouse (NMRI)	once Pnd 3 (G)			2.22 M (decreased spontaneous activity at 2 and 6 months)		Viberg et al. 2003b DecaBDE (BDE209)	
18	Mouse (NMRI)	once Pnd 10 (G)		20.1 M			Viberg et al. 2003b DecaBDE (BDE209)	No change in spontaneous activity or habituation at 2, 4, or 6 months.
19	Mouse (NMRI)	once Pnd 19 (G)		20.1 M			Viberg et al. 2003b DecaBDE (BDE209)	No change in spontaneous activity or habituation at 2, 4, or 6 months.
INTERMEDIATE EXPOSURE								
Systemic								
20	Rat (Sprague-Dawley)	36 d Gd 6 - Pnd 21 (GO)	Bd Wt	1000 F			Biesemeier et al. 2011 DecaBDE (BDE209)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Rat (Wistar)	21 d 1 x/d	Hepatic	1000 F			Bruchajzer et al. 2010 DecaBDE (BDE209)	
			Bd Wt	1000 F				
22	Rat (Wistar)	28 d 1 x/d	Hepatic	1000 F			Bruchajzer et al. 2010 DecaBDE (BDE209)	
			Bd Wt	1000 F				
23	Rat (Sprague-Dawley)	31 d Gd 10 - Pnd 21 (F)	Bd Wt	146 F			Fujimoto et al. 2011 DecaBDE (BDE209)	
24	Rat (CD)	28 d (F)	Hepatic	90			IRDC 1976 DecaBDE (technical)	
			Renal	90				
			Endocr	90				
			Bd Wt	90				
25	Rat (Sprague-Dawley)	33 d (Pnd 10-42) 1 x/d (G)	Hepatic	100 M	300 M (fatty degeneration, inflammatory foci)		Lee et al. 2010 DecaBDE (BDE209)	
			Endocr		100 M (reduced serum T3)			
			Bd Wt	600 M				

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
26	Rat (Sprague-Dawley)	~11wk Pmd 21 - Pnd 21 (GO)	Hepatic		300 F (hepatocyte degeneration, eosinophilic changes)		Liu et al. 2012 DecaBDE (BDE209)	
			Bd Wt		300 F (12% decrease in maternal body weight)			
27	Rat (Fischer- 344)	13 wk (F)	Resp	8000			NTP 1986 DecaBDE (technical, 94-97% pure)	
			Cardio	8000				
			Gastro	8000				
			Hemato	8000				
			Musc/skel	8000				
			Hepatic	8000				
			Renal	8000				
			Endocr	8000				
			Bd Wt	8000				

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
28	Rat (Wistar)	28 d (G)	Hemato	60			Van der Ven et al. 2008a DecaBDE (BDE209)	
			Musc/skel	60				
			Renal	60				
			Endocr	30 F	60 F (increased serum T3)			
			Bd Wt	60				
29	Rat (Sprague-Dawley)	90 d 1 x/d (GO)	Hepatic	100 M			Wang et al. 2010 DecaBDE (BDE209)	No change in kidney weight, clinical chemistry parameters, or serum thyroid hormones.
			Renal	100 M				
			Endocr	100 M				
			Bd Wt	100 M				
30	Rat (Sprague-Dawley)	90 d 1 x/d (GO)	Endocr	50 M			Wang et al. 2011b DecaBDE (BDE209)	No exposure-related changes in serum thyroid hormone levels.
			Bd Wt	50 M				
31	Rat (Sprague-Dawley)	8 wk 7 d/wk (GO)	Endocr		0.05[c] M (12% increase in serum glucose)		Zhang et al. 2013a DecaBDE (BDE209)	
			Bd Wt	20 M				

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
32	Mouse (Tg2576)	15 d 1 x/d (GO)	Bd Wt	20 M			Heredia et al. 2012 DecaBDE (BDE209)	
33	Mouse (CD-1)	15 d 1 x/d (G)	Bd Wt	160			Liang et al. 2010 DecaBDE (BDE209)	
34	Mouse (CD-1)	30 d 1 x/d (G)	Bd Wt	160			Liang et al. 2010 DecaBDE (BDE209)	
35	Mouse (CD-1)	60 d 1 x/d (G)	Bd Wt	160			Liang et al. 2010 DecaBDE (BDE209)	
36	Mouse (B6C3F1)	13 wk (F)	Resp	9500			NTP 1986 DecaBDE (technical, 94-97% pure)	
			Cardio	9500				
			Gastro	9500				
			Hemato	9500				
			Musc/skel	9500				
			Hepatic	9500				
			Renal	9500				
			Endocr	9500				
			Bd Wt	9500				

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
37	Mouse (C3H/HeNCrlC	4 wk (F)	Hepatic		9400 M (moderate hepatocellular hypertrophy)		Sakamoto et al. 2013 DecaBDE (BDE209)	
			Bd Wt	9400 M				
38	Mouse (Parkes)	35 d (GO)	Endocr	750 M	950 M (reduced serum T3 and T4)		Sarkar et al. 2015 DecaBDE (BDE209)	
			Bd Wt	950 M				
39	Mouse (CD-1)	50 d 1 x/d (GO)	Bd Wt	1500 M			Tseng et al. 2006 DecaBDE (BDE209)	
40	Mouse (CD-1)	18 d Gd 0-17 (GO)	Bd Wt	1500 F			Tseng et al. 2008 DecaBDE (BDE209)	
41	Mouse (BALB/c)	31 d Gd 10 - Pnd 21 (F)	Bd Wt	260 F			Watanabe et al. 2008 DecaBDE (BDE209)	
42	Mouse (BALB/c)	28 d (F)	Bd Wt	1800 F			Watanabe et al. 2010a DecaBDE (BDE209)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
43	Rat (CD)	28 d (F)		90			IRDC 1976 DecaBDE (technical)	No exposure-related changes in spleen weight or spleen or thymus histology.
44	Rat (Sprague-Dawley)	~11wk Pmd 21 - Pnd 21 (NS)			300 F (increased spleen weight, lesions in spleen and thymus, altered T-cell distribution, decreased serum IgM, IgG, decreased lymphocyte proliferation)		Liu et al. 2012 DecaBDE (BDE209)	
45	Rat (Fischer- 344)	13 wk (F)		8000			NTP 1986 DecaBDE (technical, 94-97% pure)	
46	Rat (Wistar)	28 d (G)		60 M			Van der Ven et al. 2008a DecaBDE (BDE209)	No exposure-related changes in spleen or thymus weight or histology, no change in spleen cell subpopulations.
47	Mouse (C57BL/6)	10 mo every other day (GO)			800 F (impaired CD4 T cell immune function)		Feng et al. 2016b DecaBDE (BDE209)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
48	Mouse (B6C3F1)	13 wk (F)		9500			NTP 1986 DecaBDE (technical, 94-97% pure)	
49	Mouse (BALB/c)	28 d (F)		1800 F			Watanabe et al. 2010a DecaBDE (BDE209)	No change in pulmonary viral load after RSV infection 1 week after exposure period.
Neurological								
50	Rat (Sprague-Dawley)	90 d 1 x/d (GO)		50 M			Wang et al. 2011b DecaBDE (BDE209)	No changes in open-field behavior.
51	Rat (Wistar)	20 d Pnd 22-41 (G)			20.1 (decreased synaptic potency, short-term plasticity, and long-term potentiation on Pnd 60)		Xing et al. 2009 DecaBDE (BDE209)	
52	Mouse (Tg2576)	15 d 1 x/d (GO)			20 M (decreased anxiety behaviors)		Heredia et al. 2012 DecaBDE (BDE209)	
53	Mouse (CD-1)	15 d 1 x/d (G)		160			Liang et al. 2010 DecaBDE (BDE209)	No exposure-related changes in brain weight or AchE activity.

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Mouse (CD-1)	30 d 1 x/d (G)		160			Liang et al. 2010 DecaBDE (BDE209)	No exposure-related changes in brain weight or AchE activity.
55	Mouse (CD-1)	60 d 1 x/d (G)		80	160 (transient reduction in brain AchE activity)		Liang et al. 2010 DecaBDE (BDE209)	
Reproductive								
56	Rat (Sprague-Dawley)	36 d Gd 6 - Pnd 21 (GO)		1000 F			Biesemeier et al. 2011 DecaBDE (BDE209)	No treatment-related changes in maternal toxicity, gestation length, or number of implantations.
57	Rat (Sprague-Dawley)	32 d Gd 10 - Pnd 21 (F)		146 F			Fujimoto et al. 2011 DecaBDE (BDE209)	No change in number of implantations, live pups, or sex ratio.
58	Rat (CD)	28 d (F)		90			IRDC 1976 DecaBDE (technical)	No exposure-related changes in reproductive organ weight or histology.
59	Rat (Sprague-Dawley)	Pnd 10-42 1 x/d (G)		600 M			Lee et al. 2010 DecaBDE (BDE209)	No exposure-related changes in reproductive organ weight or testicular histology.

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
60	Rat (Sprague-Dawley)	~11wk Pmd 21 - Pnd 21 (NS)			300 F (atrophic and fibrotic changes in ovary, decreased number of ovarian follicles)		Liu et al. 2012 DecaBDE (BDE209)	
61	Rat (Fischer- 344)	13 wk (F)		8000			NTP 1986 DecaBDE (technical, 94-97% pure)	No exposure-related changes in reproductive organ histology.
62	Mouse (B6C3F1)	13 wk (F)		9500			NTP 1986 DecaBDE (technical, 94-97% pure)	No exposure-related changes in reproductive organ histology.
63	Mouse (Parkes)	35 d (GO)		750 M	950 M (13-18% decrease in relative testis and epididymides weight, degenerative changes in seminiferous tubules, reduced sperm count/viability, reduced serum testosterone)		Sarkar et al. 2015 DecaBDE (BDE209)	
64	Mouse (CD-1)	50 d Pnd 21-70 (GO)		100 M	500 M (reduced amplitude of lateral head velocity of sperm; reduced sperm mitochondrial membrane potential)		Tseng et al. 2006 DecaBDE (BDE209)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
65	Mouse (CD-1)	18 d Gd 0-17 (GO)		1500 F			Tseng et al. 2008 DecaBDE (BDE209)	No change in gestational length or litter size, no change in ovary weight.
66	Mouse (BALB/c)	31 d Gd 10 - Pnd 21 (F)		260 F			Watanabe et al. 2008 DecaBDE (BDE209)	No change in the number of litters.
67	Mouse (BALB/c)	31 d Gd 10 - Pnd 21 (F)		2900 F			Watanabe et al. 2010b DecaBDE (BDE209)	No change in the number of litters.
Developmental								
68	Rat (Sprague-Dawley)	36 d Gd 6 - Pnd 21 (GO)		1000			Biesemeier et al. 2011 DecaBDE (BDE209)	No treatment-related changes in litter size, sex ratio, pup survival and development, or neurobehavior or neuropathology of offspring.
69	Rat (Sprague-Dawley)	32 d Gd 10 - Pnd 21 (F)			2 (diffuse liver cell hypertrophy with cytoplasmic eosinophilia in male offspring and cytoplasmic eosinophilia in the cortical proximal tubules of the kidney of female offspring at Pnd 20; recovered by Pnw 11)		Fujimoto et al. 2011 DecaBDE (BDE209)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
70	Rat (Sprague-Dawley)	20 d Gd 0-19 (GO)		1000 F			Hardy et al. 2002 97.34% deca-, 2.66% nona- and octa-BDE	
71	Rat (Wistar)	21 d Gd 1-21 (G)		20.1			Xing et al. 2009 DecaBDE (BDE209)	No change in hippocampal eletrophysiological readings in Pnd 60 offspring.
72	Rat (Wistar)	61 d Gd 1 - Pnd 41 (G)			20.1 (decreased synaptic potency, short-term plasticity, and long-term potentiation in hippocampus in Pnd 60 offspring)		Xing et al. 2009 DecaBDE (BDE209)	DecaBDE administered to dams Gd 1- Pnd 21 and to offspring Pnd 22-41.
73	Rat (Wistar)	21 d Pnd 1-21 (G)			20.1 (altered long-term potentiation in hippocampus of Pnd 60 offspring)		Xing et al. 2009 DecaBDE (BDE209)	DecaBDE administered to dams.
74	Rat (Wistar)	19 d Pnd 3-21 (G)			20.1 (decreased synaptic potency, short-term plasticity, and long-term potentiation in hippocampus on Pnd 60)		Xing et al. 2009 DecaBDE (BDE209)	DecaBDE administered to neonates.

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
75	Mouse (CD-1)	18 d Gd 0-17 (GO)			10 M (hepatocytic swelling in male offspring at Pnd 71)		Tseng et al. 2008 DecaBDE (BDE209)	
76	Mouse (CD-1)	18 d Gd 0-17 (GO)			10 M (vacuolization in interstitial cells of testes and sperm damage in male offspring at Pnd 71)		Tseng et al. 2013 DecaBDE (BDE209)	
77	Mouse (BALB/c)	31 d Gd 10 - Pnd 21 (F)		34	260 (15% decrease in pup weight on Pnd 21; increased viral load in lung and IFN-gamma in BALF in offspring on Pnd 33)		Watanabe et al. 2008 DecaBDE (BDE209)	Pups were infected with RSV on Pnd 28.
78	Mouse (BALB/c)	31 d Gd 10 - Pnd 21 (F)		290	2900 (increased viral load in lung and altered cytokine expression BALF in offspring on Pnd 29-33)		Watanabe et al. 2010b DecaBDE (BDE209)	Pups were infected with RSV on Pnd 28.
Cancer								
79	Mouse (C3H/HeNCrlC	27 wk (F)			9100 M (CEL: liver neoplastic nodules; altered foci)		Sakamoto et al. 2013 DecaBDE (BDE209)	
CHRONIC EXPOSURE								
Death								
80	Mouse (C57BL/6)	2 yr every other day (GO)				800 F (5/10 died vs. 1/10 controls)	Feng et al. 2015 DecaBDE (BDE209)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
81	Rat (Sprague-Dawley)	2 yr (F)	Resp	1			Kociba et al. 1975; Norris et al. 1975a 77% decaBDE, 22% nonaBDE	
			Cardio	1				
			Gastro	1				
			Hemato	1				
			Musc/skel	1				
			Hepatic	1				
			Renal	1				
			Endocr	1				
			Ocular	1				
			Bd Wt	1				

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
82	Rat (Fischer- 344)	103 wk (F)	Resp	2550 F			NTP 1986 DecaBDE (technical, 94-97% pure)	
			Cardio	2550 F				
			Gastro	1120 M	2240 M (acanthosis)			
			Hemato	2550 F				
			Musc/skel	2550 F				
			Hepatic		1120 M (precancerous neoplastic nodules)			
			Renal	2550 F				
			Endocr	2550 F				
			Bd Wt	2550 F				

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
83	Mouse (B6C3F1)	103 wk (F)	Resp	7780 F			NTP 1986 DecaBDE (technical, 94-97% pure)	
			Cardio	7780 F				
			Gastro	3760 F	7780 F (ulcers)			
			Hemato	7780 F				
			Musc/skel	7780 F				
			Hepatic		3200 M (centrilobular hypertrophy and granulomas)			
			Renal	7780 F				
			Endocr		3200 M (follicular cell hyperplasia)			
			Bd Wt	7780 F				
Immuno/ Lymphoret								
84	Rat (Sprague-Dawley)	2 yr (F)		1			Kociba et al. 1975; Norris et al. 1975a 77% decaBDE, 22% nonaBDE	No exposure-related changes in immune tissue histology.
85	Rat (Fischer- 344)	103 wk (F)			1200 F (splenic hematopoiesis)		NTP 1986 DecaBDE (technical, 94-97% pure)	
86	Mouse (B6C3F1)	103 wk (F)		7780 F			NTP 1986 DecaBDE (technical, 94-97% pure)	No exposure-related changes in immune tissue histology

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
87	Rat (Sprague-Dawley)	2 yr (F)		1 M 1 F			Kociba et al. 1975; Norris et al. 1975a 77% decaBDE, 22% nonaBDE	
88	Rat (Fischer- 344)	103 wk (F)		2240 M 2550 F			NTP 1986 DecaBDE (technical, 94-97% pure)	No exposure-related changes in reproductive organ histology.
89	Mouse (B6C3F1)	103 wk (F)		6650 M 7780 F			NTP 1986 DecaBDE (technical, 94-97% pure)	No exposure-related changes in reproductive organ histology.
Cancer								
90	Rat (Fischer- 344)	103 wk (F)				1120 M (CEL: liver neoplastic nodules)	NTP 1986 DecaBDE (technical, 94-97% pure)	

Table 3-3 Levels of Significant Exposure to Decabromodiphenyl Ether - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
91	Mouse (B6C3F1)	103 wk (F)				3200 M (CEL: hepatocellular adenomas and carcinomas)	NTP 1986 DecaBDE (technical, 94-97% pure)	

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

b Used to derive an acute oral minimal risk level (MRL); concentration divided by an uncertainty factor of 100 (10 for animal to human, and 10 for human variability), resulting in an MRL of 0.01 mg/kg/day.

c Used to derive an intermediate oral minimal risk level (MRL); concentration divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL,10 for animal to human, 10 for human variability), resulting in an MRL of 0.0002 mg/kg/day.

Note on chemical form: Mixtures are identified by composition or trade name (if reported); otherwise, they are reported as "technical". Trade names for decaBDE include DE-83R (98% decaBDE). The individual congener is identified by by IUPAC number: BDE 209 = 2,2',3,3',4,4',5,5',6,6'-decaBDE. Where study authors report use of decaBDE, without further compositional information, it is assumed the pure congener (BDE 209) was used.

AchE = acetylcholinesterase; BALF = brochoalveolar lavage fluid; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; Hemato = hematological; IFN = interferon; IgG = immunoglobulin G; IgM = immunoglobulin M; Immuno/Lymphoret = immunological/lymphoreticular; IN = ingestion ; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Pmd = pre-mating day; Pnd = post-natal day; Pnw = post-natal week; Resp = respiratory; RSV = respiratory syncytial virus; T3 = triiodothyronine; T4 = thyroxine; x = time(s); wk = week(s); yr = year(s)

Figure 3-3. Levels of Significant Exposure to Decabromodiphenyl Ether - Oral

Acute (≤14 days)

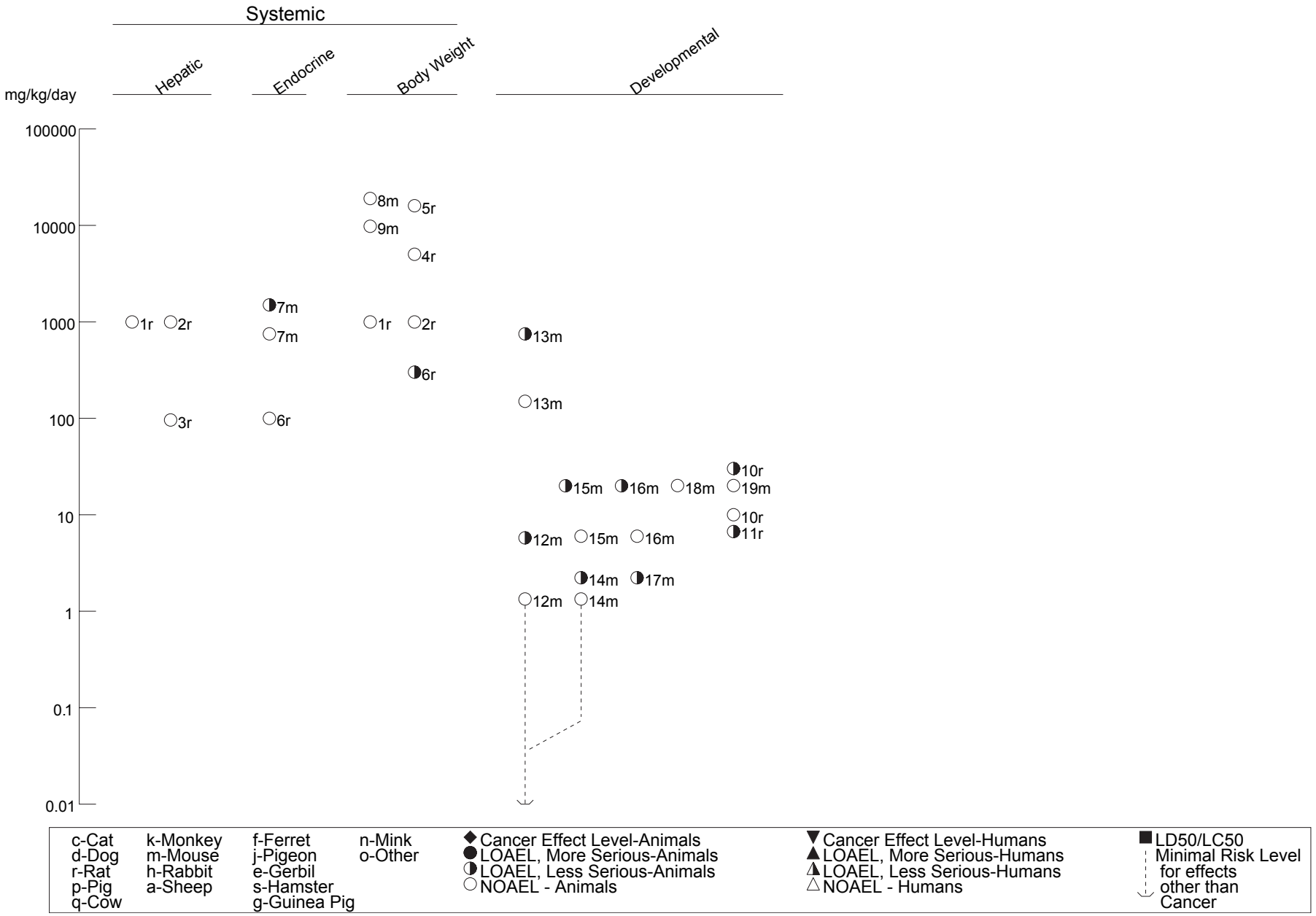


Figure 3-3. Levels of Significant Exposure to Decabromodiphenyl Ether - Oral *(Continued)*

Intermediate (15-364 days)

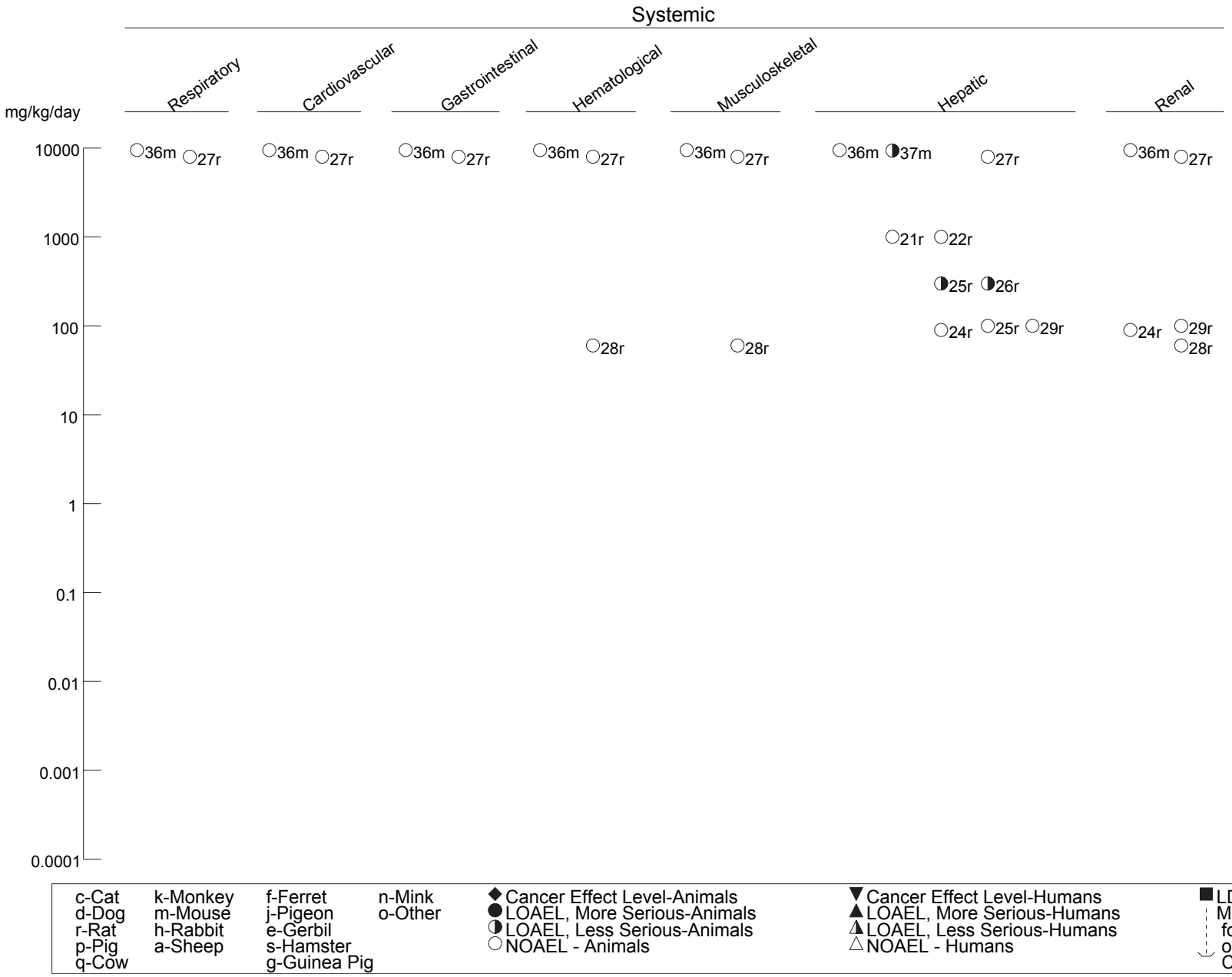


Figure 3-3. Levels of Significant Exposure to Decabromodiphenyl Ether - Oral *(Continued)*

Intermediate (15-364 days)

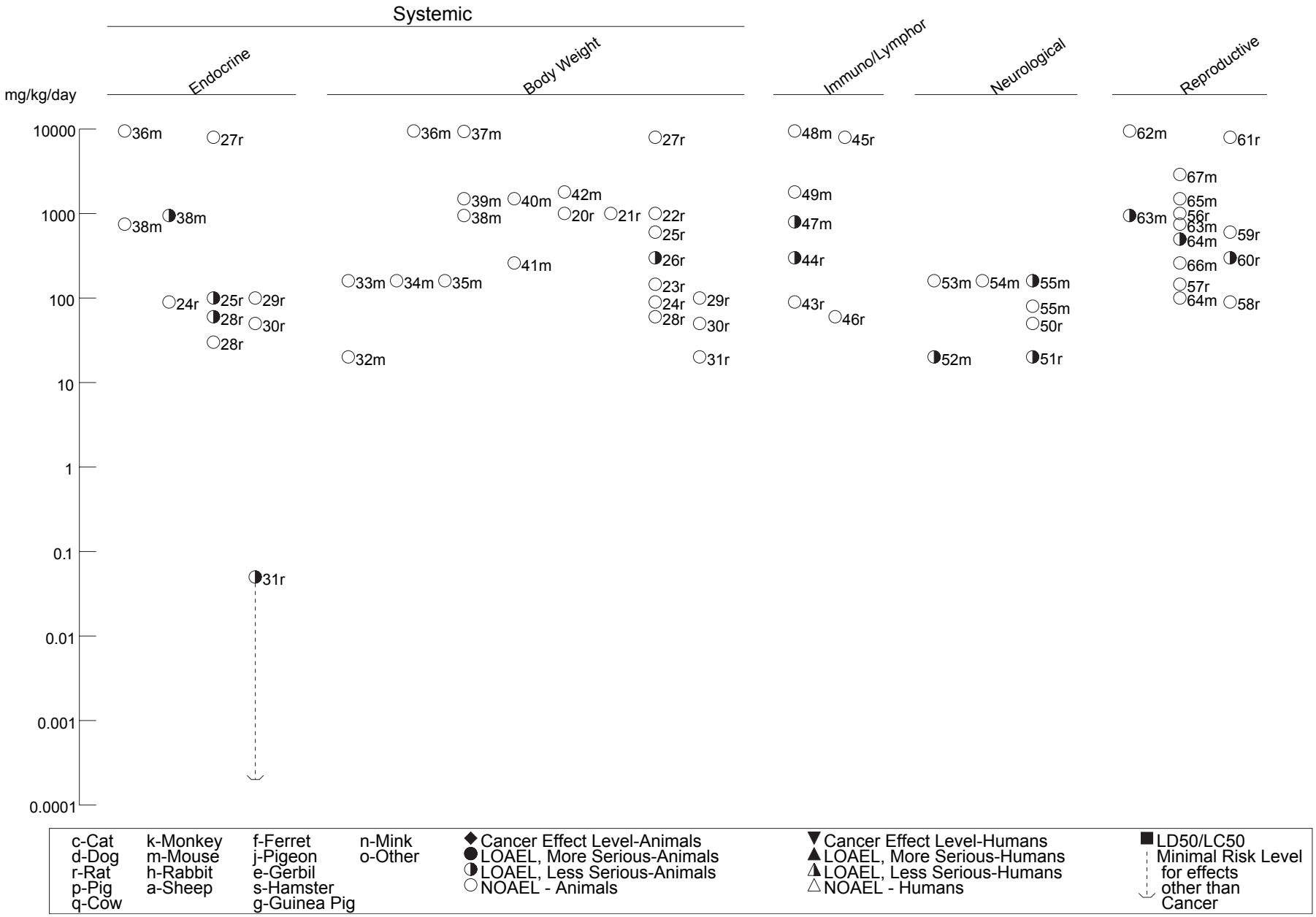
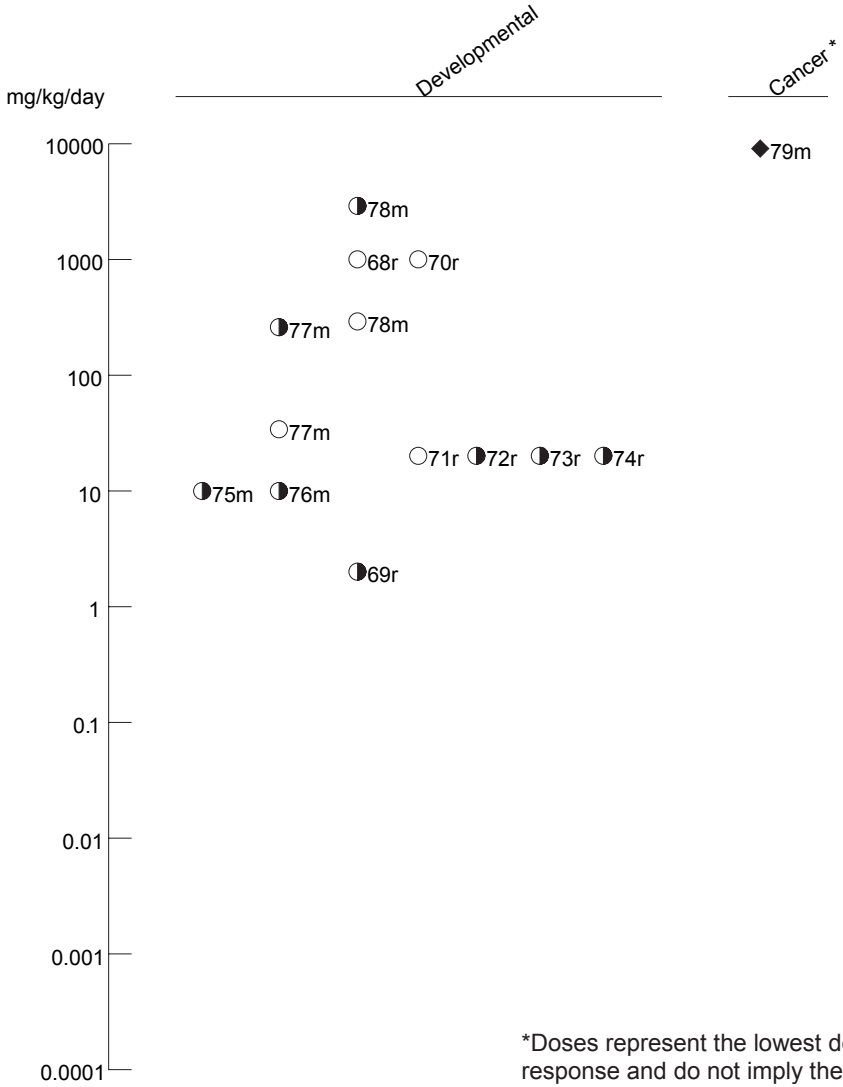


Figure 3-3. Levels of Significant Exposure to Decabromodiphenyl Ether - Oral *(Continued)*

Intermediate (15-364 days)



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

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

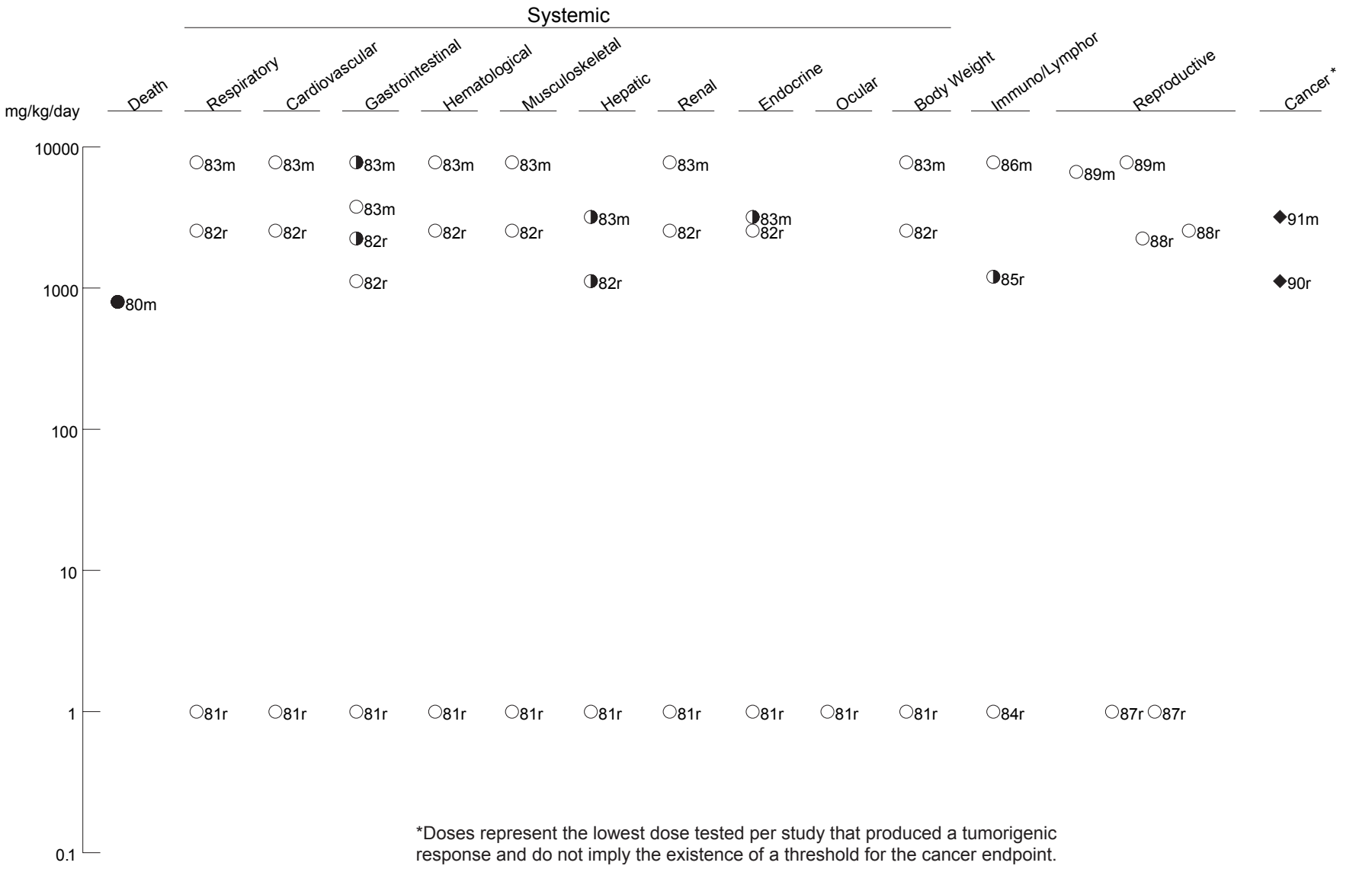
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

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

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

Figure 3-3. Levels of Significant Exposure to Decabromodiphenyl Ether - Oral *(Continued)*

Chronic (≥365 days)



In intermediate-duration dietary studies with decaBDE, there was no exposure-related mortality in rats that were exposed to estimated dietary doses of ≤90 mg/kg/day for 28 days (IRDC 1976) or rats and mice fed estimated doses of ≤8,000 and ≤9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986). In chronic studies, there were no effects on survival in rats that were fed 0.01–1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for 2 years (Kociba et al. 1975; Norris et al. 1975a), or in rats and mice fed decaBDE in estimated doses of ≤2,550 and ≤7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986). However, Feng et al. (2015) reported that 5/10 female mice died following exposure to decaBDE (98% purity) every other day via gavage for up to 2 years at a dose of 800 mg/kg/dose, compared with 1/10 vehicle control mice. No cause of death or gross or microscopic pathology was reported for animals that died. In surviving mice, various histopathological lesions were qualitatively described in the brain, heart, lung, liver, spleen, kidney, and ovaries of exposed animals, but incidence data were not provided. Due to the high mortality and lack of quantitative data, this chronic study is not discussed in the Systemic Effects section below.

The LD_{50} and LOAEL values for death are recorded in Tables 3-2 (lower BDEs) and 3-3 (decaBDE) and plotted in Figures 3-2 (lower BDEs) and 3-3 (decaBDE).

3.2.2.2 Systemic Effects

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

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to PBDEs. Effects of PBDEs on respiratory function have not been studied in orally exposed animals.

No histopathological changes in the respiratory tract or exposure-related changes in lung weight were observed in rats exposed to pentaBDE at doses up to 250 mg/kg/day for 28 days via gavage (Oberg et al. 2010; Van der ven et al. 2008a) or in rats exposed to dietary pentaBDE at doses up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984). Similarly, no changes in respiratory tract histology were observed in rats exposed to dietary octaBDE at doses up to 750 mg/kg/day for 13 weeks (IRDC 1977).

No exposure-related changes in lung weight were observed in rats exposed to a dietary penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at 20 mg/kg/day for 70 days (Ernest et al. 2012) or in F0 or F1 rats exposed pentaBDE at 18 mg/kg/day from GD 6 to PND 18 via gavage (Ellis-Hutchings et al. 2006).

To determine if PBDE exposure alters vitamin A homeostasis in rats in a manner similar to the related PBB compounds (ATSDR 2004), vitamin A levels were measured in lung tissue following exposure to pentaBDE at 0, 2.5, 25, or 250 mg/kg/day via gavage (Oberg et al. 2010). No significant changes in lung vitamin A levels were observed at any dose.

No histopathological changes in respiratory tract tissues were found in rats and mice exposed to dietary decaBDE at estimated doses of ≤8,000 and ≤9,500 mg/kg/day, respectively, for 13 weeks or estimated doses of ≤2,550 and ≤7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986). Additionally, no histopathological changes in respiratory tract tissues were observed in rats that were fed ≤1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for 2 years (Kociba et al. 1975; Norris et al. 1975a).

Based on animal studies, respiratory effects are not likely to occur following oral exposure to PBDEs.

Cardiovascular Effects. No relationship was found between serum concentrations of tetraBDE (BDE 47) and carotid atherosclerosis (carotid artery plaques determined by ultrasound) or stroke in a population of 1,016 70-year-old volunteers (50.2% female) from Uppsala, Sweden (Lee et al. 2012; Lind et al. 2012). BDE 47 was detected in the serum of 77.2% of subjects with a median concentration of 12.6 pg/mL. No associations were observed between serum PBDE levels and gestational hypertension in 258 pregnant women from the Longitudinal Investigation of Fertility and the Environment (LIFE) cohort in Michigan and Texas (Smarr et al. 2016).

A case control study of 43 children (9–11 years old) from Upstate New York reported an association between higher levels of serum PBDEs and greater sympathetic activation during acute psychological stress and greater anger (Gump et al. 2014). Specifically, BDE 28 was associated with greater heart rate, lower pre-ejection period, and lower total peripheral resistance. BDE 47 and BDE 100 were associated with significantly lower diastolic blood pressure, and BDE 100 was also associated with a shorter pre-ejection period during acute stress. Lipid-adjusted mean blood levels of BDEs 28, 47, and 100 were 1.07, 8.53, and 0.86 ng/g, respectively. The investigators speculated that PBDE-induced increased levels of

calcium/calmodulin-dependent protein kinase II in the hippocampus may mediate the heart's response to β-adrenergic stimulation.

Effects of PBDE on cardiovascular function have not been studied in orally exposed animals.

No exposure-related changes in heart histology or weight were observed in rats exposed to pentaBDE at doses up to 250 mg/kg/day for 28 days via gavage (Oberg et al. 2010; Van der ven et al. 2008a), dietary pentaBDE at doses up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984), or dietary octaBDE at doses up to 750 mg/kg/day for 13 weeks (IRDC 1977). Additionally, no exposure-related changes in heart weight were observed in rats exposed to dietary penta- or octaBDE at doses up to 90 mg/kg/day for 28 days (IRDC 1976), in rats exposed to a dietary penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at 20 mg/kg/day for 70 days (Ernest et al. 2012), in F0 or F1 rats exposed to dietary pentaBDE at doses up to 0.31 mg/kg/day for 4 weeks prior to mating through PNW 6 or 33 (Zhang et al. 2009), in F0 or F1 rats exposed pentaBDE at 18 mg/kg/day from GD 6 to PND 18 via gavage (Ellis-Hutchings et al. 2006), or in rats exposed to diBDE at 1.2 mg/kg/day for 28 days via gavage (Zhang et al. 2014).

No histopathological changes in the heart were found in rats and mice exposed to dietary decaBDE at estimated doses of ≤8,000 and ≤9,500 mg/kg/day, respectively, for 13 weeks or estimated doses of ≤2,550 and ≤7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986). No exposure-related changes in heart histology or weight were observed in rats that were fed ≤1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for 2 years (Kociba et al. 1975; Norris et al. 1975a). In addition, no exposure-related changes in heart weight were observed in rats exposed decaBDE at doses up to 20 mg/kg/day for 8 weeks via gavage (Zhang et al. 2013a) or to dietary decaBDE at doses up to 90 mg/kg/day for 28 days (IRDC 1976).

Based on human and animal studies, cardiovascular effects are not likely to occur following oral exposure to PBDEs.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to PBDEs.

No histopathological changes in the gastrointestinal tract were found in rats exposed to pentaBDE at doses up to 200 mg/kg/day for 28 days via gavage (Van der ven et al. 2008b), dietary pentaBDE at doses

up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984), or dietary octaBDE at doses up to 750 mg/kg/day for 13 weeks (IRDC 1977).

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

Based on animal studies, gastrointestinal effects are not likely to occur following oral exposure to PBDEs at environmentally-relevant exposure concentrations.

Hematological Effects.

Human Studies. Hematological end points were evaluated in a subset of 18 of a cohort of 33 children (18 girls and 15 boys) born in the Amsterdam/Zaandam area of the Netherlands and aged 14–19 years at the time of the study (Leijs et al. 2009). Serum PBDE concentrations (determined as the sum of congeners 28, 47, 85, 99, 100, 153, 154, and 183) ranged from 5 to 74 ng/g lipid with a mean of 13.9 ng/g lipid. Serum samples were used to assess hemoglobin, thrombocytes, and white blood cell count and differential. The researchers found a negative statistical association (not further described) between number of lymphocytes and PBDE concentrations in serum. Congener-specific analysis showed the main contributors to be BDE 183, BDE 154, and BDE 85. Although dioxins and PCBs were also assessed, no association with lymphocytes was found for these chemicals. The only other finding for PBDE was a positive association between serum hemoglobin and PBDE, primarily due to congeners 85 and 153. A Chinese study of 40 subjects exposed to PBDEs in an electronic waste dismantling area reported a significantly elevated neutrophil percentage among the workers compared to a group of 15 unexposed controls (Xu et al. 2015a). In addition, exposed subjects had significantly lower percentages of monocytes, lymphocytes, hemoglobin, and platelets than controls, while total white cell counts were not significantly different between the two groups. PBDEs assessed included congeners 15, 27, 85, 99, 100, 153, 154, and 184. Exposure was likely by multiple routes. PCBs also were found associated with lowered percentages of monocytes and lymphocytes.

Animal Studies

Lower-brominated PBDEs: Following exposure to dietary octaBDE at 750 mg/kg/day for 13 weeks, female rats showed 26, 22, and 22% decreases in erythrocytes, hematocrit, and hemoglobin, respectively; male rats showed a 10% decrease in erythrocytes at 600 mg/kg/day (IRDC 1977). No changes were observed in total or differential white blood cell counts (IRDC 1977). No changes in hematological parameters, including erythrocyte count, hemoglobin, hematocrit, full and differential leukocyte count, and platelet count, were observed in rats following pentaBDE exposure to dietary doses up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984) or gavage up to 250 mg/kg/day for 28 days (Oberg et al. 2010).

In another 28-day study, rats were exposed to pentaBDE at 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day via gavage (Van der ven et al. 2008b). The study authors reported minor dose-related changes in white blood cell differentials from femoral shaft bone marrow in male rats (blood hematology not evaluated); however, the doses at which these effects were observed were not reported. Instead, results were reported in terms of benchmark dose (BMD) analysis (Van der ven et al. 2008b). Statistically significant changes included increased number and percentage of monocytes (maximum increase of 69.5 and 66.7%, respectively; BMD/$BMDL_{RD20\%}$=11.2/0.7 and 31.8/3 mg/kg/day, respectively) and decreased percentage of eosinophilic granulocytes (maximum decrease of 20%; ($BMD_{RD20\%}$=28.6, BMDL not determined). The study authors also reported a significant, dose-related increase in the number and percentage of large unstained cells (maximum increase of 79.7 and 85.1%, respectively; BMD/$BMDL_{RD20\%}$=76.3/42.8 and 64.3/9.8 mg/kg/day, respectively), which they indicated may represent large or reactive lymphocytes, monocytes, or leukemic blasts (abnormal myeloblasts), typically associated with viral disease, leukemia, or endocrine active compounds. Since results were reported in terms of BMD analysis only, data and statistics for individual dose groups were not available for independent analysis. No data regarding other standard hematological end points were reported (Van der ven et al. 2008b).

Male mink exposed to dietary pentaBDE at doses of 0.63 or 0.78 mg/kg/day for 9 weeks showed significant 13 and 12% decreases in hematocrit, respectively; neither the number of red blood cells nor hemoglobin levels were evaluated (Martin et al. 2007). According to study authors, most of the ranges in the differential white blood cell counts fell within that expected for male mink of this age; however, the percentage of neutrophils was increased significantly by ~22% at 0.63 mg/kg/day and 37% at 0.78 mg/kg/day, the percentage of lymphocytes decreased significantly by ~33% at 0.78 mg/kg/day, and

the neutrophil:lymphocyte ratio increased significantly by ~90% at 0.78 mg/kg/day (data reported graphically) (Martin et al. 2007). Total white blood cell counts were not reported. No hematological effects were observed at 0.08 mg/kg/day (Martin et al. 2007). The minor hematological changes are of uncertain toxicological significance.

In a poorly-reported study, mouse dams exposed to pentaBDE from GD 6 to PND 21 via gavage did not show any hematological effects at doses up to 200 mg/kg/day (Hong et al. 2010).

DecaBDE: No hematological changes were observed in rats exposed to ≤60 mg/kg/day of decaBDE via gavage for 28 days (Van der ven et al. 2008a). In dietary studies with decaBDE, no hematological changes were found in rats exposed to ≤800 mg/kg/day for 30 days (Norris et al. 1973, 1975a), ≤8,000 mg/kg/day for 13 weeks (NTP 1986), or ≤2,550 mg/kg/day for 103 weeks (NTP 1986), or in mice exposed to ≤9,500 mg/kg/day for 13 weeks or ≤7,780 mg/kg/day for 103 weeks (NTP 1986). There also were no hematological effects in rats exposed by diet to ≤1.0 mg/kg/day of a 77.4% decaBDE mixture (containing 21.8% nonaBDE and 0.8% octaBDE) for 2 years (Kociba et al. 1975; Norris et al. 1975a).

In a poorly-reported study, mouse dams exposed to decaBDE from GD 6 to PND 21 via gavage showed significant increases in the number of white blood cells and neutrophils at 500 mg/kg/day, compared with controls, but not at 2,500 or 12,500 mg/kg/day (Hong et al. 2010).

Summary. Minor hematological changes observed in humans and animal are of uncertain toxicological significance. Based on the available information, it is unlikely that adverse effects would occur in the human hematological system following oral PBDE exposure.

Musculoskeletal Effects. No association was found between serum PBDE concentrations (BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 209, and their sum) and bone mineral density (measured by x-ray in the forearm) or serum concentrations of biochemical markers of bone metabolism (osteocalcin and crosslaps [a peptide of type I collagen]) in a population of 50 post-menopausal Swedish women married or previously married to professional fisherman on the east coast of the country and born before 1954 (Weiss et al. 2006). Median serum ∑PBDE concentration in this population was 3.6 ng/g fat.

No musculoskeletal changes were seen in rats following exposure to pentaBDE at doses up to 200 mg/kg/day for 28 days via gavage (Van der ven et al. 2008b) or dietary pentaBDE at doses up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984).

No changes in bone parameters were observed in rats exposed to decaBDE at doses up to 60 mg/kg/day for 28 days via gavage (Van der ven et al. 2008a). Dietary studies with decaBDE found no histopathological changes in musculoskeletal tissues in rats exposed to ≤8,000 mg/kg/day for 13 weeks (NTP 1986), ≤1.0 mg/kg/day (77.4% containing 21.8% nonaBDE and 0.8% octaBDE) for 2 years (Kociba et al. 1975; Norris et al. 1975a), or ≤2,550 mg/kg/day for 103 weeks (NTP 1986), or in mice exposed to ≤9,500 mg/kg/day for 13 weeks or ≤7,780 mg/kg/day for 103 weeks (NTP 1986).

Based on human and animal studies, musculoskeletal effects are not likely to occur following oral exposure to PBDEs.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to PBDEs.

Acute-Duration Animal Studies

Lower-brominated PBDEs: A series of gavage studies evaluated liver histology following a single exposure to pentaBDE doses of 0, 25, 200, or 2,000 mg/kg or repeat exposures to pentaBDE doses of 0, 8, 40, or 200 mg/kg/day for 7 or 14 days (Bruchajzer et al. 2010, 2011). Fatty degeneration of the liver was observed in female rats following pentaBDE exposure via gavage at 2,000 mg/kg for 1 day (Bruchajzer et al. 2011) or 200 mg/kg/day for 7 or 14 days (Bruchajzer et al. 2010). In the single-exposure study, rats from the 2,000 mg/kg group showed steatosis of the microvesicular type, which was most frequently observed in the central and intermediate zones of lobules; however, animal incidence numbers were not reported (Bruchajzer et al. 2011). At 4 and 12 hours after pentaBDE administration, these changes were noted in no more than 25% of hepatocytes; after 24–120 hours, fatty degeneration embraced 26–75% of hepatocytes; and after 120 hours, a mixed type of change (micro- and macrovesicular) was observed (Bruchajzer et al. 2011). In the repeated-exposure studies, rats from the 200 mg/kg/day group showed steatosis of the microvesicular type in 3–25% of hepatocytes after 7 days and steatosis of the microvesicular and mascrovesicular type in 26–75% of hepatocytes in the central and intermediate zones of lobules (Bruchazjer et al. 2010). Again, animal incidence data were not reported. No exposure-related histological changes in the liver were reported for single doses ≤200 mg/kg or repeated doses ≤40 mg/kg/day (Bruchazjer et al. 2010, 2011). In the only other study that included histopathological examination, histological changes were not observed in male rats 45 days after a single administration of pentaBDE at doses up to 1.2 mg/kg (Albina et al. 2010).

In the Bruchazjer et al. (2010, 2011) studies, no biologically relevant changes were observed in serum clinical chemistry values. Serum alanine transaminase (ALT) and aspartate transaminase (AST) activity levels were slightly increased to 130 and 170–190% of control values following a single gavage exposure to 2,000 mg/kg, respectively, after 72–120 hours; no changes were reported for doses ≤200 mg/kg (Bruchazjer et al. 2011). The study authors did not report statistics; however, these serum chemistry changes are not considered biologically relevant since the magnitude of change, compared with control, is <2-fold. Similarly, no exposure-related changes were observed in serum ALT or AST at doses up to 200 mg/kg/day for 7 or 14 days (Bruchajzer et al. 2010). Another 14-day gavage study found no exposure-related changes in serum sorbital dehydrogenase (SDH) levels in rats exposed to pentaBDE at 56.4 mg/kg/day or octaBDE at 76.6 mg/kg/day (equimolar doses) (Carlson 1980b). In male rats exposed once to pentaBDE at doses of 0, 0.6, or 1.2 mg/kg, serum ALT activity was significantly increased by ~72% in the 1.2 mg/kg group, compared with control, when evaluated 45 days after exposure (Alonso et al. 2010). However, this change is not considered biologically relevant because the magnitude of change, compared with control, is <2-fold, the measured ALT activity of 31 U/l was well within reference value ranges for adult male rats (20–81 U/l) (Charles River Laboratories 1998), and no changes were observed in serum AST, alkaline phosphatase (ALP), or lactate dehydrogenase (LDH) (Alonso et al. 2010).

Bruchajzer et al. (2010, 2011) also reported altered markers of oxidative stress in the liver following exposure to pentaBDE. Liver malondialdehyde (MDA) levels were significantly elevated after exposure to ≥200 mg/kg/day for 1–14 days (Bruchajzer et al. 2010, 2011). Levels of reduced glutathione (GSH) in the liver were not increased following a single exposure; however, GSH concentration was elevated at ≥40 mg/kg/day after 7 days and ≥8 mg/kg/day after 14 days (Bruchajzer et al. 2010, 2011). Oxidized glutathione (GSSG) was significantly elevated after single exposures to ≥25 mg/kg, but no changes in glutathione S-transferase (GST) activity were observed (Bruchajzer et al. 2010). Liver GSSG levels and GST activity were not evaluated following 7- or 14-day exposures. In another study, liver GSH levels were significantly decreased and liver SOD activity, GSSG levels, and GSSG/GSH ratio were significantly increased in male rats 45 days after a single gavage administration of pentaBDE at 0.6 or 1.2 mg/kg (Albina et al. 2010).

In two other studies by Bruchazjer and colleagues (Bruchazjer 2011; Bruchazjer et al. 2012), female rats were examined for hepatic porphyria following exposure to pentaBDE at doses of 0, 8, 40, or 200 mg/kg/day or octaBDE at doses of 0, 2, 8, 40, or 200 mg/kg/day via gavage for 7 or 14 days. PentaBDE caused significant dose-related elevations in total porphyrin levels in the liver following

exposure to ≥40 mg/kg/day for 7 days (~2–6-fold) or ≥8 mg/kg/day for 14 days (~3–11-fold). Following gavage exposure to octaBDE for 7 days, liver concentrations of high carboxylated porphyrins (octa- and hepta-) were significantly elevated at 8, 40, and 200 mg/kg/day by ~4-, 4-, and 7-fold, respectively, compared with vehicle controls (Bruchajzer et al. 2012). Lower carboxylated porphyrins were <1% of total liver porphyrins measured, and were not further analyzed. Following exposure to octaBDE for 14-days, total liver concentrations of high carboxylated porphyrins were increased by ~3-fold in the 200 mg/kg/day group only, compared with vehicle controls (Bruchajzer et al. 2012). However, the vehicle controls at this duration had an unusually high hepatic porphyrin levels (4-fold increase compared with untreated control). When compared with the untreated controls, porphyrin levels were significantly increased by ~2-, 4-, 6-, and 7-fold in the 2, 8, 40, and 200 mg/kg/day groups, respectively, supporting that exposure to octaBDE for 14 days causes porphyria as observed in the 7-day study. These studies also measured hepatic delta-aminolevulinate synthase (ALA-S) activity and delta-aminolevilinate dehydratase (ALA-D) activity, two enzymes involved in heme biosynthesis. The results were mixed. PentaBDE exposure caused a significant elevation in ALA-S activity at ≥40 mg/kg/day after 7 or 14 days (ALA-D was not measured), while octaBDE exposure caused a significant increase in ALA-S activity at ≥8 mg/kg/day after 7 days and significant decreases in ALA-S activity at 200 mg/kg/day after 14 days and ALA-D activity at ≥40 mg/kg/day after 7 or 14 days (Bruchajzer 2011; Bruchajzer et al. 2012).

The gavage studies by Bruchajzer and colleagues (Bruchajzer 2011; Bruchajzer et al. 2012) also reported elevated liver weights accompanied by hepatic microsomal enzyme induction. Significant relative liver weight increases (data reported graphically) were about ≥30% after a single exposure to pentaBDE at ≥200 mg/kg (Bruchajzer et al. 2011), ≥13% after exposure to pentaBDE at 8 or 200 mg/kg/day for 7 days (Bruchajzer et al. 2010), or ≥25% after exposure to pentaBDE at ≥40 mg/kg/day for 14 days (Bruchazjer et al. 2010). Hepatic enzyme induction (e.g., increased CYP1A and CYP2B activity and/or CYP1A1, CYP4A, and total cytochrome P450 protein levels) was observed at lower doses: ≥25 mg/kg in the single dose study and ≥8 mg/kg/day in the 7- and 14-day studies (Bruchazjer et al. 2010, 2011).

Consistent with the findings of Bruchazjer and colleagues (Bruchajzer 2011; Bruchajzer et al. 2012), elevated liver weights have been reported following acute exposure to penta-, octa-, or tetraBDE in several other animal studies. Significantly increased liver weights were reported in rats and mice exposed to penta-, tetra-, or octaBDE via gavage at ≥10 and ≥18 mg/kg/day, respectively, for 1–14 days (Carlson 1980b; Fowles et al. 1994; Hallgren et al. 2001; Mercado-Feliciano and Bigsby 2008a; Richardson et al. 2008; Stoker et al. 2004, 2005; Zhou et al. 2001). However, no exposure-related changes in relative liver weight were observed in female rats exposed to tetraBDE at doses up to18 mg/kg/day for 14 days via

gavage (Hallgren and Darnerud 2002). In the studies that evaluated hepatic enzyme induction (e.g., elevated EROD, MROD, PROD, and UDPGT activity and/or increased CYP protein levels), significantly increased enzyme levels and activities were observed in rats and mice at gavage doses of ≥6 and ≥3 mg/kg/day, respectively, and were always observed at doses at or below the dose causing elevated liver weights in the same study (Carlson 1980b; Fowles et al. 1994; Hallgren and Darnerud 2002; Hallgren et al. 2001; Richardson et al. 2008; Stoker et al. 2004; Zhou et al. 2001). Exposure to a single pentaBDE dose of 0.03 or 0.6 mg/kg on GD 6 via gavage caused significant induction of hepatic enzymes (EROD, UDPGT) in dams and pups from the 0.6 mg/kg group on PND 22; liver weight was not evaluated (Kuriyama et al. 2007). Collectively, these findings support that elevated liver weight following exposure to lower-brominated PBDEs is associated with hepatic enzyme induction.

Richardson et al. (2008) evaluated genomic changes in mice following exposure to tetraBDE at 0, 3, 10, or 100 mg/kg/day for 4 days via gavage. The mRNA levels of several hepatic enzymes were significantly elevated at ≥20 mg/kg/day (Cyp2b10, Ugt1a1, Ugt1a7, Ugt2b2). In addition, several exposure-related changes were observed in hepatic efflux transporter (Mrp3, Mdr1a) and thyroid hormone transporter (Ttr, Mct8) mRNA expression levels in hepatic tissue (Richarson et al. 2008).

To determine if PBDE exposure alters vitamin A homeostasis in a manner similar to the related PBBs (ATSDR 2004), hepatic vitamin A levels were measured in mice and rats exposed to pentaBDE at 0, 18, or 36 mg/kg/day and mice exposed to tetraBDE at 0 or 18 mg/kg/day for 14 days via gavage (Hallgren et al. 2001). In pentaBDE-exposed animals, hepatic vitamin A levels were significantly decreased by 24 and 26% in rats in the 18 and 36 mg/kg/day groups, respectively, and 22% in mice in the 36 mg/kg/day group. No changes in hepatic vitamin A levels were observed in mice exposed to penta- or tetraBDE at 18 mg/kg/day.

DecaBDE: Unlike the lower-brominated PBDEs, there is no evidence of hepatic toxicity following acute exposure to decaBDE. Exposure to decaBDE at doses up to 1,000 mg/kg/day for 7 or 14 days via gavage did not produce liver damage, as indicated by liver histology or clinical chemistry, nor did it produce increased liver weight or hepatic enzyme induction in female rats (Bruchajzer et al. 2010). Carlson (1980b) observed no changes in serum SDH activity in rats exposed to decaBDE at 95.9 mg/kg/day for 14 days via gavage; significantly elevated liver weights were found, but in the absence of hepatic enzyme induction. In a shorter-duration study, exposure to decaBDE at doses up to 100 mg/kg/day for 4 days via gavage did not cause changes in liver weight or hepatic enzyme induction in female rats; clinical chemistry and histology were not examined (Zhou et al. 2001).

Sakamoto et al. (2013) evaluated both liver weight and hepatocyte proliferation in female rats following exposure to decaBDE at 980 mg/kg/day for 1 week. Consistent with other studies, no exposure-related findings in absolute or relative liver weight were observed. Additionally, no exposure-related changes in hepatocyte proliferation were observed, as evaluated by labeling indices of proliferating cell nuclear antigen (PCNA) in paraffin-embedded liver sections.

Intermediate-Duration Animal Studies

Lower-brominated PBDEs: Histopathological effects in the liver have been consistently observed in animals exposed to lower-brominated PBDEs for 15–90 days at doses as low as 2 mg/kg/day. Hepatocytomegaly (hepatocyte hypertrophy) was observed in rats exposed to dietary pentaBDE at doses ≥2 mg/kg/day (lowest dose tested) for 13 weeks (WIL Research Laboratories 1984). The hepatocytomegaly was dose-related with respect to severity (some affected hepatocytes at higher doses had vacuoles that likely contained lipid) and was not completely reversible, as it was still evident in ≥10 mg/kg/day males and 100 mg/kg/day females at 24 weeks postexposure in lessened severity and incidence. Females exposed to 2 or 100 mg/kg/day pentaBDE for 90 days also had an increased incidence of degeneration and necrosis of individual liver parenchymal cells at 24 weeks postexposure; the investigators concluded that this may represent the final loss of previously damaged cells and probably should be considered compound-related (WIL Research Laboratories 1984). Similarly, dietary exposure to octaBDE at 0, 100, 1,000, or 10,000 ppm (0, 5, 50, or 600 mg/kg/day in males and 0, 7, 70, or 750 mg/kg/day in females) for 13 weeks caused liver lesions in 40% of males at 5 mg/kg/day and 100% of both sexes at ≥50–70 mg/kg/day (IRDC 1977). The lesions were dose-related in severity as well as incidence and characterized by cytomegaly, change in hepatocytic cytoplasm to a finely granular, homogeneous type, and cytoplasmic vacuolation. At 600–750 mg/kg/day, many of the livers had vacuolation of centrolobular hepatocytes and some had hepatocyte necrosis. Examinations performed at 8 weeks and 6 months postexposure showed that the liver effects persisted in the rats exposed to ≥50–70 mg/kg/day for 13 weeks (IRDC 1977).

Hepatocellular hypertrophy was also observed in rats exposed to dietary penta- or octaBDE at ≥9 mg/kg/day for 28 days (IRDC 1976), in rats exposed to pentaBDE at ≥3 mg/kg/day for 15–28 days via gavage (Becker et al. 2012; Fattore et al. 2001; Oberg et al. 2010), and in rats exposed to tetraBDE at 150 mg/kg/day via gavage for 12 weeks (only dose tested) (Zhang et al. 2015a, 2015b). No histopathological changes were observed in mice exposed to tetraBDE at 1 mg/kg/day via gavage for

6 weeks (only dose tested) (McIntyre et al. 2015). In another gavage study, rats were exposed to pentaBDE at doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day for 28 days (Van der ven et al. 2008b). The study authors reported centrilobular hypertrophy and an increased ratio of binucleated hepatocytes; however, the incidence data and dose(s) at which effects were observed were not reported (Van der ven et al. 2008b). Van der ven et al. (2008b) also reported a near-significant 5-fold increase in the number of apoptotic cells in males exposed to 200 mg/kg/day (p=0.067). Rats exposed to pentaBDE at 200 mg/kg/day for 21or 28 days via gavage showed "minor lesions" in the liver, but no further information regarding the type or incidence of the lesion was reported (Bruchajzer et al. 2010). In mice, exposure to dietary tetraBDE at 0.45 mg/kg/day for 28 days induced hepatocyte vacuolation, pyknotic nuclei in the hepatocytes, and periportal lymphocytic infiltration; no lesions were observed in control animals (Maranghi et al. 2013).

In rats exposed to pentaBDE via gavage for 70 days prior to mating until PND 42, significantly increased incidences of hepatocellular hypertrophy were observed in F0 males at ≥5 mg/kg/day and F0 females and F1 offspring at 25 mg/kg/day; no exposure-related effects were observed at 0.5 mg/kg/day (Bondy et al. 2013). Similarly, all F1 rats exposed to pentaBDE at 50 mg/kg/day from GD 6 to PNW 16 via gavage showed hepatocellular hypertrophy characterized by enlarged hepatocytes with an increased amount of cytoplasm, enlarged nuclei, and pale eosinophilic and granular cytoplasm. Hepatocyte vacuolization was also significantly increased in exposed F1 males, but not F1 females (Dunnick et al. 2012).

No exposure-related changes were observed in serum chemistry markers (ALT, AST, ALP, LDH, cholesterol, triglycerides, albumin, globulin) in rats exposed to dietary pentaBDE at doses up to 100 mg/kg/day for 13 weeks (WIL Research Laboratories 1984), octaBDE at doses up to 750 mg/kg/day for 90 days (IRDC 1977), or a penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at 20 mg/kg/day for 70 days (Ernest et al. 2012). Similarly, no exposure-related changes were observed in serum ALP, ALT, AST, or gamma-glutamyl transferase (GGT) following exposure to pentaBDE at low doses up to 0.015 mg/kg/day via gavage for 90 days (Daubie et al. 2011). Marginal changes (<2-fold) were observed in shorter-duration rat gavage studies with higher doses. A statistically significant 51% increase in serum ALT level was observed in male rats exposed to pentaBDE at 250 mg/kg/day via gavage for 28 days; no changes were observed in males at 2.5 or 25 mg/kg/day or females at any dose (Oberg et al. 2010). No exposure-related changes were observed in serum ALP (Oberg et al. 2010). Similarly, in female rats exposed to pentaBDE at 200 mg/kg/day via gavage for 21 or 28 days, serum ALT levels were increased to 190% of control values at 21 or 28 days and serum AST levels were increased to 185% of control values at 28 days; no changes were observed at ≤40 mg/kg/day

(Bruchajzer et al. 2010). Increases in serum cholesterol, total protein, and ALT and decreases in the albumin/globulin ratio were observed in rats exposed to pentaBDE at 250 mg/kg/day, but the magnitudes of these effects were not reported (Fattore et al. 2001). In another gavage study, rats were exposed to pentaBDE at doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day for 28 days (Van der ven et al. 2008b). The study authors reported a dose-related increase in serum ALT in male rats (maximal increase of 148.1%); however, the lowest dose at which the effect was observed was not reported. Instead, results were reported in terms of BMD analysis (BMD/$BMDL_{RD10\%}$=61.4/15.5 mg/kg/day). No changes in serum ALT were observed in female rats, and no changes in serum ALP were observed in either sex, although the authors noted procedural problems with their ALP assay (Van der ven et al. 2008b). The study authors reported dose-related increases in serum cholesterol in male and female rats (maximal increases in males and females were 257 and 144%, respectively). Again, the lowest dose at which the effect was observed was not reported (BMD/$BMDL_{RD10\%}$=15.4/8.4 mg/kg/day in males and 22.4/11.6 mg/kg/day in females) (Van der ven et al. 2008b). In mice, serum ALT levels were significantly elevated by approximately 2-fold in males exposed to tetraBDE at gavage doses of 150 mg/kg/day for 12 weeks, compared with control (only dose tested); no other serum biochemistry endpoints were evaluated (Zhang et al. 2015a, 2015b).

Significant changes in hepatic oxidative stress parameters were observed in rats following exposure to pentaBDE at doses ≥8 mg/kg/day via gavage for 21 or 28 days, including increased hepatic GSH and MDA levels (Bruchajzer et al. 2010). Oxidative stress markers were also significantly altered in the livers of rat offspring following exposure to pentaBDE from GD 6 to PND 21, including significantly increased activities of catalase (CAT) activity at ≥1 mg/kg/day and SOD at 2 mg/kg/day (Blanco et al. 2014). There was no change in total levels of thiobarbituric acid reactive substances (TBARS) in offspring (Blanco et al. 2014). In mice, exposure to diBDE at 1.2 mg/kg/day via gavage for 28 days caused significantly decreased levels of GSH, decreased activities of SOD and glutathione peroxidase (GPx), and increased levels of MDA in the liver (Zhang et al. 2014).

Female rats were examined for hepatic porphyria following exposure to pentaBDE or octaBDE at doses of 0, 2, 8, 40, or 200 mg/kg/day via gavage for 21 or 28 days (Bruchajzer 2011; Bruchajzer et al. 2012). PentaBDE caused significant dose-related elevations in total porphyrin levels in the liver following exposure to ≥8 mg/kg/day for 21 days (~3–8-fold) or 28 days (~3–19-fold), compared to vehicle controls (Bruchajzer 2011), OctaBDE cause significant elevations in liver concentrations of high carboxylated porphyrins (octa- and hepta-) following exposure to ≥8 mg/kg/day for 21 days (~2–3-fold) or 2 or 8 mg/kg/day for 28 days (~3–4-fold) (Bruchajzer et al. 2012). At 28 days, high carboxylated porphyrin

levels in the 40 and 200 mg/kg/day groups were not were not significantly elevated compared to the vehicle control. However, the vehicle controls at this duration had an unusually high hepatic porphyrin levels (4-fold increase compared with untreated control). When compared with the untreated controls, porphyrin levels were significantly increased by ~10-, 14-, 4-, and 5-fold in the 2, 8, 40, and 200 mg/kg/day groups, respectively. Lower carboxylated porphyrins were <1% of total liver porphyrins measured, and were not further analyzed. These studies also measured ALA-S and ALA-D activity, two enzymes involved in heme biosynthesis. The results were mixed. PentaBDE exposure caused a significant elevation in ALA-S activity at ≥8 mg/kg/day after 21 days and at ≥2 mg/kg/day after 28 days, while octaBDE exposure caused a significant decrease in ALA-S activity at 200 mg/kg/day after 21 days and at ≥40 mg/kg/day after 28 days. ALA-D activity was also significantly decreased in rats exposed to octaBDE at ≥40 mg/kg/day for 21 or 28 days (ALA-D activity was not assessed in pentaBDE-exposed rats) (Bruchajzer 2011; Bruchajzer et al. 2012). Hepatic porphyria was also observed in rats after exposure to dietary pentaBDE for 90 days (WIL Research Laboratories 1984). Liver porphyrins were significantly elevated by 8.5- and 390-fold in males and females from the 100 mg/kg/day group, respectively, and 3-fold in females from the 20 mg/kg/day group; no significant changes were observed in the 2 mg/kg/day group (WIL Research Laboratories 1984).

Elevated liver weights have been reported following intermediate-duration exposure to penta-, octa-, tetra-, or diBDE in several animal studies. Significantly increased liver weights were reported in rats and mice exposed to penta-, di-, or tetraBDE via gavage at ≥1.2, ≥50, and 150 mg/kg/day, respectively, for 15–84 days (Becker et al. 2014; Bruchajzer et al. 2010; Fattore et al. 2001; Mercado-Feliciano and Bigsby 2008a; Oberg et al. 2010; Stoker et al. 2004, 2005; Van der Ven et al. 2008b; Zhang et al. 2014, 2015a, 2015b). No exposure-related changes in liver weight were observed in mice exposed to tetraBDE at 1 mg/kg/day via gavage for 6 weeks (only dose tested) (McIntyre et al. 2015). In dietary studies, significantly increased liver weights were reported in rats exposed to penta- or octaBDE at ≥5 mg/kg/day for 28–90 days (IRDC 1976, 1977; WIL Research Laboratories 1984) or a penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at 20 mg/kg/day for 70 days (Ernest et al. 2012). In mink exposed to dietary pentaBDE at 0, 0.08, 0.63, or 0.78 mg/kg/day for 90 days, increased absolute liver weight was observed at 0.78 mg/kg/day and increased relative liver weight was observed at ≥0.08 mg/kg/day; however, these findings are confounded by significant body weight loss at ≥0.63 mg/kg/day (Martin et al. 2007). No exposure-related changes in liver weight were observed in mice exposed to dietary tetraBDE at 0.45 mg/kg/day for 28 days (Maranghi et al. 2013).

In studies that evaluated hepatic enzyme induction (e.g., elevated EROD, MROD, PROD, and UDPGT activity), significantly increased enzyme activities were observed in rats, mice, and mink at doses of ≥2.5, ≥50, and ≥0.08 mg/kg/day, respectively, and were always observed at doses at or below the dose causing elevated liver weights in the same study (Bruchajzer et al. 2010; Ernest et al. 2012; Fattore et al. 2001; Martin et al. 2007; Mercado-Feliciano and Bigsby 2008a; Oberg et al. 2010; Stoker et al. 2004). Additionally, microsomal enzyme activity was induced in rats exposed by gavage to doses as low as 0.6 mg/kg/day of octaBDE and 0.4 mg/kg/day of pentaBDE for 90 days as indicated by increases in O-ethyl O-*p*-nitrophenyl phenylphosphonothioate (EPN) detoxification, *p*-nitroanisole demethylation, and cytochrome c reductase and cytochrome P-450 levels (Carlson 1980a). Some of these changes were persistent, lasting for 30–60 days after cessation of treatment.

Maternal and pup liver weights were significantly elevated in rats exposed to pentaBDE from GD 1 or GD 6 to PND 21 via gavage or dosed cookies at 30 and ≥3 mg/kg/day, respectively (Bowers et al. 2015; Ellis-Hutchings et al. 2006; Zhou et al. 2002). In mice, elevated maternal liver weights were observed in dams exposed to 452 mg/kg/day of the pentaBDE congener BDE 99, but not the pentaBDE commercial mixture Bromkal 70-5DE, from GD 6 to PND 17 via gavage (Skarman et al. 2005). Elevated liver weights were not observed in mouse pups (Skarman et al. 2005). In a one-generation study in rats (pre-mating day 70 to PND 42), F0 males and F1 offspring showed significantly increased liver weights on PND 43 following exposure to 25 and ≥5 mg/kg/day via gavage (Bondy et al. 2011, 2013). In other one-generation studies, no changes were observed in maternal or pup liver weight in rats exposed to pentaBDE-dose vanilla wafers at doses up to 11.4 mg/kg/day from pre-mating day 28 to PND 21 (Poon et al. 2011) or adult F1 liver weight in rats exposed to pentaBDE at 50 mg/kg/day from GD 6 to PNW 16 via gavage (Dunnick et al. 2012). In mink, exposure to dietary pentaBDE from 4 weeks premating until PNW 6 or 33 led to elevated liver weights in sows at 0.31 mg/kg/day (highest dose tested) and F1 offspring at 0.06 mg/kg/day (Zhang et al. 2009). In the studies that evaluated hepatic enzyme levels (e.g., EROD, PROD, UDPGT), significantly increased enzyme activities were always observed at doses at or below the dose causing elevated liver weights in the same study, with significant changes observed in F0 and F1 rats at ≥0.3 mg/kg/day, F0 and F1 mice at 450 mg/kg/day, and F0 and F1 mink at ≥0.06 and 0.01 mg/kg/day, respectively (Bowers et al. 2015; Skarman et al. 2005; Zhang et al. 2009; Zhou et al. 2002). Additionally, significant induction of hepatic enzymes was observed in male rat pups following exposure to pentaBDE at ≥1.7 mg/kg/day from GD 6 to PND 21 via gavage (Szabo et al. 2009).

Szabo et al. (2009) also evaluated genomic changes in F1 rats following exposure to pentaBDE at 0, 1.7, 10.2, or 30.6 mg/kg/day from GD 6 to PND 4 or 21 via gavage. Significant dose-related increases were

observed in hepatic mRNA expression levels of phase I enzymes (Cyp1a1, Cyp2b1, Cyp2b2, Cyp3a1), phase II enzymes (Ugt1a6, Ugt1a7, Ugt2b, Sult1b1), phase III influx transporters (Oatp1a4), phase II efflux transporters (Mdr1, Mrp2, Mrp3), the serum binding protein transthyretin (Ttr), and deiodinase 1 (d1) during exposure (PND 4 and 21); the majority of which no longer differed from control at PND 60. Genomic changes were also evaluated in F1 rats following exposure to pentaBDE at 0, 1, or 2 mg/kg/day via gavage (Blanco et al. 2014). Various cytochrome isoforms were evaluated, but mRNA levels were only significantly elevated for CYP2B1 in pup liver tissue from the 2 mg/kg/day group. Additionally, significant changes were observed in the thyroid hormone receptor, including decreased TRα1 mRNA in both dose groups, decreased TRβ1 mRNA at 2 mg/kg/day, and decreased TRα1 protein levels at 2 mg/kg/day. Cylcin D1 protein expression was significantly decreased in both groups and the phosphorylation levels of Akt and GSK3β were significantly decreased at 2 mg/kg/day.

To determine if PBDE exposure alters vitamin A homeostasis in a manner similar to the related PBBs (ATSDR 2004), hepatic vitamin A levels were measured in rats following exposure to pentaBDE at 0, 2.5, 25, or 250 mg/kg/day via gavage for 28 days (Oberg et al. 2010). Hepatic liver vitamin A content was significantly decreased in females at 25 mg/kg/day and males and females at 250 mg/kg/day by up to 36 and 47%, respectively (Oberg et al. 2010). Hepatic vitamin A levels were also significantly decreased by 13% in dams and 50% in F1 pups on PND 18 in rats exposed to pentaBDE at 0 or 18 mg/kg/day from GD 6 to PND 18 via gavage (Ellis-Hutchings et al. 2006). Additional pup sacrifices on PNDs 12 and 31 showed significant 59 and 25% decreases in hepatic vitamin A level, respectively (Ellis-Hutchings et al. 2006).

DecaBDE: Moderate hepatocellular hypertrophy was observed in all mice exposed to dietary decaBDE at 9,400 mg/kg/day for 28 days, but in none of the controls (Sakamoto et al. 2013). Similarly, slight centrilobular hypertrophy was “occasionally” observed in rats exposed to decaBDE at doses ranging from 1.87 to 60 mg/kg/day for 28 days via gavage, which was most obvious in “some” of the 60 mg/kg/day males (incidence data not reported) (Van der ven et al. 2008a). In an older study using an impure decaBDE compound (77% purity), centrilobular cytoplasmic enlargement and vacuolation were observed in male rats exposed to dietary doses of 800 mg/kg/day for 30 days (incidences not reported); no changes were observed at 8 or 80 mg/kg/day (Norris et al. 1973, 1975a). However, no exposure-related changes in liver histology were observed in rats and mice exposed to dietary decaBDE at estimated doses as high as 2,000–8,000 and 2,375–9,500 mg/kg/day for 13 weeks, respectively (NTP 1986), or in rats exposed to gavage doses up to 1,000 mg/kg/day for 21 or 28 days (Bruchajzer et al. 2010).

Pregnant dams and developing rats and mice appear to be more susceptible to liver damage following exposure to decaBDE than adult animals. Hepatocyte degeneration and eosinophil changes were observed in the livers of rat dams exposed to decaBDE at 300 mg/kg/day for 21 days prior to mating, through mating, gestation, and lactation (PND 21) (Liu et al. 2012). Compared with control, the exposed group had significantly increased "histological scores;" however, the method of histological scoring and incidences of lesions were not reported (Liu et al. 2012). Following exposure to dietary decaBDE from GD 10 to PND 21, male and female rat pups showed significantly increased incidence of follicular cell hypertrophy in the liver at ≥2 and 146 mg/kg/day, respectively (Fujimoto et al. 2011). These findings were transient, as they were no longer evident in male and female offspring evaluated at PNW 11 (Fujimoto et al. 2011). Male offspring from mouse dams exposed to decaBDE from GD 0 to 17 via gavage showed dose-related histopathological changes in the liver on PND 71 at doses ≥10 mg/kg/day (lowest dose tested) (Tseng et al. 2008). Histological changes observed in exposed groups included acute cell swelling of hepatocytes associated with pressure occlusion of hepatic sinusoids (Tseng et al. 2008). Young male rats exposed to decaBDE at doses of 0, 100, 300, or 600 mg/kg/day from PND 10 to 42 via gavage showed fatty degeneration at ≥300 mg/kg/day (incidence data were not reported) (Lee et al. 2010).

Wang et al. (2010) found no exposure-related changes in serum ALT, AST, or ALP in male rats following gavage exposure to decaBDE at 100 mg/kg/day for 90 days, but serum total cholesterol, high density lipid-cholesterol, and total bile acid levels were significantly increased by 23, 26, and 98%, respectively. No biologically relevant, exposure-related changes were observed in either serum ALT or AST, or total cholesterol or triglyceride levels, in rats exposed to decaBDE at doses up to 1,000 mg/kg/day for 21–56 days (Bruchazjer et al. 2010; Van der ven et al. 2008a; Zhang et al. 2013a).

No exposure-related changes were observed in hepatic markers of oxidative stress (GSH, MDA) in female rats exposed to decaBDE up to doses of 1,000 mg/kg/day for 21 or 28 days (Bruchazjer et al. 2010).

Significantly elevated liver weights were observed in male rats after exposure to decaBDE at ≥1 mg/kg/day for 8 weeks via gavage (Zhang et al. 2013a) and male mice after exposure to dietary decaBDE at 9,400 mg/kg/day for 28 days (Sakamoto et al. 2013). However, no exposure-related changes in liver weight were observed in rats exposed to decaBDE up to doses of 1,000 mg/kg/day via gavage for 21–90 days (Bruchazjer et al. 2010; Van der ven et al. 2008a; Wang et al. 2010, 2011b). In an older study using an impure decaBDE compound (77% purity), increased liver weights were observed at dietary doses ≥80 mg/kg/day in male rats exposed for 30 days (Norris et al. 1973, 1975a). Following exposure to

dietary decaBDE from GD 10 to PND 21, male and female rat pups showed significantly increased liver weights at ≥2 and 146 mg/kg/day, respectively (Fujimoto et al. 2011). These findings were transient, as they were no longer evident in male and female offspring evaluated at PNW 11 (Fujimoto et al. 2011). No liver weight changes were observed in dams or PND 71 male offspring exposed to decaBDE from GD 0 to 17 via gavage at doses up to 1,500 mg/kg/day (Tseng et al. 2008). Young male rats exposed to decaBDE at doses of 0, 100, 300, or 600 mg/kg/day from PND 10 to 42 via gavage showed elevated liver weights at ≥300 mg/kg/day (Lee et al. 2010).

Hepatic enzyme induction (e.g., EROD, PRO activity, CYP protein levels) was significantly elevated in a dose-related manner in adult male and female rats exposed to decaBDE at 1.87–60 mg/kg/day for 28 days via gavage (Van der ven et al. 2008a) and young male rats exposed to decaBDE at 100–600 mg/kg/day from PND 10 to 42 via gavage (Lee et al. 2010). EROD activity was also significantly elevated in PND 71 male mice exposed to 1,500 mg/kg/day during gestation (Tseng et al. 2008). However, no exposure-related changes were observed in hepatic enzyme induction in female rats exposed to decaBDE up to doses of 1,000 mg/kg/day for 21 or 28 days (Bruchazjer et al. 2010). Genomic analyses of liver tissue reported elevated mRNA levels of CYP proteins in male mice exposed to dietary decaBDE at 9,400 mg/kg/day for 28 days (Sakamoto et al. 2013) and a dose-dependent elevation of Cyp2b2 mRNA in male rats exposed to decaBDE at doses of 1.87–60 mg/kg/day for 28 days via gavage (Van der ven et al. 2008a).

To determine if PBDE exposure alters vitamin A homeostasis in a manner similar to the related PBBs (ATSDR 2004), hepatic vitamin A levels were measured in rats following exposure to decaBDE at 0, 1.87, 3.75, 7.5, 15, 30, or 60 mg/kg/day for 28 days via gavage (Van der ven et al. 2008a). In females, but not males, hepatic vitamin A levels were increased in a dose-dependent manner by up to 14.6%, compared with controls; however, the lowest dose at which the effect was observed was not reported. The study authors conclude that the relevance of the effect is uncertain due to high variation in the data, as evidenced by a high BMD/BMDL ratio ($BMD/BMDL_{RD10\%}$ =13.8/1.2 mg/kg/day).

Chronic-Duration Animal Studies

Lower-brominated PBDEs: No chronic-duration studies analyzing hepatic effects were located for lower-brominated PBDEs.

DecaBDE: In chronic studies, exposure to 94–97% decaBDE for 103 weeks caused liver lesions that included neoplastic nodules in rats at ≥1,120 mg/kg/day, thrombosis and degeneration in rats at 2,240 mg/kg/day, and centrilobular hypertrophy and granulomas in mice at ≥3,200 mg/kg/day (NTP 1986). The thrombosis in the rats was characterized by a near total occlusion of a major hepatic blood vessel by a dense fibrin coagulum. A NOAEL was not identified in the rats or mice. The only other chronic study of decaBDE found that exposure to 1 mg/kg/day of a 77% pure mixture for 2 years caused no liver effects in rats; higher doses were not tested, precluding identification of a LOAEL (Kociba et al. 1975; Norris et al. 1975a).

Summary. No studies are available on hepatic effects of PBDEs in humans. Based on the evidence in animals, including enzyme induction, liver enlargement, histological lesions, hepatic porphyria, and markers of hepatic oxidative stress, PBDEs are potentially hepatotoxic in humans, especially lower-brominated PBDEs.

Renal Effects. Only one study was located that provides information on renal effects in humans following exposure to PBDEs. A pilot study measured serum creatinine and urinary β_2-microglobulin, as indices of renal function, in 40 Chinese residents exposed to PBDEs in an electronic waste dismantling area (Xu et al. 2015a). Mean ΣPBDEs in serum from exposed subjects was almost twice that in a control group, but the difference was not statistically significant. The results showed that neither serum creatinine nor β_2-microglobulin were correlated with PBDEs. However, congener analyses showed that BDE 28, BDE 47, BDE 85, and BDE 153 were positively correlated with urinary levels of β_2-microglobulin, and that BDE 28 and BDE 85 were positively correlated with serum creatinine levels. PCBs also played a role in the findings reported.

Acute-Duration Animal Studies

Lower-brominated PBDEs: Two studies examined renal effects in male rats 45 days after a single gavage administration of pentaBDE at doses of 0, 0.06, or 1.2 mg/kg (Albina et al. 2010; Alonso et al. 2010). In urine, a 4-fold increase in total protein levels was observed at 1.2 mg/kg (Alonso et al. 2010). Although this might suggest possible tubular damage, histopathological examination of the kidneys found no abnormalities other than a dose-related increase in phagolysosomes (incidence data not reported) (Albina et al. 2010). No other changes were observed in urinalysis or serum chemistry parameters (urea, creatinine, uric acid) (Alonso et al. 2010). Altered oxidative stress markers were found in the kidney after

exposure to 1.2 mg/kg/day, including significantly decreased CAT activity and increased GSSG and GSSG/GSH ratio (Albina et al. 2010).

No exposure-related changes in kidney weight were observed in male rats exposed to pentaBDE at doses up to 240 mg/kg/day for 9 days via gavage (Stoker et al. 2005) or female mice exposed to tetraBDE at doses up to 100 mg/kg/day for 4 days via gavage (Richardson et al. 2008).

DecaBDE: No acute-duration studies analyzing renal effects were located for decaBDE.

Intermediate-Duration Animal Studies

Lower-brominated PBDEs: Renal effects induced by dietary octaBDE included non-inflammatory kidney changes in male rats exposed to 600 mg/kg/day for 13 weeks, but not females exposed to doses up to 750 mg/kg/day (IRDC 1977). The incidence and severity of the kidney lesions (tubule regeneration, intratubular casts, and cellular debris occurred in most 600 mg/kg/day males) suggested a compound-related effect (IRDC 1977). However, no histopathological lesions of the kidney were observed in male or female rats exposed to pentaBDE at doses up to 250 mg/kg/day for 28 days via gavage (Oberg et al. 2010; Van der ven et al. 2008b), dietary penta- or octaBDE at doses up to 90 mg/kg/day for 28 days (IRDC 1976), or dietary pentaBDE doses up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984). Additionally, no histopathological kidney lesions were observed in F0 or F1 rats exposed to pentaBDE at doses up to 25 mg/kg/day from pre-mating through PND 42 (Bondy et al. 2013).

Statistically significant changes in blood urea and urea nitrogen levels were reported in some intermediate-duration studies; however, none of the changes were considered biologically relevant due to the small magnitude of change (<2-fold) compared with control. Following exposure to pentaBDE at 0, 2.5, 25, or 250 mg/kg/day via gavage for 28 days, blood urea levels in male rats from the 25 or 250 mg/kg/day groups were significantly increased by 1.5- and 1.2-fold, respectively; no changes were observed in blood urea levels in females or blood creatinine in either sex (Oberg et al. 2010). In another 28-day study, rats were exposed to pentaBDE at 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day via gavage (Van der ven et al. 2008b). Study authors reported dose-related increases in blood urea levels in male and female rats (maximal increases in males and females were 61.2 and 33.1%, respectively); however, the lowest dose at which the effect was observed was not reported. Instead, results were reported in terms of BMD analysis ($BMD/BMDL_{RD10\%}$=64.2/30.2 mg/kg/day in males and 65.1/22.2 mg/kg/day in females) (Van der ven et al. 2008b). Again, no changes in serum creatinine were

reported in either sex at doses up to 200 mg/kg/day (Van der ven et al. 2008b). Blood urea nitrogen (BUN) levels were elevated by 35% in male rats and 59% in female rats exposed to dietary octaBDE for 13 weeks at 600 and 750 mg/kg/day, respectively (IRDC 1977). No changes in BUN levels were observed in male or female rats exposed to dietary pentaBDE doses up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984).

Kidney weight changes following intermediate-duration exposure are inconsistent. A significant 10% decrease in relative kidney weight was observed in mice exposed to diBDE at 1.2 mg/kg/day for 28 days via gavage (Zhang et al. 2014). Absolute organ weights were not reported; however, no body weight effects were observed. In contrast, no change in kidney weight was reported in rats following exposure to pentaBDE at gavage doses up to 120 mg/kg/day for 20–90 days (Daubie et al. 2011; Stoker et al. 2004, 2005) or dietary penta- or octaBDE at doses up to 750 mg/kg/day for 28–90 days (IRDC 1976, 1977; WIL Research Laboratories 1984). Similarly, no change in F0 or F1 kidney weight was observed in rats exposed to pentaBDE at doses up to 25 mg/kg/day via gavage from 70 days prior to mating through PND 42 (Bondy et al. 2013) or mink exposed to dietary pentaBDE at doses up to 0.31 mg/kg/day from 4 weeks prior to mating to PNW 6 or 33 (Zhang et al. 2009). In other studies, significantly increased kidney weights have been reported, including a dose-related increase in absolute liver weight in rats exposed to pentaBDE doses up to 200 mg/kg/day for 28 days via gavage (dose at which effect was first observed was not reported; maximum increase of 11.5% in males and 15.6% in females) (Van der ven et al. 2008b), a significant 15% increase in relative, but not absolute, kidney weight following exposure to pentaBDE at 250 mg/kg/day for 28 days via gavage (Oberg et al. 2010), and a significant 18% increase in relative kidney weight following exposure to a dietary penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at 20 mg/kg/day for 70 days (absolute kidney weight not reported) (Ernest et al. 2012).

To determine if PBDE exposure alters vitamin A homeostasis in rats in a manner similar to the related PBBs (ATSDR 2004), vitamin A levels were measured in kidney tissue following exposure to pentaBDE at 0, 2.5, 25, or 250 mg/kg/day via gavage (Oberg et al. 2010). No significant changes in kidney vitamin A levels were observed at any dose.

DecaBDE: No renal histopathological changes were observed in rats or mice exposed to dietary decaBDE at doses up to 8,000 or 9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986). A 28-day study that evaluated histology of “major organs” did not report any exposure-related kidney effects in rats exposed to decaBDE at doses up to 60 mg/kg/day via gavage (Van der ven et al. 2008a). Studies of low

purity (≈77%) commercial decaBDE mixtures found kidney pathology (hyaline degenerative cytoplasmic changes) in male rats exposed to dietary levels of 800 mg/kg/day for 30 days (Norris et al. 1973,1975a), but not in rats exposed to ≤90 mg/kg/day for 28–30 days (IRDC 1976; Norris et al. 1973, 1975a). Interpretation of this finding is complicated by the fact that hyaline degenerative cytoplasmic changes are not uncommon in adult male rats and might be induced by a mechanism specific to certain aged male rats.

No exposure-related changes were observed in serum urea or creatinine levels in rats exposed to decaBDE at doses up to 100 mg/kg/day for 28–90 days via gavage (Van der ven et al. 2008a; Wang et al. 2010). Additionally, no exposure-related changes were observed in kidney weights in rats exposed to decaBDE at doses up to 600 mg/kg/day for 28–90 days via gavage (Lee et al. 2010; Van der ven et al. 2008a; Wang et al. 2010, 2011b; Zhang et al. 2013b), F0 or F1 mice exposed to decaBDE at doses up to 1,500 mg/kg/day from GD 0 to 17 via gavage (Tseng et al. 2008), or dietary decaBDE at doses up to 800 mg/kg/day for 28–30 days (IRDC 1976; Norris et al. 1973, 1975a).

Chronic-Duration Animal Studies

Lower-brominated PBDEs: No chronic-duration studies analyzing renal effects were located for lower-brominated PBDEs.

DecaBDE: No renal histopathological changes were observed in rats or mice exposed to dietary decaBDE at doses up to 2,550 or 7,780 mg/kg/day, respectively, for 2 years (NTP 1986). The only other chronic study of decaBDE found that exposure to dietary doses up to 1 mg/kg/day of the 77% pure mixture for 2 years caused no exposure-related changes in kidney histology or weight in rats (Kociba et al. 1975; Norris et al. 1975a).

Summary. No studies are available on hepatic effects of PBDEs in humans. While there is limited evidence from animal studies that lower-brominated PBDEs can cause kidney damage at high exposure levels, data are inconsistent and there is no evidence of impaired renal function. Animal studies do not indicate that decaBDE causes renal toxicity. Taken together, animals studies indicate that renal effects are not likely to occur in humans at environmentally-relevant exposure concentrations.

Endocrine Effects.

Human Studies. Numerous studies have been performed to evaluate the relationship between concentrations of PBDE in body tissues and circulating hormone levels in human populations. While these studies have demonstrated that PBDE can perturb the human endocrine system and affect hormone levels, the specific findings are not consistent across studies. For example, even limiting the discussion to studies that evaluated both PBDE concentrations and thyroid hormone levels in serum samples collected only from adult men, studies have reported positive associations with T_4 (Turyk et al. 2008), negative associations with T_4 (Abdelouahab et al. 2011), and no association with T_4 (Hagmar et al. 2001). These studies also reported either negative association with T_3 (Turyk et al. 2008) or no association with T_3 (Abdelouahab et al. 2011; Hagmar et al. 2001), and either negative association with TSH (Hagmar et al. 2001; Turyk et al. 2008) or no association with TSH (Abdelouahab et al. 2011). Populations in these studies were 308 adult male consumers of sport fish from U.S. Great Lakes with serum ∑PBDE ranging from 15.8 to 1,360 ng/g lipid (0.13–10.15 ng/g) with a median of 38.4 ng/g lipid (0.26 ng/g) (Turyk et al. 2008), 48 adult men recruited through an infertility clinic in Quebec with median serum ∑PBDE of 0.302 ng/mL and maximum of 2.250 ng/mL (Abdelouahab et al. 2011), and 110 adult men from Latvia and Sweden having varying consumption of Baltic Sea fish with serum BDE 47 ranging from 0.10 ng/g lipid (10^{th} percentile) to 5.16 ng/g lipid (90^{th} percentile) and a median of 1.04 ng/g lipid (Hagmar et al. 2001).

Similarly, studies of serum PBDE and serum thyroid hormones in populations including adults of both sexes found: (1) a negative association with free T_4 and no association with T_4, T_3, or TSH in 114 elderly residents of the upper Hudson River area of New York State (∑PBDE range of 0.04–9.80 µg/L and median of 0.19 µg/L in 48 women; range of 0.04–4.74 µg/L and median of 0.16 µg/L in 66 men) (Bloom et al. 2014); (2) a negative association with total T_4 (BDE 47, BDE 99, and BDE 100) and a positive association with TSH (BDE 153 only), but no association with free T_4 or total T_3, in a longitudinal study of 51 healthy adult office workers from Boston with serum ∑PBDE geometric means ranging from 19 to 23 ng/g lipid over 18 months (Makey et al. 2016); (3) no association with free or total T_4, T_3, or TSH in 36 New York anglers living in counties adjacent to Lakes Erie or Ontario with median serum ∑PBDE of 15 ng/g lipid and maximum of 2,303 ng/g lipid (Bloom et al. 2008); (4) a positive association with T_3 (for BDE 47 only) and no association with free T_4 or TSH in 623 Nunavik Inuits with geometric mean BDE 47=2.16 and BDE 153=2.05 µg/kg lipid (Dallaire et al. 2009); (5) no association with T_4, T_3, or TSH in 11 Swedish electronics recycling workers sampled repeatedly over 1.5 years (∑PBDE median=7.2 pmol/g lipid weight at start of employment and 9.7 pmol/g lipid weight at the conclusion of the study) (Julander

et al. 2005); (6) a positive association with TSH in 23 Chinese e-waste workers (∑PBDE median=382 ng/g lipid with range of 77–8,452 ng/g lipid) versus 26 controls (∑PBDE median=158 ng/g lipid with range of 18–436 ng/g lipid) (Yuan et al. 2008); (7) a positive association with T_4 (for BDE 126 and BDE 205 only) and no association with free T_4, T_3, free T_3, or TSH in another group of 239 Chinese e-waste workers (∑PBDE median=189.79 ng/g lipid with range of 0–6,016 ng/g lipid) and 93 farmers from the e-waste area (∑PBDE median=164.64 ng/g lipid with range of 0–8,600 ng/g lipid) versus 116 controls (∑PBDE median=122.37 ng/g lipid with range of 0–1,398 ng/g lipid) (Wang et al. 2010); (8) a negative association with T_3 (for BDE 17 and BDE 153 only) and no association with free T_4 or TSH in 124 residents of northern China with serum ∑PBDE median=7.16 ng/g lipid with range of 2.09–160.3 ng/g lipid (Huang et al. 2014); (9) no associations between serum PBDEs or their methyoxylated or hydroxylated metabolites and thyroid hormones in 77 residents living near an e-waste recycling site in Vui Dau, Vietnam or 34 residents living in rural Doung Quang, Vietnam (median ∑PBDE serum concentrations of 290 and 230 pg/g wet weight, respectively) (Eguchi et al. 2015); and (10) no associations between serum PBDEs and thyroid hormones in 40 residents living near an e-waste recycling site in Luqiao, China or 15 residents living in rural Yunhe, China (median ∑PBDE serum concentrations of 51.61 and 66.45 ng/g, respectively) (Xu et al. 2015a). Similar studies performed in children found: (1) a positive association with serum PBDE for serum TSH in 195 6–8-year-old children from an e-waste recycling area in China (∑PBDE mean=664.28 ng/g lipid) or 174 children from a control area (∑PBDE mean=375.81 ng/g lipid) (Han et al. 2011); (2) a negative association with serum PBDE for free T_3 and a positive association with serum PBDE for TSH in 162 4–6-year-old children living in an e-waste area in China (serum ∑PBDE median=189.99 ng/g lipid) (Xu et al. 2014b); (3) no association between free and total T_3 and T_4, TSH, and serum PBDE in 21 8-year-old children from an e-waste recycling area in China (∑PBDE median=31.86 ng/g lipid) or 24 children from a control area (∑PBDE median=6.97 ng/g lipid) (Xu et al.2014a); (4) positive associations with T_3 and free T_4 (for BDE 99 only) and no association with T_4 or TSH in 17 Dutch teenagers with serum ∑PBDE ranging from 4.9–22.1 ng/g lipid and a mean of 10.5 ng/g lipid (Leijs et al. 2012); and (5) and negative or no association with free T_3 (depending on type of analysis), positive or no association with TSH, and no association with free T_4 in 515 Flemish teenagers with a median serum ∑PBDE of 7 ng/L and maximum of 125 ng/L (Kicinski et al. 2012).

Oulhote et al. (2016) examined the potential association between PBDE exposure and hypothyroidism in Canadian women aged 30–79 years. PBDE levels were not significantly different in women diagnosed with hypothyroidism (n=90; geometric mean serum ∑PBDE=15.4 ng/g lipid) compared with women without hypothyroidism (n=655; geometric mean serum ∑PBDE=20.5 ng/g lipid). In a model adjusted for age, income, education, alcohol consumption, race/ethnicity, and history of breast-feeding, the

prevalence ratio of hypothyroidism was marginally increased by 1.7 per 10-fold increase in ∑PBDEs (95% CI 1.0, 3.0) or BDE 47 (95% CI 1.0, 2.9) and marginally increased by 1.8 in individuals with detectable BDE 100 compared with those without detectable BDE 100 (95% CI 1.0, 3.3). When models were adjusted for age income, education, alcohol consumption, and lipid-standardized PCB-153, these marginal associations were no longer observed.

A couple of studies were located in which exposure was estimated from concentrations of PBDE in house dust, rather than serum samples. In the earlier study, Meeker et al. (2009) found a positive association between PBDE in house dust and serum levels of free T_4, but no association with T_3 or TSH in 24 men recruited through an infertility clinic. Median and maximum concentrations of PBDE in dust collected from houses of study subjects were 500 and 7,620 ng/g dust for BDE 47, 838,and 9,220 ng/g dust for BDE 99, and 180 and 2,830 ng/g dust for BDE 100. A later study by these same researchers found positive associations between dust concentrations of pentaBDE (sum of BDE 47, BDE 99, and BDE 100; median and maximum concentrations of 1,049 and 22,300 ng/g in dust) and octaBDE (sum of BDE 183 and BDE 201; median and maximum concentrations of 30.5 and 1,181 ng/g in dust) and serum free T_4, and also between pentaBDE and T_3 and octaBDE and TSH in 38 additional men recruited through the infertility clinic (Johnson et al. 2013). There were no significant associations between thyroid hormones and exposure to decaBDE (sum of BDE 206, BDE 207, BDE 208, and BDE 209; median and maximum concentrations of 1,800 and 38,483 ng/g in dust) in this study.

As in other populations, findings in pregnant women differed across studies. Both free and total T_4 were significantly and positively associated with PBDE (several individual congeners and their sum) in serum collected during the 3rd trimester (>34 weeks) of pregnancy in a North Carolina cohort of 137 primarily African-American expectant mothers with serum ∑PBDE ranging from 3.59 to 693.95 ng/g lipid and a median of 36.56 ng/g lipid (Stapleton et al. 2011). Associations for free and total T_3 and TSH were not significant in this cohort. In contrast, a study of a California cohort of 270 mostly Latina women tested at the 27th week of pregnancy (serum ∑PBDE range of 3.6–1338.6 ng/g lipid, median of 25.2 ng/g lipid) found no association between PBDE and free or total T_4 (Chevrier et al. 2010). However, all PBDE congeners identified and their sum were significantly negatively associated with TSH in this study. Further analysis showed that women in the highest quartile of PBDE exposure had significantly increased odds of subclinical hyperthyroidism (defined as low TSH and normal free T_4) relative to women in the first quartile. A study of 105 pregnant women in South Korean that looked at blood samples collected the day before delivery (serum ∑PBDE median=2.13 ng/g lipid with 25th–75th percentile range of 1.35–4.34 ng/g lipid) found significant negative associations for PBDE with free and total T_3, a significant

positive association with free T_4, and no association with T_4 or TSH (Kim et al. 2013a). There were no correlations between PBDE and free and total T_4 and free and total T_3 in maternal serum samples (∑PBDE range from 15 to 580 ng/g lipid, median=37 ng/g lipid) collected just prior to delivery in another study of 12 patients from Indiana (Mazdai et al. 2003).

Abdelouahab et al. (2013) compared maternal serum concentrations of PBDE collected at <20 weeks of pregnancy (for ∑PBDE, median=30.92 ng/g lipid, maximum=726.09 ng/g lipid, n=380) with thyroid hormone levels in maternal blood at <20 weeks of pregnancy and in maternal blood collected at delivery for 260 pregnancies in Quebec. At <20 weeks of pregnancy, they found significant negative associations between PBDE and T_3 and T_4, but significant positive associations between PBDE and free T_3 and free T_4. However, using the thyroid hormone levels from the maternal samples at delivery, they found negative associations between maternal serum PBDE at <20 weeks and maternal free and total T_3 and T_4 at delivery. There was no significant association with TSH for either of the samples. In a Swedish cohort (n=166), a significant inverse relationship was observed between first trimester total T_3 levels and maternal body burden of BDE 153 (median breast milk concentration, 0.48 ng/g lipid); this relationship was not significant for third trimester total T_3 levels (Lignell et al. 2016). No significant associations were observed between breast milk BDE 153 levels and free T_4 or TSH in first or third trimester serum samples. No associations were observed between serum thyroid hormone levels and breast milk concentrations of tetra-pentaBDE (BDE 47, BDE 99, BDE 100; median concentration, 2.3 ng/g lipid).

A few studies included analysis of maternal serum samples collected after delivery. Kim et al. (2011d, 2012b) found significant positive relationships between serum PBDE (BDE 49 only) and free T_4, and between PBDE (BDE 154 and BDE 153 only) and TSH, and a significant negative relationship between PBDE (BDE 153 only) and T_3 in maternal blood samples collected from 12 South Korean mothers after delivery (for ∑PBDE, range=1.88–53.54 ng/g lipid, mean=18.79 ng/g lipid). There were no such correlations between serum PBDE and thyroid hormone levels in post-delivery blood samples collected from 26 mothers of infants born with congenital hypothyroidism (for ∑PBDE, range=3.81–1563 ng/g lipid, mean=65.16 ng/g lipid) (Kim et al. 2011d, 2012b). In a second study in which maternal blood samples were collected after delivery (for 21 South Korean mothers undergoing Cesarean section), there was no correlation between PBDE concentrations and thyroid hormone (free T_4, T_3, and TSH) levels in the maternal serum (Kim et al. 2012a). In this study, ∑PBDE in maternal blood ranged from 1.8 to 17.66 ng/g lipid, with a median of 7.81 ng/g lipid. Kim et al. (2011a) reported a significant positive correlation between concentrations of BDE 153 in breast milk (mean ≈0.25 ng/g lipid) and serum TSH collected post-delivery in another group of South Korean mothers.

In addition to the maternal effects, several of these studies and others reported on thyroid hormone changes in developing offspring, as identified by umbilical cord or neonatal blood samples in relation to PBDE concentrations in maternal serum, cord serum, or breast milk. The data on thyroid hormone effects in developing offspring are presented in Section 3.2.2.6 on Developmental Effects.

Few human data were located on endocrine end points other than thyroid (discussed above) or sex hormones (discussed in Section 3.2.2.5, Reproductive Effects). Lim et al. (2008) performed an analysis of cross-sectional U.S. NHANES 2003–2004 data that showed significant increases in risk of diabetes and metabolic syndrome associated with serum concentrations of BDE 153 (but not BDE 28, BDE 47, BDE 99, or BDE 100) based on 156 and 237 cases, respectively, in a population of 1,367 adults examined for diabetes status and, for metabolic syndrome, a subset of 637 participants with a morning fasting blood sample. In both analyses, the risk of disease was higher with exposure to 25th–50th percentile BDE 153 concentrations (median=3.6 ng/g lipid) and 50–75th percentile BDE 153 concentrations (median=6.6 ng/g lipid) than >75th percentile BDE 153 concentrations (median=24.6 ng/g lipid). Adjusted ORs were 2.6, 2.7, and 1.8 for diabetes and 2.5, 2.4, and 1.7 for metabolic syndrome in the respective quartiles. Serum BDE 153 concentrations (0.04 ng/g serum) were also shown to be significantly associated with increased odds of developing gestational diabetes in 258 pregnant women from the LIFE cohort in Michigan and Texas; no associations were observed for BDE 28, BDE 47, BDE 85, BDE 99, BDE 100, or BDE 154 (Smarr et al. 2016). A report from the Great Lakes Fish Consumption Study in Wisconsin found no significant difference in total serum PBDE or BDE 47 concentrations between individuals who were diagnosed with (n=64; Ln∑PBDEs reported as 0.31 ng/g) compared with non-diabetics (n=349; Ln∑PBDEs reported as 0.30 ng/g) (Turyk et al. 2015). In the Great Lakes cohort, established biomarkers of diabetes (C-reactive protein [CRP], gamma glutamyl transferase [GGT] and adiponectin) were also not associated with PBDE exposure; however, in stratified models, Ln∑PBDE and LnBDE47 were significantly associated with LnGGT and Lnadiponectin in persons above the median age.

In elderly populations, cross-sectional and prospective studies have found no relationship between serum PBDE (BDE 47 and BDE 153) concentrations and diabetes in cohorts from Finland (Airaksinen et al. 2011) or Sweden (Lee et al. 2011). In the Finnish study, 308 participants with diabetes had median serum concentrations of 2.7 ng/g lipid BDE 47 and 1.5 ng/g lipid BDE 153, while 1,680 nondiabetic participants had median serum concentrations of 2.9 ng/g lipid BDE 47 and 1.7 ng/g lipid BDE 153 (Airaksinen et al. 2011). PBDE exposure levels for the Swedish study (n=725) were not available (Lee et al. 2011).

In conclusion, although numerous studies have attempted to evaluate the relationship between tissue concentrations of PBDE and endocrine changes in humans, no clear pattern has emerged. Studies have found different results even in similar populations (e.g., adult men or pregnant women) from the same part of the world (e.g., North America or Asia) exposed to similar concentrations of PBDE. Although the specific findings are not consistent across studies, the bulk of the data have demonstrated that PBDE can interact with the human endocrine system to affect hormone levels.

Acute-Duration Animal Studies

Lower-brominated PBDEs: No exposure-related changes in thyroid weight or histology were observed in female rats exposed to penta- or tetraBDE doses up to 36 mg/kg/day for 14 days via gavage (Darnerud and Sinjari 1996; Hallgren and Darnerud 1998; Hallgren et al. 2001). No other acute studies evaluating thyroid weight or histology were identified.

Altered thyroid hormone levels have been reported following acute exposure to lower-brominated PBDEs. Significant reductions in serum T_4 of 19–92% have been reported following gavage exposure to penta-, octa-, or tetraBDE at doses ≥10 and ≥0.8 mg/kg/day in rats and mice, respectively, for 1–14 days (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998, 2002; Hallgren et al. 2001; Hoppe and Carey 2007; Richardson et al. 2008; Stoker et al. 2004, 2005; Zhou et al. 2001). The decreases in serum T_4 were associated with reduced *ex vivo* binding of T_4 to the plasma thyroid hormone transporter protein TTR (Hallgren and Darnerud 1998). Significant reductions in serum T_3 were observed in rats exposed to penta- and octaBDE at doses ≥100 and ≥60 mg/kg/day, with maximum reductions up to 25–30% at 300 and 100 mg/kg/day, respectively, for 4 days via gavage (Zhou et al. 2001). No changes in serum T_3 were observed in rats exposed to pentaBDE at lower doses (≤60 mg/kg/day) for 5 days via gavage (Stoker et al. 2004). No compound-related changes were observed in serum TSH levels in rats or mice exposed to penta- or octaBDE at doses up to 300 mg/kg/day for 4–14 days via gavage (Darnerud and Sinjari 1996; Hallgren and Darnerud 1998, 2002; Hallgren et al. 2001; Stoker et al. 2004; Zhou et al. 2001). In a low-dose study, male rats did not show exposure-related changes in serum T_4, T_3, or TSH levels measured 45 days after a single exposure pentaBDE at doses up to 1.2 mg/kg/day via gavage (Alonso et al. 2010).

Following a single gavage exposure to pentaBDE on GD 6, reductions in serum T_4 levels were observed at doses ≥0.06 mg/kg in rat dams on PND 1 (23–33%), but not PND 22, and F1 males and females at 0.3 mg/kg/day on PND 22 (19–23%), but not PND 1 or 14; no changes in serum T_3 were observed in

dams or F1 rats at any time-point at doses up to 1.2 mg/kg (Kuriyama et al. 2007). Maternal serum T_4 was also reduced on GD 20 in rat dams exposed to pentaBDE doses ≥60 mg/kg/day from GD 6.5 to 19.5 via gavage, but not on GD 12 in rat dams exposed to up to 120 mg/kg/day on GDs 6.5–11.5 (Ellis-Hutchings et al. 2009). Exposure to pentaBDE at doses up to 120 mg/kg/day on GDs 6.5–11.5 or 6.5–19.5 did not significantly alter maternal serum T_3, TSH, or TTR levels (Ellis-Hutchings et al. 2009).

A limited amount of information is available on hormonal effects of PBDEs other than thyroid. There were no clear chemical-related changes in serum corticosterone levels in female mice that were exposed to pentaBDE at doses up to 72 mg/kg/day via gavage for 14 days (Fowles et al. 1994). Limited data regarding serum reproductive hormone levels after acute-duration exposure to lower-brominated PBDEs are discussed in Section 3.2.2.5 (Reproductive Effects).

DecaBDE: No exposure-related changes in serum T_4, T_3, or TSH were observed in female rats exposed to decaBDE at doses up to 100 mg/kg/day via gavage for 4 days (Zhou et al. 2001). In neonatal male rats exposed to doses of 0, 6, or 20 mg/kg/day from PND 2 to 15, serum T_4 was reduced by ~8 and 22% at 6 and 20 mg/kg/day, respectively (Rice et al. 2007). This finding was reported as a dose-related trend; however, pair-wise statistics were not reported. No exposure-related changes in serum T_4 levels were observed in similarly exposed neonatal females (Rice et al. 2007). In pregnant mice exposed to decaBDE at 0, 150, 750, 1,500, or 2,500 from GD 7 to 9 via gavage, maternal serum T_4 was significantly reduced by ~11 and 14% on GD 16 in the 1,500 and 2,500 mg/kg/day groups, respectively (data reported graphically) (Chi et al. 2011). In the 2,500 mg/kg/day group, serum T_3 levels were also significantly reduced by ~40% (Chi et al. 2011).

Intermediate-Duration Animal Studies

Lower-brominated PBDEs: In a comprehensive 90-day study in rats, incidences of thyroid follicular cell hyperplasia were 0/10, 2/10, 2/10, and 5/10 in males and 0/10, 0/10, 1/10, and 4/10 in females exposed to dietary pentaBDE at 0, 2, 10, and 100 mg/kg/day, respectively (WIL Research Laboratories 1984). The thyroid hyperplasia was mild and transient, as it was characterized as very slight in severity at all doses and was no longer observed at 24 weeks postexposure in any animals. In a 28-day dietary study, thyroid hyperplasia was equivocally increased in male rats that were exposed to 90 mg/kg/day of penta- or octaBDE (IRDC 1976). Incidences of slight or moderate hyperplasia in the 0, 9, or 90 mg/kg/day dose groups were 0/5, 1/5, and 3/5 in pentaBDE-exposed males and 0/5, 0/5, and 3/5 in the octaBDE-exposed males, respectively; no increases were seen in females (IRDC 1976). In males rats exposed to pentaBDE

at doses of 0, 3, 30, or 60 mg/kg/day for 15 days via gavage, follicular cell hypertrophy and hyperplasia were observed in the 30 and 60 mg/kg/day groups (13/15 and 10/15, respectively); however, incidences in control and low-dose groups were not reported (Becker et al. 2012). Additionally, when this study was repeated in a different laboratory, no treatment-related histological changes were observed in the thyroid from the 60 mg/kg/day group (animals from 3- and 30-mg/kg/day group were not evaluated) (Becker et al. 2012). Follicular cell hypertrophy was observed in 50% of F1 rats exposed to pentaBDE at 50 mg/kg/day for 18 weeks (GD 6 to PNW 16) via gavage; hypertrophy was not observed in any controls (Dunnick et al. 2012).

Other histological and morphological changes observed in the thyroid included increased epithelial thickness of inner follicles of the thyroid in male rats exposed to a dietary penta-decaBDE mixture (52.1% pentaBDE, 44.2 decaBDE, and 0.4% octaBDE) at 20 mg/kg/day for 70 days (incidence data not reported) (Ernest et al. 2012); altered morphology of the epithelium (tall columnar rather than the normal cuboidal type) in 4/35 male and 1/35 female rats exposed to estimated dietary octaBDE doses of 600 and 750 mg/kg/day, respectively, for 28 days (IRDC 1977); an increased incidence of cellular debris in the follicular lumen of the thyroid in female mice exposed to dietary tetraBDE at 0.45 mg/kg/day for 28 days (Maranghi et al. 2013); a significant 60–66% increase in the follicular epithelial height score, a 23–44% decrease in the colloid area, and a 12.5–13.3% increased incidence of follicular degeneration in male and female rats exposed to pentaBDE at 60 mg/kg/day via gavage for 31 or 20 days, respectively (Stoker et al. 2004); an increase in the observed degree of vacuolation in the thyroid of female mink exposed to 0.31 mg/kg/day for 16–17 weeks (4 weeks pre-mating through PNW 6) (Zhang et al. 2009); and a borderline significant (p=0.057) increase in thyroid follicular epithelial cell height in F1 mink exposed to 0.06 mg/kg/day via gavage during a one-generation study (4 weeks pre-mating through PNW 33) (Zhang et al. 2009). Additionally, the epithelial height of the inner follicles of the thyroids showed a biphasic response in rats following dietary exposure to a penta-decaBDE mixture (52.1% pentaBDE, 44.2 decaBDE, and 0.4% octaBDE) at 0. 02, 0.2, 2, or 20 mg/kg/day for 70 days (Ernest et al. 2012). Compared with controls, the epithelial height was significantly decreased at 0.02 mg/kg/day and significantly increased at 20 mg/kg/day (other doses were not significantly different from controls; quantitative data not reported) (Ernest et al. 2012). In contrast to findings in other studies, no exposure-related changes in thyroid histology were observed in male or female rats exposed to pentaBDE doses up to 200 mg/kg/day for 28 days via gavage (Van der ven et al. 2008b).

Relative, but not absolute, thyroid weights were significantly elevated by 50% in male and females exposed to dietary pentaBDE at 100 mg/kg/day for 90 days (WIL Research Laboratories 1984). Eight

weeks postexposure, thyroid weights were still significantly elevated by 40% in female, but not male, rats; no exposure-related changes were observed 24 weeks postexposure (WIL Research Laboratories 1984). Rats that were exposed to octaBDE in estimated dietary doses of 5, 50, or 600 mg/kg/day (males) or 7, 70, or 750 mg/kg/day (females) for 13 weeks had increased absolute and relative thyroid weights of 15–31 and 32–56%, respectively, at ≥50/70 mg/kg/day (IRDC 1977). The thyroid weight increases were still observed at 8 weeks postexposure in the 600/750 mg/kg/day groups (increased 67 and 13% in males and females, respectively). However, no exposure-related thyroid weight changes were observed in rats exposed to pentaBDE at doses up to 200 mg/kg/day for 15–28 days via gavage (Becker et al. 2012; Van der ven et al. 2008b), in rats exposed to dietary penta- or octaBDE at doses up to 90 mg/kg/day for 28 days (IRDC 1976), or in F0 or F1 mink exposed to dietary pentaBDE at doses up to 0.31 mg/kg/day in one generation studies (4 weeks pre-mating through PNW 6 or 33) (Zhang et al. 2009).

Following exposure to pentaBDE doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day for 28 days via gavage, hyperemia in the zona reticularis of the adrenal gland was observed in ~50% of exposed male rats across all dose groups and occasionally in exposed female rats, but not in any control rats (incidence data for exposed animals not reported) (Van der ven et al. 2008b). In females, there was a dose-related increase in necrotic lesions in the zona reticularis, with pyknosis at 67 mg/kg/day and widespread necrosis at 200 mg/kg/day (Van der ven et al. 2008b). The authors reported that the combined incidence of hyperemia and zona reticularis necrosis was statistically significantly increased at the higher doses (precise doses not specified). No histological changes were observed in the adrenal gland of female mice exposed to dietary tetraBDE at 0.45 mg/kg/day for 28 days (Maranghi et al. 2013).

Mink that were exposed to dietary pentaBDE for 9 weeks had increased absolute and relative adrenal weights at 0.78 mg/kg/day (25 and 67%, respectively); no changes were observed at ≤0.63 mg/kg/day (Martin et al. 2007). No exposure-related adrenal weight changes were observed in rats exposed to pentaBDE at doses up to 240 mg/kg/day for 28–31 days via gavage (Stoker et al. 2005; Van der ven et al. 2008b), in rats exposed to dietary penta- or octaBDE at doses up to 90 mg/kg/day for 28 days (IRDC 1976), or in male or female rats exposed to dietary octaBDE doses up to 600 and 750 mg/kg/day, respectively, for 13 weeks (IRDC 1977). Adrenal weight was not assessed in any other intermediate-duration studies identified.

Serum T_4 levels were significantly reduced by 22–91% in rats exposed to pentaBDE at gavage doses of ≥3 mg/kg/day for 15–125 days (Becker et al. 2012; Driscol et al. 2009; Hoppe and Carey 2007; Stoker et al. 2004) or dietary pentaBDE at doses ≥20 mg/kg/day for 90 days (WIL Research Laboratories 1984).

Similarly, serum T_4 levels were significantly reduced by 22% in rats exposed to a dietary penta-decaBDE mixture (52.1% pentaBDE, 44.2 decaBDE, and 0.4% octaBDE) at 20 mg/kg/day for 70 days (Ernest et al. 2012). In a 28-day study, rats were exposed to pentaBDE at 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day via gavage (Van der ven et al. 2008b). Study authors report dose-related decreases in serum T_4 levels (maximal reduction of 88–89%); however, the doses at which these effects were observed were not reported. Instead, results were reported in terms of BMD analysis ($BMD/BMDL_{RD10\%}$= 1.4/1.1 mg/kg/day in males and 2.7/1.8 mg/kg/day in females) (Van der ven et al. 2008b). Serum T_3 levels were significantly reduced by 14–25% and serum TSH levels were significantly increased by 63–144% in male rats exposed to pentaBDE via gavage at ≥30 mg/kg/day for 15–31 days (Becker et al. 2012; Stoker et al. 2004). However, other studies reported no significant changes in serum T_3 and/or TSH levels in rats exposed to pentaBDE at doses up to 200 mg/kg/day for 20–28 days via gavage (Stoker et al. 2004; Van der ven et al. 2008b), dietary pentaBDE at doses up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984), or to a dietary penta-decaBDE mixture (52.1% pentaBDE, 44.2 decaBDE, and 0.4% octaBDE) at doses up to 20 mg/kg/day for 70 days (Ernest et al. 2012).

Altered thyroid hormone levels have also been reported in F0 animals following exposure to lower-brominated PBDEs in one-generation and gestational/lactation exposure studies. Following exposure to pentaBDE at 0, 0.5, 5, or 25 mg/kg/day via gavage for 70 days prior to mating through PND 42, serum T_4 levels were significantly reduced in F0 males at ≥5 mg/kg/day (50–87%) and females at 25 mg/kg/day (67%) (Bondy et al. 2011, 2013). In rat dams exposed to pentaBDE at 18 mg/kg/day via gavage from GD 6 to PND 18, serum T_4 levels were significantly decreased by 45%; no changes were observed in serum T_3, TSH, or TTR (Ellis-Hutchings et al. 2006). Following exposure to pentaBDE via gavage from GD 6 to PND 21, maternal serum T_4 levels were significantly reduced by ≥31% at ≥10.2 mg/kg/day, and maternal serum TSH levels were significantly increased by 127% at 30.6 mg/kg/day (Kodavanti et al. 2010; Zhou et al. 2002). No exposure-related changes were observed in serum T_3 (Kodavanti et al. 2010; Zhou et al. 2002). In dams exposed to 30 mg/kg/day via pentaBDE-dosed cookies from GD 1 to PND 21 via dose-cookies, significant decreases were observed in serum T_3 and T_4 levels (quantitative data not reported); no significant changes were observed in T_3 and T_4 levels at ≤3 mg/kg/day or TSH levels at doses up to 30 mg/kg/day (Bowers et al. 2015). In a similar study, a significant 25–50% decrease in maternal free and total T_4 levels was observed in dams exposed to ≥10 mg/kg/day via pentaBDE-dosed cookie from GD 6 to PND 21; no exposure-related changes were observed in T_3 or TSH levels at doses up to 30 mg/kg/day (Bansal et al. 2014). In rat dams exposed to tetraBDE via gavage from GD 1 to PND 14, maternal T_4 levels were significantly reduced on PND 1 and 7 by 28–31% at doses ≥3.2 mg/kg/day; no changes were observed in serum T_3 levels (Wang et al. 2011a). In mice, no exposure-related changes

were observed in maternal serum T_4 levels after exposure to pentaBDE at 452 mg/kg/day via gavage from GD 4 to PND 17 (Skarman et al. 2005). In one-generation dietary pentaBDE studies in mink (4 weeks premating through PNW 6), significant reductions in plasma T_3, but not T_4, were observed in F0 females exposed to 0.31 mg/kg/day (Zhang et al. 2009).

Numerous studies have also reported decreased serum T_3 and/or T_4 levels in pups after gestational and lactational exposure to penta- or tetraBDE at doses as low as 0.3 mg/kg/day in rats and at 452 mg/kg/day in mice (Bansal et al. 2014; Blanco et al. 2013; Bondy et al. 2011, 2013; Bowers et al. 2015; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Miller et al. 2012; Poon et al. 2011; Shah et al. 2011; Skarman et al. 2005; Szabo et al. 2009; Wang et al. 2011a; Zhou et al. 2002). Changes observed in mink juveniles included decreases in serum T_3, as in the adults, but also an increase in serum T_4 in juvenile females (Zhang et al. 2009). See Section 3.2.2.6 (Developmental Effects) for more details.

Consistent, exposure-related changes were not observed between studies that evaluated serum reproductive hormone levels after intermediate-duration exposure to lower-brominated PBDEs; see Section 3.2.2.5 (Reproductive Effects) for more details.

DecaBDE: Dose-related increases in thyroid hyperplasia were reported for male Sprague-Dawley rats exposed to dietary decaBDE at 80 or 800 mg/kg/day for 30 days (Norris et al. 1973, 1975a), although not in rats exposed to ≤90 mg/kg/day for 90 days, rats exposed to ≤8,000 mg/kg/day for 13 weeks, or mice exposed to ≤9,500 mg/kg/day for 13 weeks (IRDC 1976; NTP 1986). The occurrence of thyroid hyperplasia in the rats exposed to ≥80 mg/kg/day for 30 days could be related to the low purity composition of the older commercial decaBDE mixture tested by Norris et al. (1973, 1975a) (i.e., 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE, compared to the ≥94% decaBDE composition used in the NTP studies). Similarly, observed incidences of diffuse follicular cell hypertrophy were not significantly elevated in rat dams exposed to dietary decaBDE from GD 10 to PND 21 at doses up to 146 mg/kg/day, compared with control (Fujimoto et al. 2011). However, in young male rats exposed to decaBDE at doses of 0, 100, 300, or 600 mg/kg/day via gavage for 33 days (PNDs 10–42), multiple areas of degenerated follicular epithelium and slight attenuation of the follicular epithelium were observed in the thyroid glands of rat exposed to 300 or 600 mg/kg/day (incidence data not reported) (Lee et al. 2010).

In young male rats exposed to decaBDE at doses of 0, 100, 300, or 600 mg/kg/day via gavage for 33 days (PND 10–42), absolute and relative thyroid weights were significantly increased by 60 and 40%, respectively, in the 600 mg/kg/day group (Lee et al. 2010). Increased absolute and relative thyroid

weights were also reported in rat dams exposed to dietary decaBDE at 2, 15, or 146 mg/kg/day from GD 10 to PND 21; findings were significant at 2 mg/kg/day (21–22% decrease) and 146 mg/kg/day (21% decrease) (Fujimoto et al. 2011). No exposure-related changes in thyroid weight were observed in rats exposed to dietary decaBDE at doses up to 90 mg/kg/day for 28 days (IRDC 1976).

Unlike the lower-brominated PBDEs, serum T_4 levels were not altered in rats exposed to decaBDE at gavage doses up to 600 mg/kg/day for 28–90 days (Lee et al. 2010; Van der ven et al. 2008a; Wang et al. 2010, 2011b). Serum T_3 levels were significantly reduced by up to 25% in female, but not male, rats exposed to decaBDE at 60 mg/kg/day via gavage for 28 days (Van der ven et al. 2008a), and no changes in serum T_3 levels were observed in male rats exposed to decaBDE at doses up to 100 mg/kg/day via gavage for 90 days (Wang et al. 2010, 2011b). In young male rats exposed to decaBDE for 33 days (PNDs 10–45) via gavage, serum T_3 was significantly reduced by up to 45% at doses ≥100 mg/kg/day and serum TSH was significantly increased by ~70% following exposure to ≥300 mg/kg/day decaBDE for 33 days (PNDs 10–42) (Lee et al. 2010). In male mice, serum T_4 and T_3 were significantly reduced by 22 and 44%, respectively, following exposure to decaBDE at gavage doses of 950 mg/kg/day for 35 days, compared with controls; no exposure-related changes in serum thyroid hormone levels were observed at 750 mg/kg/day (Sarkar et al. 2015). In developing animals, significant reductions in serum T_3 levels were observed following gestational and lactational exposure to decaBDE at 146 mg/kg/day in rats and 1,500 mg/kg/day in mice; no changes were observed in serum T_4 or TSH (Fujimoto et al. 2011; Tseng et al. 2008); see Section 3.2.2.6 (Developmental Effects) for more details.

In young male rats exposed to decaBDE at doses of 0, 100, 300, or 600 mg/kg/day via gavage for 33 days (PNDs 10–42), absolute and relative adrenal weights were significantly increased by 14 and 20%, respectively, in the 600 mg/kg/day group (Lee et al. 2010). No exposure-related changes in adrenal weight were observed in rats exposed to dietary decaBDE at doses up to 90 mg/kg/day for 28 days (IRDC 1976). In mice, no significant changes in adrenal weight were observed in dams exposed to decaBDE at doses up to 1,500 mg/kg/day from GD 0 to 17 (Tseng et al. 2008).

Pancreatic effects were evaluated in rats exposed to decaBDE at doses of 0, 0.05, 1 or 20 mg/kg/day via gavage for 8 weeks (Zhang et al. 2013a). Serum insulin levels were significantly reduced by 50–60% at ≥1 mg/kg/day, and blood glucose levels were elevated by 12–21% at ≥0.05 mg/kg/day (Zhang et al. 2013a). Consistent with these findings, morphological changes in the pancreas were observed at ≥1 mg/kg/day, including blurred boundaries among pancreatic islet cells (incidence not reported).

Microarray analysis of liver tissue indicated significant alterations in genes from the canonical pathway for type I diabetes mellitus (Zhang et al. 2013a).

Chronic-Duration Animal Studies

Lower-brominated PBDEs: No chronic-duration studies analyzing endocrine effects were located for lower-brominated PBDEs,

DecaBDE: Hyperplasia of the thyroid was observed in rats and mice following repeated dietary exposures to decaBDE. Thyroid follicular cell hyperplasia was increased in male B6C3F1 mice that were exposed to ≥94% pure commercial decaBDE for 103 weeks (NTP 1986). Incidences of the lesion were 2/50 (4%), 10/50 (20%), and 19/50 (38%) in the 0, 3,200, and 6,650 mg/kg/day dose groups of this study. Slight increases in follicular cell tumors that were considered to be equivocal evidence of thyroid carcinogenicity were also observed in the male mice (see Section 3.2.2.7, Cancer). No decaBDE-related histopathological changes in the thyroid were found after 103 weeks of exposure to ≤7,780 mg/kg/day in female mice, ≤2,240 mg/kg/day in male Sprague-Dawley rats, or ≤2,550 mg/kg/day in female rats (NTP 1986).

Summary. While human data are inconsistent, they suggest that PBDEs can interact with thyroid hormone homeostasis. These data, along with available animal studies, indicate that the thyroid is a target of concern for PBDE exposure, especially lower-brominated PBDEs. One study reported pancreatic effects, including altered insulin regulation and pancreatic lesions, following intermediate decaBDE exposure; however, no other animal studies evaluated these end points. Limited human evidence is inconclusive regarding potential associations between diabetes and PBDE exposure; however, considering the animal data, the pancreas may be a target of concern for oral PBDE exposure. There is little evidence for endocrine effects other than those mediated by the thyroid and pancreas; data for altered reproductive hormones in humans and animals exposed to PBDEs are inconclusive (see Section 3.2.2.5, Reproductive Effects).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to PBDEs.

Histopathological examinations showed no dermal changes in rats following gavage exposure to ≤200 mg/kg/day of pentaBDE for 28 days (Van der ven et al. 2008b), dietary exposure to

≤100 mg/kg/day of pentaBDE for 90 days (WIL Research Laboratories 1984), or dietary exposure to ≤750 mg/kg/day of octaBDE for 13 weeks (IRDC 1977). No studies examining dermal effects after exposure to decaBDE were located.

Based on animal studies, dermal effects are unlikely with oral exposure to PBDEs.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to PBDEs.

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

Based on animal studies, ocular effects are unlikely with oral exposure to PBDEs.

Body Weight Effects. The only information located was that serum concentrations of BDE 47 in a group of 36 metabolically healthy but obese women (MHO) were not significantly different than in a group of 40 metabolically abnormal obese women (p=33 for comparison of the medians) (Gauthier et al. 2014). The significance of this isolated finding is unknown

Acute-Duration Animal Studies

Lower-brominated PBDEs: Percent body weight gain was significantly decreased by 2–19% in female rats following gavage exposure to pentaBDE at 2000 mg/kg for 1 day, pentaBDE at 200 mg/kg/day for 7 days, pentaBDE at 8–200 mg/kg/day for 14 days, or octaBDE at 40–200 mg/kg/day for 7 or 14 days (Bruchajzer et al. 2010, 2011, 2012). However, no changes in percent body weight gain were observed in female rats exposed to pentaBDE at doses up to 200 mg/kg/day for 7 or 14 days via gavage in another study by the same investigators (Bruchajzer 2011). Additionally, body weight effects were not reported in any other acute-duration study. No changes in body weight or body weight gain were observed in rats exposed to penta- or tetraBDE at doses up to 240 mg/kg/day for 3–14 days via gavage (Bruchajzer 2011; Hallgren and Darnerud 2002; Hallgren et al. 2001; Hoppe and Carey 2007; Stoker et al. 2004; Stoker et al. 2005; Zhou et al. 2001) or in mice exposed to penta-, tetra-, or octaBDE at doses up to 100 mg/kg/day

for 4–14 days via gavage (Hallgren and Darnerud 2002; Fowles et al. 1994; Hallgren et al. 2001; Richardson et al. 2008; Zhou et al. 2001).

In pregnant rats exposed to pentaBDE at 0, 10, 100, or 200 mg/kg/day via gavage from GD 6 to 15, maternal body weight gain was significantly decreased by 20 and 30% in the 100 and 200 mg/kg/day groups (Argus Research Laboratories 1985a). Pregnant rats exposed to octaBDE at 0, 2.5, 10, 15, 25, or 50 mg/kg/day via gavage from GD 6 to 15 showed a significantly 40% reduction in maternal body weight gain at 50 mg/kg/day (WIL Research Laboratories 1986). In pregnant rabbits, exposure to octaBDE at 15 mg/kg/day via gavage from GD 7 to 19 also resulted in a 7% decreased in maternal body weight gain (statistics not provided); no body weight effects were observed at ≤5 mg/kg/day (Breslin et al. 1989). In other studies, maternal body weight was not affected in rats by gestational exposure via gavage to pentaBDE at doses up to 120 mg/kg/day (Blanco et al. 2012, Ellis-Hutchings et al. 2009; Zhao et al. 2014) or tetraBDE at 0.7 mg/kg/day (Talness et al. 2008).

DecaBDE: No change in body weight or body weight gains were observed in rats exposed to decaBDE at doses up to 1,000 mg/kg/day for 4–14 days via gavage (Bruchajzer et al. 2010; Zhou et al. 2001) or in rats and mice exposed to dietary decaBDE doses up to 16,000 and 19,000 mg/kg/day, respectively, for 7–14 days (NTP 1986; Sakamoto et al. 2013). DecaBDE did not alter maternal body weight in mice exposed to doses up to 1500 mg/kg/day from GD 0 to 17 via gavage (Tseng et al. 2006).

Intermediate-Duration Animal Studies

Lower-brominated PBDEs: Percent body weight gain was significantly decreased by 8–19% in rats exposed to pentaBDE at 8–200 mg/kg/day or octaBDE at 40–200 mg/kg/day for 21 or 28 days via gavage (Bruchajzer 2011; Bruchajzer et al. 2012). However, in another study by the same investigators that exposed female rats to 0, 8, 40, or 200 mg/kg/day for 21 or 28 days via gavage, percent body weight gain was only significantly decreased at 200 mg/kg/day (Bruchajzer et al. 2010). Another 28-day gavage study reported no body weight gain changes in female rats at pentaBDE doses up to 200 mg/kg/day; however, significant changes were observed in male rats after the 28-day exposure to 0.27–200 mg/kg/day (Van der ven et al. 2008b). The $BMD_{RD10\%}$ and $BMDL_{RD10\%}$ for decreased body weight gain in male rats were 61.3 and 9.7 mg/kg/day, respectively (data were reported in terms of BMD analysis only; raw data were not reported). At higher doses (≥600 mg/kg/day), rats exposed to dietary octaBDE for 13 weeks showed ≥12% decreases in weight gain (IRDC 1977). In mink, dietary pentaBDE exposure at doses of 0.63 and 0.78 mg/kg/day for 9 weeks showed significant body weight decreases of 21 and

28%, respectively; no body weight effects were observed in mink exposed to dietary concentrations of 0.08 mg/kg/day (Martin et al. 2007).

Body weight effects were not reported in other intermediate-duration studies. No changes in body weight or body weight gain were observed in rats exposed to pentaBDE at doses up to 250 mg/kg/day for 15–90 days via gavage (Becker et al. 2012; Daubie et al. 2011; Hoppe and Carey 2007; IRDC 1976; Oberg et al. 2010; Stoker et al. 2004, 2005; WIL Research Laboratories 1984), in mice exposed to tetra- or diBDE at doses up to 30 mg/kg/day for 28–30 days via gavage (Wang et al. 2013; Zhang et al. 2014), in mice exposed to tetraBDE at doses up to 150 mg/kg/day for 6–12 weeks via gavage (McIntyre et al. 2015; Zhang et al. 2015a, 2015b), in rats exposed to dietary penta- or octaBDE or a penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, and 0.4% octaBDE) at doses up to 90 mg/kg/day for 28–125 days (Driscol et al. 2009; Ernest et al. 2012; IRDC 1976), or in mice exposed to dietary tetraBDE at doses up to 0.45 mg/kg/day (Maranghi et al. 2013).

Maternal body weight effects were not observed following gavage exposure to pentaBDE during gestation and lactation in rats at doses up to 30.6 mg/kg/day (Bowers et al. 2015; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Zhou et al. 2002) or in mice at doses up to 452 mg/kg/day (Branchi et al. 2005; Skarman et al. 2005). In one-generation studies, no body weight effects were observed in F0 or F1 rats following pentaBDE exposure to gavage doses up to ≤50 mg/kg/day (Bondy et al. 2011, 2013; Dunnick et al. 2012), in F0 dams following administration of doses up to 11.4 mg/kg/day via pentaBDE-dosed vanilla wafers (Poon et al. 2011), in F0 or F1 mink exposed to dietary pentaBDE doses of ≤0.31 mg/kg/day (Zhang et al. 2009), or in female F0 mice fed cornflakes dosed with 1 mg/kg/day of tetraBDE for 4 weeks prior to mating through PND 21 (Koenig et al. 2012; Ta et al. 2011)

DecaBDE: One study reported significant decreases in growth in rats exposed to decaBDE via gavage for 90 days (Wang et al. 2011b). "Whole-body growth rates," defined by the study authors as the average growth rate after 90 days, were reported as 1.57, 0.59, and 0.76% in the 0, 10, and 50 mg/kg/day groups, respectively (Wang et al. 2011b). No changes in body weight or body weight gain were observed in other studies of rats exposed to decaBDE doses up to 1,000 mg/kg/day for 21–90 days via gavage (Bruchajzer et al. 2010; Lee et al. 2010; Van der ven et al. 2008a; Wang et al. 2010; Zhang et al. 2013a), in mice exposed to decaBDE at doses up to 1,500 mg/kg/day for 15–60 days via gavage (Heredia et al. 2012; Liang et al. 2010; Sarkar et al. 2015; Tseng et al. 2006), or in rats and mice exposed to dietary decaBDE at doses of ≤8,000 and ≤9,500 mg/kg/day, respectively, for 28–90 days (NTP 1986; Sakamoto et al. 2013; Watanabe et al. 2010a). Dietary ingestion of 77.4% decaBDE mixture (containing 21.8% nonaBDE and

0.8% octaBDE) similarly caused no body weight changes in rats exposed to ≤800 mg/kg/day for 30 days or ≤1.0 mg/kg/day for 2 years (Kociba et al. 1975; Norris et al. 1973, 1975a).

Mean maternal weight was suppressed by ~10% in mice exposed to dietary decaBDE doses of 290 or 2,900 mg/kg/day from GD 10 to PND 21; however, the study authors did not report whether or not this finding was statistically significant (raw data not available for statistical analysis) (Watanabe et al. 2010b). A significant 12% decrease in body weight was also reported in rat dams exposed to decaBDE at 300 mg/kg/day via gavage for 3 weeks prior to mating until PND 21 (Liu et al. 2012). In other studies, decaBDE did not alter maternal body weight in rats exposed to doses up to 1,000 mg/kg/day from GD 10 to PND 21 via gavage (Biesemeir et al. 2011; Fujimoto et al. 2011) or in mice exposed to dietary decaBDE at doses up to 260 mg/kg/day from GD 10 to PND 21 (Watanabe et al. 2008).

Chronic-Duration Animal Studies

Lower-brominated PBDEs: No chronic-duration studies analyzing body weight effects were located for lower-brominated PBDEs.

DecaBDE: Body weight effects were not observed in rats and mice that were exposed to dietary decaBDE doses of ≤2,550 and ≤7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986).

Summary. No studies are available on body weight effects of PBDEs in humans. Although some acute- and intermediate-duration animal studies reported decreased body weight, several others reported no exposure-related changes in body weight. No changes in body weight were observed in chronic studies. Based on the body of evidence from animal studies, body weight effects are unlikely to occur following oral exposure to PBDEs at environmentally-relevant doses.

Metabolic Effects. No studies were located regarding metabolic effects in humans after oral exposure to PBDEs.

Animal Studies

Lower-brominated PBDEs: Exposure to pentaBDE via gavage for 28 days at doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day caused significant, dose-related decreases in blood glucose levels in male rats (Van der ven et al. 2008b). Results, reported in terms of BMD analysis, indicated a BMD_{10} of

179.55 mg/kg/day and a $BMDL_{10}$ of 66.7 mg/kg/day (raw data and statistics for individual dose groups were not reported). No significant changes in blood glucose levels were found in female rats exposed to doses up to 200 mg/kg/day (Van der ven et al. 2008b). Reduced serum glucose levels were also reported in male rats exposed to 20 mg/kg/day of a dietary PBDE mixture containing 52.1% penta-decaBDE (DE-71), 44.2% decaBDE (BDE 209), and 0.4% octaBDE (DE-79) for 70 days; no changes were observed at ≤2 mg/kg/day (Ernest et al. 2012).

In wild-type mice exposed to tetraBDE at 0 or 1 mg/kg/day via gavage for 6 weeks, no exposure-related changes in circulating insulin levels, glucose tolerance, insulin resistance, or lipogenesis in the liver were observed (McIntyre et al. 2015). However, insulin sensitivity was significantly decreased in similarly-exposed *Pten -/-* mice (mice hypersensitive to insulin), compared to control *Pten -/-* mice. No exposure-related effects were observed in *Tsc1 -/-* (mice with mild insulin resistance).

Exposure to pentaBDE via gavage at 250 mg/kg/day for 28 days caused hypercalcemia, hypermagnesemia, and hyperphosphatemia in male rats and hyperatremia and hypokalemia in female rats (Oberg et al. 2010). No changes in blood calcium, magnesmium, potassium, phosphorus, or sodium levels were observed at doses ≤25 mg/kg/day (Oberg et al. 2010). No significant changes in blood calcium, magnesium, or phosphorus levels were observed in male rats exposed to ≤20 mg/kg/day of a dietary penta-decaBDE mixture containing 52.1% pentaBDE (DE-71), 44.2% decaBDE (BDE 209), and 0.4% octaBDE (DE-79) for 70 days (Ernest et al. 2012).

A single study evaluated fat pad weight and adipocyte number, size, viability, lipolysis, and glucose oxidation in male rats following exposure to pentaBDE at 14 mg/kg/day via gavage for 2 or 4 weeks (Hoppee and Carey 2007). No exposure-related effects were noted at 2 weeks. At 4 weeks, significant observations included increased adipocyte lipolysis and decreased adipocyte glucose oxidation; however, no changes in fat pad weight or the number, size, or viability of adipocytes were observed.

DecaBDE: DecaBDE exposure via gavage for 8 weeks caused elevated blood glucose levels at ≥0.05 mg/kg/day in male rats (Zhang et al. 2013a). Elevated glucose levels were increased 12–21% compared with controls, and were accompanied by significantly decreased serum insulin levels at ≥1 mg/kg/day; see Section 3.2.2.2, Endocrine System Effects for more details.

Summary. Data regarding metabolic effects of PBDE are too limited to adequately characterize if PBDE exposure could alter metabolism in humans.

3.2.2.3 Immunological and Lymphoreticular Effects

Human Studies. A significant negative statistical association (not further described) was found between serum concentrations of PBDE and number of circulating lymphocytes in a subset of 18 of a cohort of 33 children (18 girls and 15 boys) born in the Amsterdam/Zaandam area of the Netherlands and aged 14–19 years at the time of this study (Leijs et al. 2009). Serum PBDE concentrations (determined as the sum of congeners 28, 47, 85, 99, 100, 153, 154, and 183) ranged from 5 to 74 ng/g lipid with a mean of 13.9 ng/g lipid. Congener-specific analysis showed the main contributors to be BDE 183, BDE 154, and BDE 85. There were no other effects on leukocyte count or differential. Although dioxins and PCBs were also assessed, no association with lymphocytes was found for these chemicals. No effects on pokeweed mitogen-stimulated DNA proliferation or IgG immunoglobulin synthesis were found in human lymphocytes exposed to BDE 47 or BDE 85 *in vitro* (Fernlof et al. 1997). A cross-sectional study of 992 subjects from Sweden aged 70 years reported that serum levels of BDE 47 (median 12.6 ng/g lipid) were significantly ($p=0.03$) negatively associated with blood levels of protein complement 3 (C3), but not with serum levels of C3a or C4 (Kumar et al. 2014a); no other BDE congener was assessed. PCB levels were also negatively associated with protein complements. In a similar study of the same cohort, Kumar et al. 2014b) found no association between serum levels of BDE 47 and multiple inflammatory markers.

Acute-Duration Animal Studies

Lower-brominated PBDEs: Limited information is available on effects of acute-duration exposure to lower-brominated PBDEs on immunologic function in animals. A single gavage dose of 0.8–500 mg/kg pentaBDE did not affect the plaque-forming splenic cell antibody response to injected sheep red blood cells in mice (Fowles et al. 1994). Mice that were given 18, 36, or 72 mg/kg/day doses of pentaBDE via gavage for 14 days had significantly reduced antibody response to sheep red blood cells (63% of control value, $p<0.02$) and decreased thymus weight at 72 mg/kg/day (Fowles et al. 1994). There were no exposure-related effects of the 14-day exposure to ≤72 mg/kg/day on NKC activity to murine YAC-1 target cells; NKC activity was not evaluated in the single-dose study. Another 14-day study was conducted in which mice and rats were administered pentaBDE at 0, 18, or 36 mg/kg/day via gavage and were evaluated for spleen and thymus weights, numbers of splenic and thymic lymphocyte subsets (CD4+, CD8+, and CD45R+ cells), and *in vitro* IgG immunoglobulin production in pokeweed mitogen-stimulated splenocytes (Darnerud and Thuvander 1998). The only exposure-related effect in either species was significantly reduced *in vitro* production of IgG in pokeweed-stimulated splenocyte cultures

from the mice exposed to 36 mg/kg/day. Mice that were similarly exposed to tetraBDE at 18 mg/kg/day via gavage for 14 days had significantly reduced numbers of total splenocytes as well as CD4+, CD8+, and CD45R+ cells in spleen (Darnerud and Thuvander 1998), but no changes in spleen or thymic weight (Hallgren et al. 2001).

DecaBDE: No acute-duration studies analyzing immune effects were located for lower-brominated PBDEs.

Intermediate-Duration Animal Studies

Lower-brominated PBDEs: Immune function was evaluated in male mink exposed to dietary pentaBDE for 9 weeks (Martin et al. 2007). Initial exposure concentrations were 0, 1, 10, or 100 ppm; however, after the first week of exposure, the 100 ppm group was switched to 5 ppm for weeks 2–9 because of food avoidance and weight loss concerns. Dose levels in the 1, 5/100, and 10 ppm groups were calculated to be 0.08, 0.63, and 0.78 mg/kg/day, respectively, based on estimated daily intake ranges (Martin et al. 2007). Mink were assessed weekly during exposure for antibody-mediated immunity to KLH (a carrier protein from keyhole limpet that binds to haptens and is used to stimulate a response from the immune system in the form of antibody production) and at 9 weeks for PHA skin response. No dose-related effects were observed for antibody production to KLH; however, at each time-point tested, antibody production in the 0.63 mg/kg/day group (the 100 ppm/5 ppm group) was significantly increased compared with controls. No exposure-related changes were observed in the skin response to PHA challenge.

Martin et al. (2007) also reported a significant increase in the incidence of spleen hyperplasia in mink from the 0.63 and 0.78 mg/kg/day groups, with 25 and 40% incidence, respectively, compared with 0% incidence in the controls. In the 0.78 mg/kg/day group, the number of germinal centers in the spleen was also significantly increased. In mice, histological and morphometric changes were observed in the spleen and thymus of females exposed to dietary tetraBDE at 0.45 mg/kg/day for 28 days (only dose tested; males not evaluated) (Maranghi et al. 2013). In the spleen, follicular hyperplasia with germinal center development was observed in 9/10 exposed mice, compared with 4/10 controls, and lymphocytic infiltration involving the red pulp was observed in 5/10 exposed mice, compared with 0/10 controls. In the thymus, 7/9 exposed mice showed Hassal's bodies, compared with 2/10 controls, and 5/9 showed lymphocytic apoptosis, compared with 0/10 controls. The ratio between area of cortex and medulla in the thymus was significantly increased by 43% in exposed mice, compared with controls. In the thyroid, cellular debris was observed in the follicular lumen of 5/7 exposed mice, compared with 0/10 controls

(Maranghi et al. 2013). In other studies, no exposure-related changes were observed in spleen, thymus, lymph node, and/or bone marrow tissue histology in rats exposed to pentaBDE at gavage doses up to 250 mg/kg/day for 28 days (Oberg et al. 2010; Van der ven et al. 2008b), pentaBDE at dietary doses up to 100 mg/kg/day for 90 days (WIL Research Laboratories 1984), or octaBDE at dietary doses up to 750 mg/kg/day for 13 weeks (IRDC 1977). Additionally, no exposure-related changes were observed in the histology of the spleen, thymus, Peyer's patches, or mesenteric lymph nodes in rat dams exposed to pentaBDE at doses up to 25 mg/kg/day via gavage for 70 days prior to mating through PND 21 (~21 weeks) (Bondy et al. 2013). In offspring, a significant dose-related trend was observed in the incidence of apoptotic lymphocytes and tingible macrophages in the thymus of PND 43 males, but not females (Bondy et al. 2013); see Section 3.2.2.6 (Developmental Effects) for more details.

Martin et al. (2007) reported a significant 29% increase in relative, but not absolute, spleen weight in mink exposed to dietary pentaBDE at 0.78 mg/kg/day for 9 weeks. In a 28-day study, rats were exposed to pentaBDE at 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day via gavage (Van der ven et al. 2008b). Study authors reported a dose-related decrease in thymus weight in male rats (maximal decrease of 19.4%); however, the lowest dose at which the effect was observed was not reported. Instead, results were reported in terms of BMD analysis ($BMD/BMDL_{RD20\%}$=194.2/110 mg/kg/day). No dose-related changes were reported for female thymus weight, male or female spleen weight, or T-cell, B-cell, or macrophage population distribution in the spleen in either sex (Van der ven et al. 2008b). In other studies, no exposure-related changes were observed in spleen or thymus weights in rats exposed to penta- or diBDE at gavage doses up to 250 mg/kg/day for 28 days (Oberg et al. 2010; Zhang et al. 2014), in rats exposed to pentaBDE at gavage doses up to 0.015 mg/kg/day for 90 days (Daubie et al. 2011), in rats exposed to dietary penta- or octaBDE at doses up to 100 mg/kg/day for 28 or 90 days (IRDC 1976; WIL Research Laboratories 1984), in rats exposed to a dietary penta-decaBDE mixture (52.1% pentaBDE [DE-71], 44.2% decaBDE [BDE 209], 0.4% octaBDE [DE-79]) at doses up to 20 mg/kg/day for 70 days (Ernest et al. 2012), in rats exposed to dietary octaBDE at doses up to 750 mg/kg/day for 13 weeks (IRDC 1977), or in mice exposed to dietary tetraBDE at 0.45 mg/kg/day for 28 days (Maranghi et al. 2013). Additionally, no exposure-related changes in spleen or thymus weights were observed in rat dams or offspring exposed to pentaBDE at 18 mg/kg/day via gavage from GD 6 to PND 21 (Ellis-Hutchings et al. 2006), in rat dams exposed to pentaBDE at doses up to 25 mg/kg/day via gavage for 70 days prior to mating through PND 21 (~21 weeks) (Bondy et al. 2013), or in mink sows exposed to dietary pentaBDE at doses up to 0.31 mg/kg/day for 4 weeks prior to mating through PNW 6 (Zhang et al. 2009). Although immune function was not altered, increased thymus weights, as well as altered serum immunoglobin levels and lymphocyte proliferation, were observed in the offspring of rat dams exposed to pentaBDE at

doses ≥5 mg/kg/day via gavage for 70 days prior to mating through PND 21 (~21 weeks) (Bondy et al. 2013); see Section 3.2.2.6 (Developmental Effects) for more details.

In a poorly-reported study, immune end points were evaluated in mouse dams and offspring following exposure to pentaBDE at 0, 50, 100, or 200 mg/kg/day via gavage from GD 6 to PND 21 (Hong et al. 2010). The absolute and relative spleen weights were significantly decreased in the 100 and 200 mg/kg/day groups and the thymi of exposed dams were "weighed decreasingly" (quantitative data were not reported). No histopathological alterations were observed in the spleen or thymus. The study abstract reports decreased cellularity of the spleen and thymus in dams; however, cellularity data for the dams are not reported in the results section of the paper. No statistically significant increases in T- or B-cell lymphocyte proliferation were observed, and no exposure-related changes in T-cell, B-cell, or macrophage population distribution were observed in the spleen. The study authors reported decreases in serum IgM levels, but statistical significance was not reported. No changes in serum IgG1 were observed. The study authors also noted some immune effects in offspring, including decreased spleen weight and cellularity and altered serum immunoglobin levels on PND 21 in groups exposed to ≥100 mg/kg/day and increased T-cell proliferation following *in vitro* exposure to concanavalin A (ConA) at 200 mg/kg/day on PND 63; see Section 3.2.2.6 (Developmental Effects) for more details.

DecaBDE: One week following exposure to dietary decaBDE at 0 or 1,800 mg/kg/day for 28 days, mice were intranasally infected with the RSV (Watanabe et al. 2010a). No exposure-related differences in pulmonary viral titers were observed 5 days post-infection (Watanabe et al. 2010a). In contrast, pulmonary viral loads were increased post-infection in PND 28 offspring of mouse dams exposed to dietary decaBDE at doses ≥260 mg/kg/day from GD 10 to PND 21 (Watanabe et al. 2008, 2010b); see Section 3.2.2.6 (Developmental Effects) for more details. In another high-dose study, female mice exposed to decaBDE at 800 mg/kg every other day showed impaired CD4 T-cell function from 4 to 10 months of exposure, compared with controls (Feng et al. 2016b). Significant alterations in peripheral CD4 T-cells from exposed mice included significant decreases in *in vitro* cytokine production of TNF-α, IFN-γ, and IL-2, decreased percentage of multi-functional CD4 T-cells (cells capable of producing multiple cytokines following mitogen production), increased percentage of T regulatory cells (CD4+CD25+Foxp3+), decreased percentage of proliferating CD4 T-cells, and decreased percentage of antigen-specific CD4 T cells following *in vivo Listeria monocytogenes* infection.

In rats exposed to decaBDE at 0 or 300 mg/kg/day via gavage for 21 days prior to mating through PND 21, the distribution of T-lymphocytes in the thymus was significantly altered in exposed rat dams,

with significantly decreased CD3+, CD4+, CD4+/CD8+, CC3+/CD8+, and CD3+/CD4+ T-cells and significantly increased CD4-/CD8- T-cells compared with control dams (Liu et al. 2012). CD161+ NKCs were also significantly decreased, compared with controls. Additionally, the lymphocyte stimulation index in response to *in vitro* PHA exposure was significantly reduced by ~2-fold in lymphocytes harvested from exposed rat dams, compared with control dams (Liu et al. 2012). In another study, no dose-related changes were reported for T-cell, B-cell, or macrophage population distribution in the spleen of rats exposed to decaBDE at doses up to 60 mg/kg/day via gavage for 28 days (Van der ven et al. 2008a).

Following exposure to decaBDE at 300 mg/kg/day via gavage for 21 days prior to mating through PND 21, serum IgM and IgG were significantly decreased by 28 and 4%, respectively, compared with controls (Liu et al. 2012). No exposure-related changes were observed in IFN- γ or IL-4 (Liu et al. 2012).

Histopathological examinations of spleen, thymus, lymph node, and/or bone marrow tissues showed no effects in rats or mice exposed to dietary decaBDE at doses up 8,000 or 9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986). In rat dams exposed to decaBDE at 0 or 300 mg/kg/day via gavage for 21 days prior to mating through PND 21 (~11 weeks), the exposed group showed significantly increased "histological scores" in the spleen and thymus compared with controls (methods of histological scoring and incidences of lesions were not reported) (Liu et al. 2012). Lesions observed in the thymus of exposed rats included thickened thymus capsule, decreased lymphoid tissue in the cortex with adipose tissue replacement, increased medulla size, and obscured corticomedullary junction. The spleen showed decreased size and number of lymphoid nodules, thinner lymphatic sheath around arteries, and fibrotic tissue with macrophages in the medulla.

In a 28-day study, rats were exposed to decaBDE at 0, 1.87, 3.45, 7.5, 15, 30, or 60 mg/kg/day via gavage (Van der ven et al. 2008a). The study authors reported a dose-related decreased in thymus weight in female rats (maximal decrease of 16.6%); however, the lowest dose at which the effect was observed was not reported. Instead, results were reported in terms of BMD analysis ($BMD/BMDL_{RD20\%}$= 75/43 mg/kg/day). No dose-related changes were reported for male thymus weight or male or female spleen weight (Van der ven et al. 2008a). Absolute and relative spleen weights were significantly decreased by 12 and 27%, respectively, in rat dams exposed to decaBDE at 300 mg/kg/day via gavage for 21 days prior to mating through PND 21 (~11 weeks); no exposure-related changes were observed in thymus weight (Liu et al. 2012). In other studies, no exposure-related changes in spleen weight were observed in rats exposed to decaBDE at doses up to 20 mg/kg/day via gavage for 8 weeks (Zhang et al.

2013a) or in mouse dams or PND 71 male offspring exposed to decaBDE at doses up to 1,500 mg/kg/day from GD 0 to 17 via gavage (Tseng et al. 2008).

In a poorly-reported study, immune end points were evaluated in mouse dams and offspring following exposure to decaBDE at 0, 500, 2,500, or 12,500 mg/kg/day via gavage on GD 6 to PND 21 (Hong et al. 2010). No exposure-related changes were reported for maternal spleen or thymus weight or histology. T-cell lymphocyte proliferation (in response to ConA) was "slightly" increased. No statistically significant increases in B-cell lymphocyte proliferation were observed and no exposure-related changes in T-cell, B-cell, or macrophage population distribution were observed in the spleen. The study authors reported increased serum IgG1 and IgM levels; however, statistics were not reported and changes do not appear dose-related in graphically-presented data. In offspring, altered spleen cell populations were noted on PND 21; see Section 3.2.2.6 (Developmental Effects) for more details.

Chronic-Duration Animal Studies

Lower-brominated PBDEs: No chronic-duration studies analyzing immune effects were located for lower-brominated PBDEs.

DecaBDE: Following chronic ingestion of decaBDE for 103 weeks, an increased incidence of splenic hematopoiesis was observed in female rats at ≥1,200 mg/kg/day (12/49, 24/48, and 17/50 at 0, 1,200, and 2,550 mg/kg/day, respectively); only the incidence in the mid-dose group was statistically significant. In male rats, the incidence of splenic fibrosis was significantly increased at 2,240 mg/kg/day (5/49, 8/50, and 13/49 at 0, 1,120, and 2,240 mg/kg/day, respectively) (NTP 1983). The incidence of lymphoid hyperplasia in the mandibular lymph node was also significantly increased in male rats at 2,240 mg/kg/day (4/50, 6/50, and 13/49 at 0, 1,120, and 2,240 mg/kg/day, respectively) (NTP 1983). No exposure-related histopathological lesions were observed in male or female mice following chronic ingestion of decaBDE for 103 weeks at doses up to 6,650 and 7,780 mg/kg/day, respectively (NTP 1983).

Summary. Evidence from animals suggest that PBDE exposure may cause immune suppression, particularly in infants or children (see Section 3.2.2.6, Developmental Effects for more details), but data are limited and inconsistent. Additionally, comprehensive immunological evaluations have not been performed and human data are limited. Therefore, currently available information is insufficient to adequately characterize the human immunotoxic potential of PBDEs. The highest NOAEL values and all

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

3.2.2.4 Neurological Effects

Human Studies. No association was found between serum PBDE concentrations (BDE 28, BDE 47, BDE 66, BDE 85, BDE 99, BDE 100, BDE 138, BDE 153, BDE 154, and their sum) and neuropsychological function assessed by 34 tests of cognitive and motor function, affective state, and olfactory function in a study population of 144 volunteers (67 males and 77 females) between the ages of 55 and 74 who lived for at least 25 years in the upper Hudson valley of New York State (Fitzgerald et al. 2012). Median total serum PBDE concentration in the study population was 23.9 ppb (lipid weight), with the detection limit exceeded in 89% of the population. Neurobehavioral function in adolescents was studied by Kicinski et al. (2012). The study population included 515 secondary school students (271 boys) from Flanders, Belgium, with a mean age of 14.9 years. The students were given a computerized battery of neurological tests. PBDE concentrations (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, and BDE 209) were measured in the serum. The median concentration of total PBDE in the serum was 7 ng/L. Serum PBDE concentrations were not associated with most aspects of neurological performance investigated, but there was a significant deterioration in performance in the finger tapping test with increasing PBDE level, suggesting an effect of PBDE on motor activity. Studies of neurological function in relation to PBDE concentrations in young children are discussed in Section 3.2.2.6 on Developmental Effects.

Acute-Duration Animal Studies

Lower-brominated PBDEs: In a neurotoxicity screen, adult male rats were exposed once to pentaBDE at 0, 0.6, or 1.2 mg/kg via gavage (Belles et al. 2010). Rats were assessed using a functional observation battery 3, 21, and 44 days after pentaBDE administration. After 45 days, rats were assessed in a variety of behavioral tests over 9 days, including open-field activity, passive avoidance test, and the Morris water maze. Following completion of behavioral tests, rats were sacrificed and brains were removed for biochemical analysis of oxidative stress markers (right hemisphere) and histopathological (left hemisphere) examinations of the cortex, hippocampus, and cerebellum. No exposure-related neurobehavioral, histological, or biochemical effects were observed.

In developing animals, a series of studies evaluated neurobehavior at 2–8 months of age following single-day exposure to lower-brominated PBDEs on PND 3, 10, or 19 in rats and mice. Collectively, these studies showed altered open-field activity, impaired habituation and altered learning and memory in rats and mice exposed to penta-, hexa-, tetra-, or octaBDE at doses as low as 0.4, 0.45, 1, or 16.8 mg/kg, respectively (Eriksson et al. 2001, 2002b, 2006; Fischer et al. 2008; Hallgren et al. 2015; He et al. 2009, 2011; Gee and Moser 2008; Sand et al. 2004; Viberg et al. 2002, 2003a, 2004a, 2004b, 2005, 2006). No changes in open-field behavior were observed in mice exposed to heptaBDE at 15.2 mg/kg or nonaBDE at 18.5 on PND 10 (Viberg et al. 2006). Besides behavioral changes, other significant neuro-developmental effects observed in these studies included ultrastructural changes, altered nicotinic receptor density, and altered gene and protein expression levels in the hippocampus. Altered open-field behavior was also observed in PND 36 offspring following acute gestational exposure to pentaBDE at doses as low as 0.06 mg/kg via gavage on GD 6 (Kuriyama et al. 2004). See Section 3.2.2.6 (Developmental Effects) for more details regarding neurodevelopmental effects of acute exposure to lower-brominated PBDEs.

DecaBDE: No studies evaluating neurobehavior or neuropathology in adult rats or mice following acute exposure to decaBDE were identified; however, there were no overt signs of neurotoxicity in rats and mice exposed to decaBDE in estimated dietary doses of ≤16,000 and ≤19,000 mg/kg/day, respectively, for 14 days (NTP 1986).

In developing animals, a series of studies reported decreased spontaneous activity and impaired habituation in open-field testing in 2–6-month-old mice that were exposed to decaBDE on PND 3 at doses as low as 2.22 mg/kg (Buratovic et al. 2014; Johansson et al. 2008; Viberg et al. 2003b, 2007). These changes in open-field behaviors were not observed in animals exposed on PND 10 or 19. In contrast, significantly increased locomotor activity during the first 1.5 hours of a 2-hour observation period was observed in PND 70 males following exposure to decaBDE at 20 mg/kg/day via micropipette from PND 2 to 15 (Rice et al. 2007). No changes in locomotor activity were observed at PND 70 in females or at 1 year in either sex at doses up to 20 mg/kg/day (Rice et al. 2007). In operant training and visual discrimination tasks, learning impairments and impulsivity were observed in aging mice (16 months old), but not young adult mice (3 months old), that had been exposed to decaBDE at 20 mg/kg/day from PND 2 to 15 (Rice et al. 2009). See Section 3.2.2.6 (Developmental Effects) for more details regarding neurodevelopmental effects of acute exposure to decaBDE.

Intermediate-Duration Animal Studies

Lower-brominated PBDEs: No exposure-related changes were observed in open-field behavior, anxiety-like behavior in the elevated plus-maze performance, or learning and memory in the Morris water maze in male rats following exposure to pentaBDE at doses up to 0.015 mg/kg/day (highest dose tested) via gavage for 90 days (Daubie et al. 2011). In a higher dose study, impaired attention and inhibitory control was observed in a series of 5-choice serial reaction time tasks assessed from PND 40 to 125 in male mice exposed to dietary pentaBDE at 26.2 mg/kg/day from PND 1 to 125; no exposure-related changes were observed at 17.5 mg/kg/day (Driscoll et al. 2009). In adult male rats exposed to tetraBDE at 0, 0.1, 0.5, or 1 mg/kg/day via gavage for 30 days, rats in all exposure groups showed impaired learning and memory in the Morris water maze (Yan et al. 2012). Exposed rats required significantly more time to find the hidden platform in the Morris water maze compared with control group, without showing any differences in swim speed. Additionally, significant decreases in the time spent in the target quadrant and the number of crossings over the original platform location were observed during the retention trial on day 5 (Yan et al. 2012).

No exposure-related changes in brain weight and/or histology were observed in rats exposed to pentaBDE at gavage doses up to 250 mg/kg/day for 28 days (Oberg et al. 2010; Van der ven et al. 2008b), in rats exposed to pentaBDE at gavage doses up to 0.015 mg/kg/day for 90 days (Daubie et al. 2011), in rats exposed to penta- or octaBDE at dietary doses up to 750 mg/kg/day for 28 or 90 days (IRDC 1976, 1977; WIL Research Laboratories 1984), in rat dams or pups exposed to pentaBDE at a gavage dose of 18 mg/kg/day from GD 6 to PND 18 (Ellis-Hutchings et al. 2006), or in mink sows or kits exposed to pentaBDE at dietary doses up to 0.31 mg/kg/day for 4 weeks prior to mating through PNW 6 or 33 (Zhang et al. 2009).

The density of NMDA receptor subunits, NR1 and NR2B, and the glutamate receptor, Glu, was determined in the CA1, CA3, and dentate gyrus of the hippocampus in adult male rats exposed to tetraBDE at 0, 0.1, 0.5, or 1 mg/kg/day via gavage for 30 days (Yan et al. 2012). Immunohistochemical staining showed significant decreases in the density of NR_1 and Glu in the hippocampus of all exposed rats and NR_2B in the hippocampus of rats exposed to 0.5 and 1 mg/kg/day. Additionally, significant decreases in hippocampal mRNA levels were observed for NR1 and NR2C in all dose groups and NR_2D in the 0.5 and 1 mg/kg/day groups. No exposure-related changes were observed in NR_2A or NR_2B mRNA levels (Yan et al. 2012).

Cholinergic effects were evaluated in mink sows and kits exposed to dietary pentaBDE at 0, 0.01, 0.05, or 0.25 mg/kg/day from pre-mating day 28 to PNW 6 (Bull et al. 2007). No exposure-related effects were observed in acetylcholinesterase concentration (ACh), acetylcholinesterase activity (ChE), or muscarinic receptor (mAChR) or nicotinic receptor (nAChR) binding in the cerebral cortices of sows or kits. Plasma ChE activity in sows from the 0.25 mg/kg/day group was significantly increased by 3-fold, compared with controls. Plasma ChE activity was not significantly correlated with cortical ChE activity; however, it was significantly correlated with absolute and relative liver weights. Therefore, altered ChE activity in plasma in the high-dose sows may reflect exposure-related effects in the liver, rather than the central nervous system. No changes were observed in plasma ChE activity in kits (Bull et al. 2007).

Several studies have reported delayed ontogeny of reflexes, neurobehavioral impairments, and ultrastructural and biochemical changes in the hippocampus of offspring after gestational and lactational exposure to penta- or tetraBDE in rats and mice at doses as low as 2 and 0.03 mg/kg/day, respectively (Blanco et al. 2013; Bowers et al. 2015; Branchi et al. 2001, 2002, 2005; Cheng et al. 2009; Koenig et al. 2012; Ta et al. 2011; Woods et al. 2012). See Section 3.2.2.6 (Developmental Effects) for more details regarding neurodevelopmental effects of intermediate-duration exposure to lower-brominated PBDEs.

DecaBDE: Following a 15-day exposure to decaBDE at 20 mg/kg/day via gavage, male mice showed decreased anxiety behavior in the elevated zero maze, including decreased latency to first entry into the open region, increased time spent and number of entries into the open region, and increased number of head dips, compared with controls (Heredia et al. 2012). No exposure-related changes were observed in anxiety behaviors in the light/dark test, in learning or memory in the Morris water maze, or in general neurological behaviors assessed using a functional observation battery (Heredia et al. 2012). In another study, no changes were observed in open-field behavior of male rats exposed to decaBDE at doses up to 50 mg/kg/day via gavage for 90 days (Wang et al. 2011b). No overt signs of neurotoxicity were observed in rats and mice exposed to decaBDE in estimated dietary doses of ≤8,000 and ≤9,500 mg/kg/day, respectively, for 13 weeks (NTP 1986).

Rats exposed to decaBDE at dietary doses up to 90 mg/kg/day for 28 days showed no change in brain weight (IRDC 1976). No exposure-related changes in brain weight or AchE activity were observed in mice exposed to decaBDE at doses up to 160 mg/kg/day via gavage for 15, 30, or 60 days (Liang et al. 2010).

There is limited evidence for neurodevelopmental effects following gestational and lactational exposure to decaBDE. No neurobehavioral changes were observed in rat offspring exposed to decaBDE at doses up to 1,000 mg/kg/day from GD 6 to PND 21 (Biesemeier et al. 2011). However, impaired spatial learning was observed in offspring of rat dams exposed to decaBDE at doses ≥30 mg/kg/day from GD 1 to 14 (Chen et al. 2014). Additionally, altered hippocampal electrophysiology was observed in mice offspring exposed to 20.1 mg/kg/day from GD 1 to PND 41 (Xing et al. 2009) and altered hippocampal immunohistochemistry was observed in mice offspring exposed to ≥15 mg/kg/day from GD 10 to PND 21 (Fujimoto et al. 2011). See Section 3.2.2.6 (Developmental Effects) for more details regarding neurodevelopmental effects of intermediate-duration exposure to decaBDE.

Chronic-Duration Animal Studies

Lower-brominated PBDEs: No chronic-duration studies analyzing neurological effects were located for lower-brominated PBDEs.

DecaBDE: There were no indications of neurotoxicity in rats and mice in lifetime feeding studies of decaBDE at doses as high as 2,550 and 7,780 mg/kg/day, respectively, as assessed by overt clinical signs and nervous system histopathology (NTP 1986). Although the high doses and extended exposure durations in the NTP (1986) studies provided opportunities for the induction and/or development of effects, neurotoxicity is incompletely evaluated due to the lack of testing for subtle behavioral and other sensitive neurological end points.

Summary. While the nervous system is a target of concern during early development (see Section 3.2.2.6, Development Effects for more details), it is unclear if the developed nervous system is a target of oral PBDE toxicity. Animal data suggest the oral PBDE exposure may lead to neurobehavioral changes; however, available information is insufficient to adequately characterize the neurotoxic potential of PBDEs in adults and adolescents. 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 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

Human Studies. Two studies have demonstrated reproductive effects in men associated with exposure to PBDEs. In a small study limited to 10 young adult Japanese males, strong, statistically significant inverse

correlations were found between serum levels of BDE 153 and sperm concentration and testis size (Akutsu et al. 2008). Both blood and sperm were collected monthly and pooled for each participant over 1 year. BDE 153 concentrations for the 10 participants ranged from 0.37 to 1.1 ng/g lipid. There was no relationship to sperm concentration or testes size for other PBDE congeners or for the sum of the most prevalent congeners, which included BDE 153 (BDE 47, BDE 99, BDE 100, and BDE 153) and ranged from 1.1 to 8.6 ng/g lipid for the 10 participants. Among a group of 52 Canadian men recruited at a fertility clinic, sperm mobility was significantly reduced in association with increased serum PBDE concentrations (BDE 47, BDE 100, and total) (Abdelouahab et al. 2011). Results for BDE 153 were similar, but not statistically significant. Relationships between PBDE and sperm concentration were consistently negative as well, but also not significant. The median ∑PBDE concentration in this population was 0.302 ng/mL and the maximum was 2.250 ng/mL. A study of 468 male partners of couples discontinuing contraception for purposes of becoming pregnant from Michigan and Texas found that, in general, serum concentrations PBDEs were negatively associated with parameters of semen quality, specifically increased percentages of abnormal morphology (Mumford et al. 2015). The study evaluated 10 BDEs: BDE 17, BDE 28, BDE 47, BDE 66, BDE 85, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 183. BDE 153, however, was associated with increased sperm concentration. The 95th percentile serum concentrations (unadjusted for lipid content) for the BDEs analyzed ranged from 0.007 ng/g serum for BDE 183 to 0.761 ng/g serum for BDE 47. Significant associations at the α=0.01 level were found only for BDE 17 (increased sperm with coiled tail) and for BDE 28 (increased bicephalic sperm). A cross-sectional study that included 99 men from Greenland, 100 from Poland, and 100 from Ukraine found no association between serum levels of BDE 47 and BDE 153 with parameters of semen quality including markers of DNA damage and apoptosis (Toft et al. 2014). Among the three groups, median concentrations of BDE 47 ranged from 0.2 to 2.0 ng/g lipid and median concentrations of BDE 153 ranged from 0.3 to 2.7 ng/g lipid.

Studies of hormone levels in men in relation to PBDE concentrations have not produced consistent results. Concentrations of PBDE (BDE 47, BDE 99, and BDE 100) in house dust samples were significantly associated with changes in some sex hormone levels (decreased FSH, LH, and free androgen index, and increased Inhibin B and sex hormone binding globulin [SHBG]), although not testosterone or estradiol, in 24 adult men recruited through a Massachusetts infertility clinic (Meeker et al. 2009). Median and maximum concentrations of PBDE in dust collected from houses of study subjects were 500 and 7,620 ng/g dust for BDE 47, 838 and 9,220 ng/g dust for BDE 99, and 180 and 2,830 ng/g dust for BDE 100. A larger subsequent study by the same researchers with 38 additional subjects using the same design found a significant negative correlation with FSH and significant positive correlations with

estradiol and SHBG for pentaBDE (sum of BDE 47, BDE 99, and BDE 100; median and maximum concentrations of 1,049 and 22,300 ng/g in dust), significant positive correlations with testosterone and LH for octaBDE (sum of BDE 183 and BDE 201; median and maximum concentrations of 30.5 and 1,181 ng/g in dust), and a significant negative correlation with testosterone for decaBDE (sum of BDE 206, BDE 207, BDE 208, and BDE 209; median and maximum concentrations of 1,800 and 38,483 ng/g in dust) (Johnson et al. 2013). No relationships were found between serum concentrations of BDE 47 and testosterone, FSH, LH, or prolactin in adult male Baltic Sea area residents of Sweden and Latvia with a wide range of fish consumption behavior and BDE 47 concentrations ranging from 0.10 ng/g lipid at the 10^{th} percentile to 5.16 ng/g lipid at the 90^{th} percentile (median=1.04 ng/g lipid) (Hagmar et al. 2001). In a study of serum PBDE and hormone levels in adult male sport fish consumers from the Great Lakes, a significant positive relationship was found for BDE 47 (but not other congeners) and serum testosterone levels (Turyk et al. 2008). BDE 47 concentrations in this population ranged from 0.01 to 5.90 ng/g (median=0.11 ng/g), while ∑PBDE concentrations ranged from 0.13 to 10.15 ng/g (median=0.26 ng/g). Serum concentrations of FSH, LH, or estradiol were not associated with serum levels of BDE 47 or BDE 153 in a study of 299 spouses of pregnant women from Greenland, Poland, and Ukraine (Toft et al. 2014). Median concentrations of BDE 47 ranged from 0.2 to 2.0 ng/g lipid and median concentrations of BDE 153 ranged from 0.3 to 2.7 ng/g lipid.

In women, Chao et al. (2007) found no significant relationship between concentrations of PBDE in breast milk and pre-pregnancy menstrual cycle length (by questionnaire) in an analysis of 20 pregnant women from Taiwan with median PBDE concentrations in breast milk of 3.65 ng/g lipid, predominantly BDE 47 and BDE 153. However, in a larger study of 46 pregnant Taiwanese women recruited several years later, Chao et al. (2010) found significant increases in average length of pre-pregnancy menstrual cycle with increased breast milk concentrations of PBDE (total and multiple individual congeners). Median breast milk total PBDE concentration in this study group was 2.84 ng/g lipid, with predominant congeners being BDE 47, BDE 153, and BDE 209. A study of 42 Cree women of James Bay, Canada, reported that concentrations of BDE 47 and BDE 153 in plasma were associated with increased menstrual cycle length (Wainman et al. 2016). Geometric mean plasma concentrations of BDE 47 and BDE 153 were 14.1 and 4.5 ng/g lipid, respectively, which according to the investigators, were comparable to those reported for women 20–39 years old from the general Canadian population; serum cadmium and selenium were also associated with increased cycle length. In the study by Chao et al. (2010), age at menarche was not related to breast milk PBDE concentrations, but an analysis of data from a sample of 271 adolescent U.S. girls age 12–19 years with serum total PBDE concentrations ranging from 6.4 to 636.5 ng/g lipid (median=44.7 ng/g lipid) from NHANES (2003–2004) found that higher serum PBDE concentrations

were associated with younger age of menarche in this population (Chen et al. 2011). There was no relationship between mid-pregnancy serum PBDE concentrations and pre-pregnancy menstrual cycling in a cohort of 223 pregnant low-income women from the Salinas Valley of California (part of the CHAMACOS study) (Harley et al. 2010), but there were significant decreases in fecundability (i.e., increases in time to pregnancy between stopping contraception and becoming pregnant) associated with increased serum concentrations of BDE 47 (geometric mean=14.9 ng/g lipid), BDE 99 (geometic mean=4.4 ng/g lipid), BDE 100 (geometic mean=2.8 ng/g lipid), BDE 153 (geometic mean=2.5 ng/g lipid), and their sum in this population and/or a subset comprising 107 women actively trying to become pregnant. However, fecundability was not significantly related to serum PBDE concentrations (concentrations not reported) in a cohort of 501 Michigan and Texas couples followed prospectively for 1 year after discontinuing contraception for the purpose of becoming pregnant (Buck Louis et al. 2013). Blood was collected from both male and female partners in this study and fecundity of the couple was assessed in relation to each partner's exposure. A study of 65 women undergoing *in vitro* fertilization found no association between serum PBDE concentrations (median=12.6 ng/g lipid, maximum=113 ng/g lipid) and risk of implantation failure, but did find a significantly increased risk of failure associated with increased (i.e., detectable) concentrations of BDE 153 (but not other congeners or total PBDE) in follicular fluid (Johnson et al. 2012). No significant relationship was found between concentrations of the PBDE metabolite 6-OH-BDE-47, which ranged from <4 to 127 pg/g wet weight, with a median of 26 pg/g wet weight) and 17β-estradiol in umbilical cord serum collected from 26 births in South Korea (Wan et al. 2010). Serum PBDE concentrations had no effect on expression of genes for the sex steroid enzymes aromatase (CYP19A1) and 17-α-hydroxylase or estrogen receptors α and β (ESR1 and ESR2) in leukocytes collected from 139 adult daughters of Michigan fisheaters with serum total PBDE concentrations ranging from 4.3 ng/g lipid at the 5^{th} percentile to 209.5 ng/g lipid at the 95^{th} percentile (median=33.8 ng/g lipid) (Karmaus et al. 2011).

Vagi et al. (2014 examined the association between blood levels of multiple environmental pollutants and Polycystic Ovary Syndrome (PCOS). Fifty-two PCOs patients and 50 controls were included in the study. PCOS is an endocrine- metabolic disorder characterized by ovulatory dysfunction, hirsutism, or elevated levels of androgens in blood. Eleven PBDEs were analyzed in blood, but only six had detectable serum concentrations (however, only five are listed in the report: BDE 28, BDE 47, BDE 99, BDE 100, and BDE 153). Cases and controls had comparable serum concentrations of these BDEs, and in both groups, BDE 47 had the highest concentration (~25.5 ng/g lipid). After controlling for age, BMI, and ethnicity, none of the measured BDEs was associated with increased risk of PCOS.

Concentrations of PBDEs in omental fat or serum were not associated with risk of uterine fibroids in women undergoing laparoscopy or laparotomy in a study conducted in Salt Lake City, Utah, and San Francisco, California (Trabert et al. 2015). Ninety-nine women had fibroids and 374 had none. Seven PBDEs were measured: BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, and BDE 209. Whether in omental fat or serum, geometric mean concentrations of PBDEs were comparable between women who had fibroids and those who did not. Odds of a fibroid diagnosis (and corresponding 95% CIs) showed no association with PBDEs.

Acute-Duration Animal Studies

Lower-brominated PBDEs: There are limited data regarding the reproductive effects of acute exposure to lower-brominated PBDEs in females. In rat dams exposed once to tetraBDE at 0, 0.14, or 0.7 mg/kg on GD 6 via gavage, a significant 17% increase in paired ovary weight was observed at 0.14 mg/kg, but not 0.7 mg/kg (Talsness et al. 2008). No treatment-related changes in gravid uterine weight or number of implantation or resorptions were observed in rat dams exposed to pentaBDE at doses up to 2 mg/kg/day from GD 6 to 19 (Blanco et al. 2012). In ovariectomized female mice, no exposure-related changes were observed in uterine wet weight, uterine epithelial height, or vaginal epithelium thickness following exposure to pentaBDE at doses up to 300 mg/kg/day for 3 days via gavage, with or without co-exposure to β-estradiol-3-benzoate (Mercado-Feliciano and Bigsby 2008a).

The effects of acute pentaBDE exposure on androgen-dependent tissue weights was assessed in castrated male rats supplemented with subcutaneous injections of testosterone (to ensure equal levels of circulating testosterone in the exposed and control groups) in a Herschberger assay (Stoker et al. 2005). Male rats that were castrated on PND 42 were exposed to pentaBDE at 0, 30, 60, 120, or 240 mg/kg/day from PND 53 to 61 via gavage, and daily gavage exposures were followed by daily subcutaneous injections of 0.4 mg/kg testosterone. On PND 62, significant decreases in androgen-dependent tissue weights included a ~20–55% decrease in ventral prostate weight at ≥30 mg/kg/day, a ~20–60% decrease in seminal vesicle weight at ≥60 mg/kg/day, a ~28–41% decrease in Cowper's gland weight at ≥120 mg/kg/day, and a 22–29% decrease in the gland penis and levator ani bulbo cavernosus weight at 240 mg/kg/day (Stoker et al. 2005).

There is limited evidence for exposure-related effects on serum reproductive hormones levels in male rats following acute exposure to pentaBDE. Serum testosterone levels were significantly decreased by ~40–45% in male rats 45 days after a single gavage exposure to pentaBDE at doses ≥0.6 mg/kg; serum

progesterone was significantly decreased by ~40% at 1.2 mg/kg (data presented graphically) (Alonso et al. 2010). Significantly increased serum levels of LH were reported in male rats (~65%, data reported graphically) following exposure to pentaBDE at 60 mg/kg/day for 3 days (Stoker et al. 2005). No exposure-related changes were observed in serum testosterone, androsteridione, or estrone levels at doses up to 60 mg/kg/day (Stoker et al. 2005). Following a single gavage administration of pentaBDE at 0, 0.06, or 0.3 mg/kg on GD 6, no exposure-related changes in serum testosterone or LH levels were observed in F1 male rats on PND 140 (Kuriyama et al. 2005).

As discussed in Section 3.2.2.6 (Developmental Effects), F1 reproductive success was assessed following a single gavage administration of pentaBDE at 0, 0.06 or 0.3 mg/kg or tetraBDE at 0, 0.14, or 0.7 mg/kg on GD 6 in rat dams (Kuriyama et al. 2005; Talsness et al. 2005, 2008). Following pentaBDE exposure, no significant exposure-related effects were observed in F1 male fertility when exposed males were mated with unexposed females, and the only mating behavior significantly altered was a 32% decrease in the percent of males with two or more ejaculations in F1 males from the 0.3 mg/kg group (Kuriyama et al. 2005). Similarly, no changes in female pregnancy rate was observed in F1 females mated to unexposed males following exposure to pentaBDE or tetraBDE (Talsness et al. 2005, 2008). F1 male reproductive performance was not assessed following tetraBDE exposure. Despite a lack of exposure-related impairment in reproductive success following acute developmental exposure to penta- or tetraBDE, reductions in testicular weight, sperm/spermatid number, and daily sperm production were observed in F1 males exposed to pentaBDE at ≥0.06 mg/kg/day, and a decreased number of secondary follicles and ultrastructural changes in the ovaries were observed in F1 females exposed to pentaBDE at ≥0.06 mg/kg/day or tetraBDE at ≥0.14 mg/kg/day (Kuriyama et al. 2005; Talsness et al. 2005, 2008).

In a one-generation study in mink, females exposed to pentaBDE at doses ≥0.25 mg/kg/day from pre-mating day 28 through PNW 6 did not whelp (Bull et al. 2007; Zhang et al. 2009). It is not clear in the Bull et al. (2007) study whether mink exposed to 0.25 mg/kg/day never became pregnant or had complete litter loss. However, Zhang et al. (2009) reported that females exposed to 0.31 mg/kg/day had no exposure-related changes in mating success; rather, sows showed complete litter loss with 70% showing clear postimplantation loss.

DecaBDE: In mouse dams exposed to decaBDE at 0, 150, 750, 1,500, or 2,000 mg/kg/day via gavage from GD 7 to 9, the percentage of postimplantation loss per litter was significantly increased by 3, 2.7, and 9.8% at 750, 1,500, and 2,000 mg/kg/day, respectively, compared with control (Chi et al. 2011). At 1,500 and 2,000 mg/kg/day, the percentage of resorptions per litter was also significantly increased by

2.7 and 8.6%, respectively. Additionally, the percentage of live fetuses per litter was significantly decreased by 10% in the high-dose group (Chi et al. 2011). These effects could reflect reproductive toxicity in the dams or developmental toxicity in the fetuses (see Section 3.2.2.6, Developmental Effects). No other acute-duration studies analyzing reproductive effects were located for decaBDE.

Intermediate-Duration Animal Studies

Lower-brominated PBDEs: No exposure-related changes were observed in reproductive end points (number of pregnancies, gestation length, number, size, or sex ratio of litters) in rats exposed to pentaBDE at doses up to 25 mg/kg/day for 70 days prior to mating until PND 42 via gavage (Bondy et al. 2013), in rats fed vanilla wafers containing pentaBDE at doses up to 11.4 mg/kg/day from pre-mating day 28 through PND 21 (Poon et al. 2011), in mice exposed to tetraBDE at doses up to 0.1 mg/kg/day via gavage from pre-mating day 28 through PND 21 (Woods et al. 2012), or in mice fed cornflakes containing tetraBDE at doses up to 1 mg/kg/day from pre-mating day 28 through PND 21 (Koenig et al. 2012; Ta et al. 2011). Similarly, no exposure-related effects on litter parameters (successful delivery of litters, gestation length, litter size, sex ratio, number of live pups) were observed in rats or mice exposed to pentaBDE at doses up to 2 or 10 mg/kg/day, respectively, from GD 1 or 6 to PND 21 via gavage (Branchi et al. 2005; Cheng et al. 2009; Zhao et al. 2014), in rats exposed to pentaBDE at doses up to 30 mg/kg/day from GD 1 to PND 21 via dosed cookies (Bowers et al. 2015), or rats exposed to dietary tetraBDE at doses up to 32 mg/kg/day from GD 1 to PND 14 (Wang et al. 2011a). The number of litters surviving until PND 8 was significantly decreased following exposure to tetraBDE at 0.1 mg/kg/day from pre-mating day 28 through PND 21 in one study (Woods et al. 2012); however, reduced pup survival was not reported in other studies (Bondy et al. 2013; Koenig et al. 2012; Poon et al. 2011; Ta et al. 2011; Wang et al. 2011a).

Male rats exposed to tetraBDE at 1 mg/kg/day via gavage for 8 weeks showed a significant 24% decrease in daily sperm production; no exposure-related effects were observed at doses ≤0.03 mg/kg/day (Zhang et al. 2013b). In another study, sperm morphology, motility, and capacitation were evaluated in mice following gavage exposure to tetraBDE at 0, 0.0015, 0.045, 1.5, or 30 mg/kg/day for 30 days (Wang et al. 2013). No exposure-related changes in sperm morphology or sperm motility were observed. A significantly decreased rate of sperm capacitation (% B-type [mature] sperm) was observed in the 0.0015, 0.045, and 30 mg/kg/day groups, but not in the 1.5 mg/kg/day group (Wang et al. 2013). No exposure-related changes in sperm counts, motility, or DNA damage were observed in rats exposed to a penta-

decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at dietary doses up to 20 mg/kg/day for 70 days (Ernest et al. 2012).

Microscopic changes in the testes of rats were observed following exposure to tetraBDE at ≥0.03 mg/kg/day via gavage for 8 weeks, including increased epithelial thickness, vacuolar spaces in the seminiferous epithelium, and increased number of multinucleated giant cells (arising from spermatocytes that aborted meiosis); no histopathological changes were observed at 0.001 mg/kg/day (Huang et al. 2015; Zhang et al. 2013b). Additionally, the number of apoptotic cells was significantly increased by 2- and 3-fold in the testes of rats from the 0.03 and 1 mg/kg/day groups, respectively (Huang et al. 2015; Zhang et al. 2013b). In similarly-exposed rats, co-treatment with dexamethasone phosphate (DEX; a CYP3A1 inducer) "aggravated" the observed histopathological effects (Zhang et al. 2013b). Mice exposed to tetraBDE at 0, 0.0015, 0.045, 1.5, or 30 mg/kg/day via gavage for 30 days also showed testicular effects at doses ≥0.045 mg/kg/day, including "some" seminiferous tubules with complete germ cell loss and a Sertoli cell-only phenotype (incidence not reported) and a dose-related increase in the number of apoptotic cells (Wang et al. 2013). No exposure-related changes were observed in testes weight at doses up to 30 mg/kg/day (Wang et al. 2013). In other studies, exposure-related changes were not observed in organ weight or histology in male or female reproductive tissues from mice exposed to tetraBDE at dietary doses of 0.45 mg/kg/day for 28 days (Maranghi et al. 2013), rats exposed to penta- or octaBDE at dietary doses up to 750 mg/kg/day for 28–90 days (IRDC 1976, 1977; WIL Research Laboratories), rats exposed to a penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at dietary doses up to 20 mg/kg/day for 70 days (Ernest et al. 2012), rats exposed to pentaBDE at gavage doses up to 250 mg/kg/day for 15–28 days (Becker et al. 2012; Oberg et al. 2010), or ovariectomized mice exposed to pentaBDE at 50 mg/kg/day for 34 days via gavage (with or without β-estradiol-3-benzoate co-exposure) (Mercado-Feliciano and Bigsby 2008a). Additionally, organ weight changes were not observed in F0 or F1 rats exposed to pentaBDE at doses up to 25 mg/kg/day via gavage from pre-mating day 70 to PND 42 (Bondy et al. 2013) or F0 or F1 mink exposed to dietary pentaBDE at doses up to 0.31 mg/kg/day for 4 weeks prior to mating through PNW 6 or 33 (Zhang et al. 2009).

Following exposure to pentaBDE at 0, 3, 30, or 60 mg/kg/day for 15 days via gavage, serum prolactin was significantly decreased by 67% at 60 mg/kg/day in male rats (Becker et al. 2012). While testosterone and FSH levels were not significantly altered at any specific dose (based on pair-wise analysis), trend tests showed significant dose-dependent increases in testosterone and FSH levels; LH and E2 were below the detection limit in all groups (Becker et al. 2012). In contrast, a repeat of the same study in a different laboratory showed no exposure-related changes in serum testosterone, LH, FSH, E2, or prolactin in male

rats exposed to pentaBDE at doses up to 60 mg/kg/day for 15 days (Becker et al. 2012). Similarly, male rats exposed to a penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at dietary doses up to 20 mg/kg/day for 70 days did not show altered serum testosterone levels (Ernest et al. 2012). After exposure to tetraBDE for 8 weeks via gavage (6 days/week), male rats showed significant reductions in serum testosterone of ~35, 54, and 63% at 0.001, 0.03, or 1 mg/kg/day, respectively (data reported graphically) (Zhang et al. 2013b). No exposure-related changes were observed in serum E2, FSH, or LH levels at doses up to 1 mg/kg/day (Zhang et al. 2013b). In female mice exposed to dietary tetraBDE for 28 days, serum testosterone and E2 were significantly increased by 57 and 18% at 0.45 mg/kg/day (only tested dose) (Maranghi et al. 2013).

Biochemical analysis of rat testes showed significant dose-related elevations of mRNA levels of several apoptosis genes following exposure to tetraBDE at doses of 0.001–1 mg/kg/day via gavage for 8 weeks (6 days/week) (Zhang et al. 2013b). Additionally, elevated levels of ROS were observed at 1 mg/kg/day (Zhang et al. 2013b). Co-exposure to DEX (a CYP3A1 inducer) enhanced ROS-induction in the testes, with significant elevations observed at ≥0.001 mg/kg/day (Zhang et al. 2013b). No exposure-related changes were observed in testicular mRNA expression levels for genes involved in steroidogenesis (Star, Cyp17a1, Ar, Srd5a1, Srd 5a2, Cyp19a1, Esr1, Esr2) in rats following exposure to a penta-decaBDE mixture (52.1% pentaBDE, 44.2% decaBDE, 0.4% octaBDE) at dietary doses up to 20 mg/kg/day for 70 days (Ernest et al. 2012).

Exposure to lower-brominated PBDEs has been reported to cause reproductive effects in developing rats. Two companion studies evaluated reproductive system development following exposure to pentaBDE at 0, 3, 30, or 60 mg/kg/day via gavage during pubertal development (PNDs 23–53 in males or PNDs 22–41 in females) (Stoker et al. 2004) or 0, 60 or 120 mg/kg/day via gavage during pubertal development in males (PNDs 23–53) (Stoker et al. 2005). In males, preputial separation (PPS) was significantly delayed by 1.7–5 days at ≥30 mg/kg/day, absolute ventral and lateral prostate weights and seminal vesicle weights were significantly decreased 16–29% at ≥60 mg/kg/day (in the absence of body weight effects), and serum prolactin was increased 2-fold at 60 mg/kg/day (not evaluated in the 120 mg/kg/day group). There were no exposure-related changes in testicular weight or histology, epididymides histology, serum testosterone or LH, or pituitary LH or prolactin levels at doses up to 60–120 mg/kg/day (Stoker et al. 2004, 2005). In females, vaginal opening was significantly delayed by 1.8 days in the 60 mg/kg/day group. No changes were observed in estrous cycling or ovarian or uterine weight or histology at doses up to 60 mg/kg/day (Stoker et al. 2004). As summarized in Section 3.2.2.6 Developmental Effects, observed effects in F1 rats exposed to pentaBDE at 30.1 mg/kg/day from GD 6 to PND 21 included decreased

anogenital distance, delayed PPS, and decreased serum testosterone in male offspring and decreased mammary gland development in female offspring (Kodavanti et al. 2010).

DecaBDE: Information on effects of intermediate-duration exposure to decaBDE on reproductive function is limited to negative findings in a one-generation study in rats using a low-purity (77.4%) decaBDE mixture (Dow Chemical Co. 1975; Norris et al. 1975a). Male and female rats were exposed to 0, 3, 30, or 100 mg/kg/day doses in the diet for 60 days prior to mating through PND 21. Parameters monitored included length of time between first day of cohabitation and parturition, numbers of live and dead newborn, number of live pups (PNDs 1, 7, 14, and 21), litter weight (PNDs 1, 7, and 14), and weanling weight (PND 21). Comprehensive histological examinations (adults and weanlings), skeletal examinations (weanlings), and cytogenetic evaluation of bone marrow (adults and weanlings) were also performed on PND 21. There were no exposure-related effects on reproductive parameters or any indications of maternal or neonatal toxicity. Additionally, no exposure-related changes were observed in litter parameters in mice exposed to decaBDE at gavage doses up to 1,500 mg/kg/day from GD 0 to 17 (Tseng et al. 2008), in rats exposed to decaBDE at gavage doses up to 1,000 mg/kg/day from GD 6 to PND 21 (Biesemeier et al. 2011), or in rats or mice exposed to decaBDE at dietary doses up to 146 or 3,100 mg/kg/day, respectively, from GD 10 to PND 21 (Fujimoto et al. 2011; Watanabe et al. 2008, 2010b).

Sperm parameters have been assessed in rats and mice following intermediate-duration exposure to decaBDE. In the rat study, no exposure-related changes were observed in male epididymal sperm counts or morphology following exposure to decaBDE at gavage doses up to 60 mg/kg/day for 28 days (Van der ven et al. 2008a). In one mouse study, sperm count and viability were significantly reduced by about 40% in males exposed to 950 mg/kg/day via gavage for 35 days, compared with controls; no exposure-related changes in sperm count and viability were observed at 750 mg/kg/day (Sarkar et al. 2015). In contrast, no exposure-related changes were observed in sperm count, sperm motility, or the percent of abnormal sperm heads in mice exposed to decaBDE at doses up to 1,500 mg/kg/day via gavage for 50 days (Tseng et al. 2006). For sperm velocity, the lateral head amplitude was significantly decreased in the 500 and 1,500 mg/kg/day groups, compared with control; no exposure-related changes were observed in curvilinear, average path, or straight line velocity or beat-cross frequency. No exposure-related changes were observed in sperm damage parameters; however, sperm H_2O_2 production was significantly increased at 500 and 1,500 mg/kg/day (no change in O_{2^-} production). The percentage of sperm with high mitochondrial membrane potential was significantly decreased in the 1,500 mg/kg/day group, compared with controls.

There is limited evidence of histopathological damage in reproductive organs following intermediate-duration exposure to decaBDE. Various degenerative changes were observed in the seminiferous tubules of mice exposed to decaBDE at gavage doses of 950 mg/kg/day for 35 days, including thinning of the germinal epithelium, decreased diameter of the seminiferous tubules, depletion of germ cells, exfoliation of germ cells, and intraepithelial vacuolation (Sarkar et al. 2015). Both the height of the germinal epithelium and the diameter of seminiferous tubules were significantly decreased at 950 mg/kg/day, compared with controls. No exposure-related testicular lesions were observed at 750 mg/kg/day. In female rats exposed to decaBDE at 0 or 300 mg/kg/day from 3 weeks of age, through mating to untreated males, gestation, and lactation (~11 weeks), the ovaries in the exposed rats had significantly increased "histological scores" than the ovaries from the control rats (methods of histological scoring and incidences of lesions were not reported) (Liu et al. 2012). Observations in the ovaries of exposed rats included atrophic changes, decreased number of follicles, and increased fibrotic tissue (Liu et al. 2012). F0 reproductive success and F1 developmental end points were not reported in this study. However, in other intermediate-duration studies, no histopathological changes were observed following exposure to decaBDE in male or female reproductive tissues from rats exposed for 28–50 days at gavage doses up to 1,500 mg/kg/day (Tseng et al. 2006; Van der ven et al. 2008a), rats exposed for 28–30 days at dietary doses up to 800 mg/kg/day (IRDC 1976; Norris et al. 1973, 1975a), or rats or mice exposed for 13 weeks at dietary doses up to 8,000 or 9,500 mg/kg/day, respectively (NTP 1986).

In a 28-day study, rats were exposed to decaBDE at 0, 1.7, 3.75, 7.5, 15, 30, or 60 mg/kg/day via gavage (Van der ven et al. 2008a). The study authors reported a dose-related decrease in epididymis weight in male rats (maximal decrease of 22.5%) and a dose-related increase in seminal vesicle/coagulation gland weight (maximal increase of 38.3%); however, the lowest doses at which the effects were observed were not reported. Instead, results were reported in terms of BMD analysis ($BMD_{RD10\%}$ for epididymis= 4.0 mg/kg/day, $BMDL_{RD10\%}$ was not determined; $BMD/BMDL_{RD10\%}$ for seminal vesicle= 1.5/0.2 mg/kg/day). No exposure-related changes in organ weight were reported for testes, ovaries, or uterus at doses up to 60 mg/kg/day (Van der ven et al. 2008a). In other rat studies, no exposure-related changes in testes, epididymides, or seminal vesicle weights were observed following exposure to dietary decaBDE doses up to 800 mg/kg/day for 28–30 days (IRDC 1976; Norris et al. 1973, 1975a). In mice, one study reports a significant 13–18% decrease in relative testis and epididymides weight following exposure to decaBDE at 950 mg/kg/day via gavage for 35 days, compared with controls; no exposure-related changes in male reproductive organ weights were observed at 750 mg/kg/day (Sarkar et al. 2015). In contrast, no exposure-related changes in testes, epididymides, or seminal vesicle weights were

observed in another mouse study that exposed animals to decaBDE at gavage doses up to 1,500 mg/kg/day for 50 days (Tseng et al. 2006).

In a 35-day study, serum testosterone levels were significantly decreased by 65% in mice following exposure to decaBDE at gavage doses of 950 mg/kg/day, compared with controls; testosterone levels at 750 mg/kg/day were comparable to control (Sarkar et al. 2015).

There is limited evidence that exposure to decaBDE in developing animals results in reproductive effects. In male rats exposed during pubertal development, exposure to decaBDE at doses up to 600 mg/kg/day did not cause exposure-related changes in testes, epididmides, or prostate organ weight, testicular histology, or testicular mRNA expression levels of steriodogensis-related genes (Lee et al. 2010). As summarized in Section 3.2.2.6 (Developmental Effects), only one intermediate-duration gestational exposure study reported reproductive effects in mouse offspring exposed to decaBDE doses of 10–1,500 mg/kg/day from GD 0 to 17 via gavage, including testicular lesions, decreased AGD, and altered sperm parameters (Tseng et al. 2013). No exposure-related changes in AGD, onset of puberty (PPS or vaginal opening), estrous parameters, or reproductive organ weight and histology were reported in offspring exposed to decaBDE at doses up to 1,000 mg/kg/day during gestation and lactation (Biesemeier et al. 2011; Fujimoto et al. 2011) or doses up to 20 mg/kg/day from PND 2 to 15 (Rice et al. 2007).

Chronic-Duration Animal Studies

Lower-brominated PBDEs: No chronic-duration studies evaluating reproductive system effects were located for lower-brominated PBDEs.

DecaBDE: No histopathological changes were observed in male or female reproductive tissues from rats or mice that were exposed to decaBDE at dietary doses up to 2,550 or 7,780 mg/kg/day, respectively, for 103 weeks (NTP 1986). In the only other chronic-duration study, a low-purity mixture (77.4% purity) did not cause histopathological changes in male or female reproductive tissues from rats at doses up to 1.0 mg/kg/day for 2 years (Kociba et al. 1975; Norris et al. 1975a),

Summary. Based on the evidence in humans and animals, lower-brominated PBDEs are potentially toxic to the male reproductive system in humans, including the developing reproductive system in children (see Section 3.2.2.6, Developmental Effects for more details). Available data for decaBDE provide very limited evidence of male reproductive damage, and are insufficient to determine if oral decaBDE

exposure can damage the male reproductive system in humans. For female reproductive end points, data are inconsistent in humans and animals; therefore, it is unclear whether PBDEs affect the female reproductive system in adults or developing infants/children. The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

Human Studies. Numerous studies have investigated potential relationships between developmental PBDE exposure and birth outcomes (e.g., birth weight, length, head circumference, gestational age) and/or postnatal development of various systems (neurological, reproductive, endocrine, immune).

Physical Growth and Development and Related Birth Outcomes

Robledo et al. (2015a) studied potential relationships between pre-conception maternal and paternal serum levels of 10 PBDEs (BDE 17, BDE 28, BDE 47, BDE 66, BDE 85, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 183) and birth weight and length, head circumference, and ponderal index (100x[birth weight in g/birth length in cm^3]) in a prospective cohort study in Michigan and Texas (LIFE study). Geometric means of maternal and paternal serum PBDE levels (n=234 pairs) were 0.001–0.116 ng/g serum and 0.001–0.113 ng/g serum, respectively. The relative concentrations of PBDEs was similar in maternal and paternal serum, with BDE 47 having the highest level (Robledo et al. 2015b). Levels were not reported in terms of ng/g lipid. Maternal serum BDE 28 and BDE 183 levels and paternal serum BDE 183 were significantly associated with lower birth weight in female infants, with a decrease of 84.6–151.33 g per 1 standard deviation (SD) increase in ln- transformed chemical concentration. Maternal serum BDE 28 was also significantly associated with smaller birth length (-1.14 cm per 1-SD increase) and head circumference (-1.05 cm per 1-SD increase) in female infants. However, in male infants, maternal serum BDE 66 and BDE 99 were significantly associated with higher birth weight (+85.21–125.04 g per 1-SD increase) and larger head circumference (+0.6–0.91 cm per 1-SD increase. Maternal serum BDE 99 was also significantly associated with larger birth length in boy infants (+0.76 cm per 1-SD increase). No other significant associations were observed.

Maternal serum concentrations were studied in a population of 286 low-income women living in the Salinas Valley of California (a subset of the CHAMACOS study) (Harley et al. 2011). The main PBDEs detected in maternal blood, collected during the second trimester of pregnancy, were BDE 47, BDE 99, BDE 100, and BDE 153 (median concentrations of 14.57, 3.85, 2.45 and 2.03 ng/g lipid, respectively).

Serum concentrations of each of these congeners, and their sum, were significantly inversely related to infant birth weight in crude analysis. After adjustment for covariates, regression analysis showed that each 10-fold increase in BDE 47, BDE 99, or BDE 100 was associated with roughly a 115-g decrease in birth weight. These associations were no longer statistically significant when maternal weight gain was included in the models. There were no significant relationships between maternal serum PBDE and infant birth length or head circumference, or length of gestation. In a follow-up study of the CHAMACOS cohort, the potential association between obesity indices (BMI, waist circumference, obesity/overweight status) at 2–7 years of age and maternal serum PBDE levels was evaluated (BDE 47, BDE 99, BDE 100, BDE 153, and their sum); child serum PBDE levels were also determined at age 7. The geometric means of the total maternal (n=224) and child (n=216) serum PBDE concentration were 25.35 and 83.03 ng/g lipid, respectively (Erkin-Cakmak et al. 2015). No significant associations were observed between obesity measures and maternal serum concentrations of individual or summed PBDEs at any age when both sexes were examined together; however, statistical analysis revealed a significant effect modification by sex. When evaluated separately, a significant negative relationship was observed between BMI *z*-score in 3.5-year-old females and a 10-fold increase in summed maternal serum PBDE levels (adjusted β -0.64, 95% CI -1.23, -0.06), and a significant positive relationship was observed between BMI *z*-score in 3.5-year-old males and a 10-fold increase in summed maternal serum PBDE levels (adjusted β 0.99, 95% CI 0.32, 1.66). This sex difference was also observed at 7 years of age, with a significant negative association in females (adjusted β -0.41, 95% CI -0.87, -0.05) and a near-significant positive association in males (adjusted β 0.26, 95% CI: -0.19, 0.72). Similar trends were observed for waist circumference and obesity status (data not reported). When evaluating child serum PBDE levels, significant associations after adjustment for potential cofounders included a negative association between BDE 153 and ∑PBDEs and BMI and waist circumference and a reduced risk for being overweight. There was no significant effect by sex modification in the analysis of child serum levels. This follow-up study suggests possible obesogenic effects of *in utero* PBDE exposure in boys. In contrast, Vuong et al. (2016b) found no significant association between PBDEs (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, and their sum) measured in maternal serum at 16 weeks of gestation (geometric mean 39.1 ng/g lipid) and height or weight of boys and girls at 1–8 years of age. However, BDE 153 was associated with lower BMI at 2–8 years, smaller waist circumference at 4–8 years, and lower percent body fat at 8 years. The Vuong et al. (2016b) study comprised 318 mother-child pairs in the Health Outcomes and Measures of the Environment (HOME) Study in Cincinnati, Ohio. Agay-Shay et al. (2015) also evaluated the potential association between maternal PBDE exposure and childhood obesity. This study did not find significant associations between maternal PBDE colostrum levels (BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 209, and their sum) and BMI *z*-scores or risk of being overweight (BMI >85th percentile) in

470 7-year-old boys and girls from a Spanish birth cohort study; however, sex-specific analyses were not conducted. Geometric mean concentrations of BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 209 in colostrum were 0.5, 0.3, 0.2, 0.7, 0.7,and 0.8 ng/g lipid, respectively.

Results from other studies evaluating potential associations between maternal serum PBDE levels during pregnancy and/or at delivery and birth outcomes are inconsistent between studies and congeners. The Healthy Pregnancy, Healthy Baby (HPHB) birth cohort in North Carolina also evaluated potential associations between third trimester maternal serum PBDE concentrations and birth weight, length, head circumference, and birth weight percentile for gestational age (Miranda et al. 2015). Serum was evaluated for 27 PBDE congeners and 6 OH-PBDEs; however, only congeners and metabolites detected in >50% of the subjects (n=137) were included in the analysis, including BDE 47, BDE 99, BDE 100, BDE 153, 4'-OH-BDE-49, and 6'-OH-BDE-47 (median serum concentrations of 18.87, 5.5, 4.61, 5.65, 0.12, and 0.19 ng/g lipid, respectively). The only significant finding was a negative association between maternal BDE 153 and head circumference (0.32 cm decrease per 2-fold increase in BDE 153); however, this association was no longer significant after adjustment for maternal risk factors. Similarly, Serme-Gbedo et al. (2016) did not find a statistically significant relationship between birth weight and BDE 47, BDE 99, BDE 100, BDE 153, or their sum in maternal serum collected during early pregnancy (~12 weeks; median concentration of 32.99 ng/g lipid for total PBDE). This study evaluated 349 Canadian women (GESTE birth cohort), and utilized both unadjusted models and multivariate regression models adjusted for a full range of clinical risk factors known to affect fetal growth as well as other environmental pollutants that are likely to impact fetal growth (PCBs, mercury, lead, cadmium, manganese). In contrast, Chen et al. (2015) reported negative associations between lower levels of maternal serum PBDEs and birth weight and length in the prospective Laizhou Wan birth cohort (LWBC) in 215 Chinese women. In this study, median maternal serum levels of PBDEs, collected at delivery, were 2.27, 2.26, 3.53, 2.13, and 4.87 ng/g lipid for BDE 28, BDE 47, BDE 99, BDE 100, and BDE 153, respectively (median concentration of total PBDEs was 21.68 ng/g lipid). After adjustment for potential covariants, a near-significant negative association was observed between birth weight and maternal serum BDE 28; when stratified by sex, this decrease was significant for males (253.76 g decreased per 10-fold increase in BDE 28), but not females. A negative association was observed between birth length and maternal serum levels of all congeners; however, the association was only statistically significant for BDE 28 and BDE 100 when males and females were combined (0.92–0.97 cm decrease per 10-fold BDE increase). When stratified by sex, BDE 99 was significantly negatively associated with male infant length and BDE 100 was significantly negatively associated with female infant length (1.47–1.50 cm decrease per 10-fold BDE increase). There were no significant relationships between maternal serum PBDE and

infant head circumference or length of gestation. In a case-control study of 197 full-term births and 82 pre-term births, identified at the Centennial Women's Hospital in Nashville, serum BDE 47 levels were divided into the following ordinal scale: 25–135, 136–200, 200–321, 322–1,000, and >1,000 pg/mL (Peltier et al. 2015). The distribution for controls into the five bins was 23, 22, 21, 22, and 12%, respectively, while the distribution for cases was 10, 6, 20, 35, and 29%, respectively; these distributions are statistically significantly different. When cases and controls were combined for analysis, women from the two higher exposure bins (>323 pg/mL BDE 47) showed a significantly increased risk for preterm birth.

Several investigators have also evaluated associations between serum maternal and umbilical cord PBDE levels, and their potential associations with birth indices. As observed in maternal serum studies, data are inconsistent between studies and congeners. In a study of 97 Canadian women (a subset of the FAMILY study), Foster et al. (2011) found no significant relationship between infant birth weight and maternal serum PBDE (BDE 17, BDE 28, BDE 47, BDE 66, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, and their sum), whether the serum was collected during the second trimester of pregnancy or at delivery. PBDE concentrations in this study were relatively high (median concentrations of 52.1 and 50.1 ng/g lipid for total PBDE at mid-pregnancy and delivery). Foster et al. (2011) also evaluated the potential relationship between umbilical cord serum PBDE (BDE 17, BDE 28, BDE 47, BDE 66, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, and their sum) and birth weight. They found a significant negative association between birth weight and concentrations of one PBDE congener (BDE 99) in umbilical cord serum. PBDE concentrations in umbilical cord serum were 1.7–3.4 times higher than in maternal serum at delivery (median concentration of 100.0 ng/g lipid for total PBDE). These results are in contrast to Mazdai et al. (2003), who found umbilical cord concentrations of PBDE (BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, and their sum) to be similar to maternal serum concentrations at delivery (median concentrations of 39 and 37 ng/g lipid for total PBDE, respectively) in a small study of 12 women recruited upon presenting in labor to Indianapolis hospitals. In this study, no relationship of maternal or cord blood serum to infant birth weight was observed. In contrast to these findings, a low exposure study in 686 Spanish women (INMA cohort; median total serum PBDE concentrations in maternal blood collected at gestational week 12 and umbilical cords of 10.74 and 7.51 ng/g lipid, respectively) reported a significant relationships between PBDE levels and some birth indices (Lopez-Espinosa et al. 2015). While concentrations were similar between maternal and umbilical cords serum, Pearson's correlations between maternal and cord $\log_2$(PBDEs) were low (0.18, 0.06, 0.04, 0.09, and 0.07 for BDE 47, BDE 99, BDE 153, BDE 159 and BDE 209, respectively). Potential associations were examined between maternal or cord serum and birth weight, length, and head circumference for each

congener and their sum. A significant inverse association was observed between birth weight and maternal serum BDE 99 levels (Lopez-Espinosa et al. 2015). After adjustment for covariates, regression analysis showed that each 2-fold increase in BDE 99 was associated a 1.4% decrease (~46.8 g) decrease in birth weight. Maternal serum BDE 99, as well as the sum of all PBDEs, was also significantly associated with a 2.1–2.9% decrease in head circumference per 2-fold increase in PBDE concentration (~0.7–1.0 cm). No significant associations were observed between birth weight or head circumference for other maternal serum congeners or any cord serum congeners, and no significant associations were observed for birth length. Lopez-Espinosa et al. (2015) also evaluated fetal growth indices during pregnancy using ultrasound measurements in mid-pregnancy (gestational weeks 12–20) and late pregnancy (gestational weeks 20–34), including abdominal circumference, fetal length, biparietal distance, and estimated fetal weight. Significant associations, observed only during gestational weeks 20–34, included inverse relationships between maternal BDE 99 and biparietal distance, abdominal circumference, and estimated fetal weight; cord BDE 99 and ∑PBDEs and fetal abdominal circumference and estimated fetal weight; and maternal ∑PBDEs and biparietal distance (1.3–3.5% decrease per 2-fold increase in PBDE concentration). In another low-exposure study, Tan et al. (2009) also found no relationship between PBDE in umbilical cord blood and infant birth weight (or length, head circumference, or sex) in babies from 41 native mothers admitted to the Singapore National Hospital for Cesarean section. Median PBDE concentrations in this study population 3.3 ng/g lipid for total PBDE in cord blood. There was reported to be a small positive association between cord blood concentrations of the PBDE congeners BDE 47 and BDE 99 and Apgar score at 1 minute in this study.

Wu et al. (2010) also studied cord blood, but did not assess effect on birth weight alone, using instead a composite of adverse birth outcomes, including low birth weight but also premature delivery and stillbirth. These researchers reported significant associations between umbilical cord PBDE (BDE 28, BDE 47, BDE 99, BDE 153, BDE 183, and total) and adverse birth outcomes in a comparison of 128 normal births and 25 cases of adverse birth outcomes from two towns (Guiyu and Chaonan) in China. The two towns represent an e-waste recycling area (Guiyu, with a median total PBDE concentration of 13.8 ng/g lipid [n=102]) and a control area with no e-waste recycling workshops (Chaonan, with a median total PBDE concentration of 5.2 ng/g lipid [n=51]). In a companion study, neonatal physiological indices were compared between 69 births in Guiyu (e-waste recycling) and 86 births in Haojiang (no e-waste re cycling), using placental PBDE concentrations as an exposure metric (Xu et al. 2015b). Median total placental PBDE concentrations were 32.25 ng/g lipid in Guiyu and 5.13 ng/g lipid in Haojiang; measured congeners included BDE 29, BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, and BDE 209 (mean placental concentrations of 11.66, 1.61, 0.32, 0.14, 3.17, 0.34, 2.20, and 3.30 ng/g lipid,

respectively). Head circumference, BMI, and Apgar1 score were significantly decreased by 4–8% and body length significantly increased by 4% in the Guiyu cohort, compared with the Haojiang cohort. No differences were observed in birth weight between the two cohorts. When data from both cohorts were combined for multiple linear regression analysis, significant negative associations were observed between ∑PBDEs and BDE 47 and head circumference; ∑PBDEs, BDE 47, and BDE 99 and neonatal BMI, and ∑PBDEs, BDE 29, BDE 47, BDE 153, and BDE 183 and Apgar1 score. A significant positive association was observed between BDE 47 and body length.

Concentrations of PBDE in breast milk have also been studied in relation to adverse birth outcomes. A study of births from 20 healthy pregnant women in Taiwan found that increased PBDE (BDE 47, BDE 99, BDE 100, and BDE 209) in breast milk was associated with significantly reduced infant birth weight, length, chest circumference, and Quetelet's index (BMI) (Chao et al. 2007). The median total PBDE concentration in breast milk was 3.65 ng/g lipid in the study population. A significant negative association between breast milk PBDE concentrations (BDE 47, BDE 99, BDE 100, BDE 153, and their sum) and birth weight was also identified in a Swedish cohort of 254 women with a median total PBDE concentration of 2.4 ng/g lipid (Lignell et al. 2013). In contrast, a significant positive association was observed between colostrum (breast milk collected in the first week after delivery) PBDE concentrations (BDE 47, BDE 99, BDE 100, BDE 153, and their sum) and birth weight and birth length in a Tanzanian cohort of 95 women with a median total PBDE concentration of 19.8 ng/g lipid (Müller et al. 2016). When stratified by sex, the only significant finding was a positive association between birth weight and PBDE concentration in female infants. The high PBDE levels were attributed to the consumption of Pemba (clay soil), which is sold in Tanzanian markers to pregnant women as a mineral supplement and nausea-relieving aid. Women who ate Pemba (64%) had significantly higher PBDE concentrations in colostrum, compared to non-Pemba eating women.

Reproductive System Development

Main et al. (2007) found a significant positive relationship between concentrations of PBDE in breast milk and congenital cryptorchidism (undescended testes) in male offspring. The study compared concentrations of 14 PBDE congeners in breast milk of mothers of 62 Danish and Finnish boys with cryptorchidism to mothers of 68 controls from the same population. Significant increases were seen for the sum of the 7 most prevalent congeners (found in all mothers), for several of the individual congeners, and for the sum of all 14 congeners in cases versus controls. No such relationship was found, however, when placental blood PBDE concentrations, rather than maternal breast milk PBDE concentrations, were

used to represent exposure. In a comparison of 86 paired samples from this study, PBDE concentrations in placenta and breast milk were correlated, but absolute PBDE concentrations were 3–4 times higher in breast milk (median of 3.23 ng/g fat for total PBDE) than in placenta (median of 1.19 ng/g fat for total PBDE). The researchers hypothesized that while breast milk PBDE concentrations reflect the accumulated body burden of the mother, placental PBDE concentrations may resemble measurements in single blood samples, reflecting the situation at delivery, but not the long-term exposure. In another case-control study in Danish and Finnish boys, no significant difference was observed in the concentrations of 14 PBDE congeners in subcutaneous tissue samples from the inguinal region during orichidopexy surgery (44 cases) or hernia surgery (38 controls) (Koskenniemi et al. 2015). Mean age at surgery was 2.3 and 2.9 years for cases and controls, respectively. Median concentrations of total PBDEs in adipose tissue were 4.90 ng/g in cases and 5.54 ng/g in controls.

Other studies of reproductive development found no relationship between PBDE concentrations in mid-pregnancy serum samples from California mothers (median ∑PBDE=33.7 ng/g lipid for 20 cases and 38.6 ng/g lipid for 28 controls) and hypospadias in their male offspring (Carmichael et al. 2010) and no relationship between current serum concentrations of PBDE (range of 4.9–73.6 ng/g lipid, with median of 9.9 ng/g lipid) and various measures of sexual maturation (e.g., initiation of breast development, current breast development, age at menarche), in a small cohort of 18 (9 boys and 9 girls) teen-aged Dutch children (Leijs et al. 2008). A study of 55 Dutch boys found significant positive associations between maternal serum concentrations of BDE 154 (median=0.5 ng/g lipid) collected on week 35 of pregnancy (but not other congeners measured, including BDE 47 and BDE 153 that occurred at higher concentrations [medians of 0.9 and 1.6 ng/g lipid, respectively]) and serum concentrations of the sex hormones, E2, free E2, and inhibin B (but not testosterone, LH, FSH, or sex hormone binding globulin), in the baby boys at 3 months of age and testes volume in the boys at 18 months of age, but no effect on penile length at either age (Meijer et al. 2012). In a French birth cohort (n=262 mother-child pairs; 141 male infants, 141 female infants), cord blood total testosterone was significantly decreased in male infants with detectable BDE 209 levels (>0.05 ng/g lipid) compared with male infants without detectable BDE 209 levels (Warembourg et al. 2016). No associations were observed for female total testosterone or other sex hormones measured in male and/or female infants (sex hormone-binding globulin, E2, free testosterone, aromatase index, or Anti-Müllerian hormone).

Delayed onset of puberty was significantly associated with higher PBDE concentrations in serum in a cohort of 645 ethnically diverse girls (recruited at 6–8 years of age and followed annually) from California and Ohio (Breast Cancer and the Environment Research program [BCERP] cohort) (Windham

et al. 2015a). A cross-sectional analysis, conducted at enrollment, showed a significant decrease in the percentage of females showing Tanner stage 2 breast development per quartile increase in serum ∑PBDE levels; no association was observed with pubic hair development. Median serum ∑PBDE levels at enrollment were 78.3 ng/g lipid (Windham et al. 2015b). In follow-up evaluations, the longitudinal analysis showed a significant increase in age at pubertal transition (both breast and pubic hair Tanner stages) with per quartile increase in serum ∑PBDE levels. When analyzed by individual congener, significant delays in pubic hair development were observed for all congers evaluated (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154) and significant delays in breast development were observed for BDE 47, BDE 99, BDE 100, and BDE 153 (associations were marginal for BDE 28 and BDE 154).

Neurodevelopment

Numerous studies have reported results suggestive of an effect of PBDE on neurodevelopment in children. Associations are more consistent when blood concentrations were used as a biomarker of exposure, compared with studies utilizing breast milk concentrations as a biomarker of exposure.

A series of studies evaluated neurodevelopmental outcomes in a longitudinal study of the HOME study cohort from Cincinnati, Ohio (full sample 349 mother-child pairs) (Braun et al. 2014; Chen et al. 2014; Donauer et al. 2015; Vuong et al. 2016a). Several environmental chemicals, including PBDEs, were quantified in maternal blood collected at approximately 16 weeks of gestation. In 5-week-old infants (n=326), no associations were observed between neonatal neurobehavior and maternal serum PBDEs (Donauer et al. 2015). The geometric mean of the sum of the most frequently detected PBDEs (sum_4BDE=BDE 47, BDE 99, BDE 100, and BDE 153) in maternal serum from mother-child pairs in the neonatal study was 37.12 ng/g lipid (Donauer et al. 2015). The majority of children from the HOME cohort (n=309) were examined for cognitive and motor abilities at 1, 2, and 3 years of age, intelligence at 5 years of age, and general behavior at 2, 3, 4, and 5 years of age (Behavioral Assessment System for Children 2 [BASC-2]) (Chen et al. 2014). This analysis focused primarily on maternal BDE 47 exposure (geometric mean=20.1 ng/g lipid; median=18.9 ng/g lipid); however, some analysis were conducted for sum_4BDE (geometric mean=37.7 ng/g lipid; median=34.6 ng/g lipid). Maternal serum levels of BDE 47 or sum_4BDE were not significantly associated with Bayley mental or psychomotor development indices at 1–3 years of age. At 5 years, however, adjusted regression analysis showed a significant 4.5-point decrease in full-scale IQ per 10-fold increase in maternal serum BDE 47 (95% CI -8.8, -0.1). For the sum_4BDE analysis, a marginal decrease in full-scale IQ was observed (β [95% CI] -4.38 [-8.9, 0.14]). In the BASC-2 behavioral assessments at 2–5 years of age, significant associations observed included a

positive association between maternal BDE 47 serum levels and the Externalizing Problems score at 2 and 3 years of age (~2–3-point increase per 10-fold increase in serum BDE 47) and a positive association between maternal BDE 47 serum levels and the Hyperactivity subscore at 2, 3, and 5 years of age (~2–3-point increase per 10-fold increase in serum BDE 47); other ages showed marginal positive associations in these domains. Similar trends were observed in BASC-2 analysis of sum_4BDE analysis. Further analysis of neurodevelopment at 4 and 5 years of age in a subset of the HOME cohort (n=175) was reported by Braun et al. (2014), with a specific focus on autistic behaviors (social, repetitive, and stereotypic behaviors). Specific analysis were conducted for BDE 28, BDE 47, BDE 85, BDE 99, BDE 100, BDE 153, and BDE 154 (maternal serum geometric mean of 0.8, 20.1, 3.1, 4.7, 3.8, 5.1, and 2.6 ng/g lipid, respectively). A marginal positive association was observed between maternal serum BDE 28 levels and autistic behaviors (β [95% CI] 2.5 [-0.6, 5.6]). In contrast, a significant negative association was observed between maternal serum BDE 85 levels and autistic behaviors (β [95% CI] -3.2 [-5.9, -0.5]); however, BDE 85 was detected in <50% of the maternal serum samples. In the most recent report, Vuong et al. (2016a) evaluated potential associations between maternal PBDE levels and executive function at 5 and/or 8 years in 256 children from the HOME cohort. Specific analysis were conducted for BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, and their sum (maternal serum geometric mean of 1.2, 21.5, 5.0, 4.2, 5.5, and 41.3 ng/g lipid, respectively). After adjusted regression analysis, a significant positive association was observed between impaired behavior regulation and maternal serum BDE 153. Increased BDE 153 was also significantly associated with higher odds of having a behavior regulation (OR, 3.92 95% CI 1.76, 8.73) or a global executive function score (OR 2.34, 95% CI 1.05, 5.23) greater than 1 standard deviation above the mean, indicating increased risk of impaired behavior regulation and/or executive function deficits. No significant associations were observed for other congeners or their sums.

In another longitudinal birth cohort of predominantly Mexican-American families in the Salinas Valley of California (CHAMACOS), PBDE levels were analyzed in maternal serum (collected at mid-pregnancy or at delivery) and child serum at 7 years of age (Eskenazi et al. 2013). Significant negative associations were found for both maternal serum PBDE and current child serum PBDE and measures of attention, fine motor coordination, and cognitive function (particularly verbal comprehension) in children evaluated at 5 (n=249) and/or 7 (n=270) years of age. PBDE concentrations for this subset of the CHAMACOS cohort are not available. A follow-up study in the CHAMACOS birth cohort (n=622) evaluated potential associations between PBDE levels in maternal serum (collected at mid-pregnancy or delivery) and current child serum (collected at age 9) and numerous measures of attention and executive function at 9, 10.5, and 12 years of age (Sagiv et al. 2015). Significant negative associations were observed between several

measures of attention and executive function at 9–12 years of age and maternal serum PBDE (geometric mean of BDE 47, BDE 99, BDE 100, and BDE 153 of 26.3 ng/g lipid), but not current child serum PBDE (geometric mean of BDE 47, BDE 99, BDE 100, and BDE 153 of 63.2 ng/g lipid).

Several studies in infants and toddlers report associations between neurodevelopmental deficits and umbilical cord serum PBDE levels. Taiwanese infants (n=36) evaluated for neurological development at age 8–12 months by Bayley Scales of Infant and Toddler Development and parental questionnaire showed significant deficits in cognitive score and adaptive behavior associated with umbilical cord blood concentrations of total PBDE (range of 2.24–49.1 ng/g lipid, with median of 4.63 ng/g lipid) and concentrations of several individual congeners (Shy et al. 2011). Children from a New York City cohort (n=152) who had higher cord blood concentrations of PBDE congeners BDE 47, BDE 99, and BDE 100 scored significantly lower on tests of mental and physical development at ages 12, 24, and 36 months (Bayley Scales of Infant Development) and ages 48 and 72 months (Wechsler Preschool and Primary Scale of Intelligence) than children with lower cord blood concentrations (Herbstman et al. 2010). Median and maximum concentrations of BDE congeners in cord blood were 11.2 and 613.1 ng/g lipid for BDE 47, 3.2 and 202.8 ng/g lipid for BDE 99, and 1.4 and 71.9 ng/g lipid for BDE 100. Ding et al. (2015) evaluated the potential association between motor, adaptive, language, and social developmental quotients in Chinese children at 12 months (n=192) and 24 months (n=149) and cord blood concentrations of BDE 28, BDE 47, BDE 85, BDE 99, BDE 100, and BDE 153 (median concentrations of 2.05, 3.71, 1.47, 6.70, 2.63, and 2.19 ng/g lipid, respectively) and the sum of BDE 47, BDE 99, BDE 100, and BDE 153 (the four congeners detected in >80% of samples). No significant associations were observed at 12 months. At 24 months, a 10-fold increase in cord blood BDE 99 was significantly associated with a 2.16-fold decrease in the language domain developmental quotient and a 10-fold increase in cord blood BDE 47 was significantly associated with a 1.89-fold decrease in the social domain developmental quotient. No significant associations were observed for the other congeners or the sum of BDE 47, BDE 99, BDE 100, and BDE 153.

Studies in preschool and school-aged children (≥4 years of age) also report associations between neurodevelopmental impairments and maternal, child, or umbilical cord serum/plasma PBDEs. Both cord and current blood concentrations of BDE 47 (cord blood median and maximum of 2.10 and 16.8 ng/g lipid [n=88], current blood median and maximum of 0.12 and 130.2 ng/g lipid [n=244]) were also negatively associated with cognitive and motor functions in 4-year-old children from a Spanish cohort (McCarthy Scales of Children's Abilities), although in this study, the results were not statistically significant, except for associations with symptoms of poor social competence and ADHD (Gascon et al.

2011). Positive associations between attention problems (Child Behavior Checklist) and cord plasma levels of BDE 47, BDE 99, BDE 100, and BDE 153 were also observed in 4-year-old children (n=109) from a New York City cohort of mothers pregnant during the September 11, 2001 World Trade Center terrorist attacks; however, associations were only significant for BDE 47 and BDE 153 (Cowell et al. 2015). No significant associations were observed in 6-year-old children. Median BDE 47, BDE 99, BDE 100, and BDE 153 cord plasma levels were 11.2, 3.2, 1.4, and 07 ng/g lipid, respectively. Significant negative correlations were observed for maternal serum PBDE (median ∑PBDE=3.4 ng/g lipid, n=62) in the 35th week of pregnancy and fine manipulative abilities, verbal memory, and sustained attention in a cohort of Dutch children tested at age 5–6 years (Roze et al. 2009), although some aspects of neurodevelopment appeared to be improved with higher PBDE concentrations in this study, including coordination, visual perception, and behavioral outcome reported by parents and teachers. A case-control study of 100 California children, including 51 with autism/autism spectrum, 26 developmentally delayed but not autistic, and 23 with typical development, found no association of autism or developmental delay with concentrations of PBDE in serum collected from the children after assessment of developmental status at 36 months (Hertz-Picciotto et al. 2011). PBDE concentrations for this study were not available numerically.

Studies attempting to discern relationships between PBDE concentrations in breast milk, rather than blood, and neurodevelopmental end points produced more uncertain results. A study of 70 infants in Taiwan found no correlation between total PBDE concentrations in breast milk collected within 1 month of delivery (range=1.44–118 ng/g lipid, median=2.92 ng/g lipid) and neurodevelopment as assessed in infants at 8–12 months of age using the Bayley Scales (Chao et al. 2011). There was, however, a significant inverse association between BDE 209 concentration in breast milk and cognitive score, suggesting delayed cognitive development associated with that particular congener. Gascon et al. (2012) reported similar findings in a Spanish cohort of 290 infants. In this study, total PBDE concentrations in colostrum collected at the hospital within 4 days of delivery (range=0.31–32.66 ng/g lipid, median= 4.05 ng/g lipid) were negatively, but not significantly, associated with the Bayley score for cognitive development in children assessed at age 12–18 months, but again, a significant negative relationship was found for BDE 209, the congener found at the highest concentrations in this population (median of 1.02 ng/g lipid). Studies of a North Carolina cohort found modest and imprecisely estimated associations between PBDEs (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, and their sum) in breast milk collected 3 months postpartum (median ∑PBDE=47.3 ng/g lipid, n=222) and (1) increased extermalizing behaviors, primarily driven by activity/impulsivity behaviors, in children assessed at 24–36 months for social and emotional development; (2) higher anxiety and withdrawal in children assessed at 36 months

for behavioral development using a parental rating scale; and (3) improved cognitive skills in children assessed at 36 months for cognitive development using the Mullen Scales of Early Learning (Adgent et al. 2014; Hoffman et al. 2012).

Potential associations between household BDE 99 and BDE 209 dust and cognitive ability of 6-year-old children (verbal comprehension, working memory) were evaluated in French birth cohort (n=246); potential associations with cord blood BDE 209 were also evaluated (Chevrier et al. 2016). After adjustment for potential covariates, children from homes with BDE 99 dust levels above the median value (54 ng/g) or BDE 209 dust levels in the 2nd or 3rd exposure tertile (≥257 ng/g) had significantly increased risk of poor performance on verbal comprehension assessments. No association was observed between dust BDE 99 or BDE 209 levels and working memory, and no association was observed between cord BDE 209 and cognitive function.

A case-control study of a Chinese population found no relationship between risk of neural tube defects and placental PBDE concentrations (median ∑PBDE=0.55 ng/g lipid for 80 cases and 0.54 ng/g lipid for 50 controls) (Ma et al. 2012b; Ren et al. 2011).

Endocrine System Development

A number of studies evaluated effects on thyroid hormones in neonatal serum or cord blood associated with developmental exposure to PBDEs; however, findings are inconsistent between studies and congeners.

Abdelouahab et al. (2013) evaluated the potential associations between thyroid hormone levels in the umbilical cord blood and maternal serum concentrations of PBDEs collected at <20 weeks of pregnancy (for ∑PBDE, median=30.92 ng/g lipid, maximum=726.09 ng/g lipid, n=380). Significant negative associations were observed between maternal PBDE levels and both free and total T_4 in cord blood, but not free or total T_3 or TSH in cord blood. Similarly, neonatal TSH assessed in blood samples collected 24 hours after birth (on average) was not related to PBDE concentrations (median ∑PBDE=25.4 ng/g lipid) in maternal serum collected at the start of the third trimester or at delivery from 289 expectant mothers living in the Salinas Valley of California (Chevrier et al. 2011). In a low-exposure Korean birth cohort (n=104), no significant associations were observed between neonatal free or total T_3, free or total T_4, or TSH and maternal PBDE concentrations in maternal serum collected at delivery (median ∑PBDE=2.2 ng/g lipid) (Kim et al. 2015)

Other studies of thyroid hormone changes in infants looked at hormone levels in umbilical cord or neonatal blood in relation to PBDE concentrations in maternal breast milk. Kim et al. (2011a) reported a significant negative correlation between breast milk PBDE (BDE 28 only, mean ≈0.1 ng/g lipid) and free T_4 in cord blood. Other studies that measured PBDEs in breast milk to assess exposure found no association with TSH in neonatal blood collected 3 days after delivery in a Norwegian population of 239 mother-baby pairs (median ∑PBDE in breast milk=1.91 ng/g lipid) (Eggesbo et al. 2011), no association with T_3, T_4, free T_4, or TSH in cord blood in a population of 149 Taiwanese mothers (median ∑PBDE in breast milk=3.38 ng/g lipid from 42 mothers in Central Taiwan and 3.13 ng/g lipid from 107 mothers in Southern Taiwan) (Shy et al. 2012), and no association with free T_4, total T_3, or TSH in infant serum at 3 weeks or 3 months in 186 Swedish mother-child pairs (median breast milk concentrations of tetra-pentaBDE [BDE 47, BDE 99, BDE 100] of 2.3 ng/g lipid and BDE 153 of 0.48 ng/g lipid) (Lignell et al. 2016).

Inconsistent findings were also observed when thyroid hormones and PBDEs levels were evaluated in infant serum and/or cord blood. For example, Mazdai et al. (2003) found no correlations between PBDE concentrations (for ∑PBDE, range=14–460 ng/g lipid, median=39 ng/g lipid, n=12) and thyroid hormone levels (free and total T_4 and free and total T_3) in umbilical cord blood. Similarly, there was no correlation between PBDEs and thyroid hormone levels in umbilical cord blood in another study of 21 South Korean mothers undergoing Cesarean section (Kim et al. 2012a). In this study, ∑PBDE in cord blood ranged from 2.28 to 30.94 ng/g lipid, with a median of 12.04 ng/g lipid. Both T_3 and free T_3 in cord blood were significantly inversely related to PBDE in cord blood (median ∑PBDE=3.49 ng/g lipid) in another study of 54 Taiwanese births (Lin et al. 2011). T_4, free T_4, and TSH were unaffected in this study. Wan et al. (2010) found no significant relationship between the PBDE metabolite, 6-OH-BDE-47 (which ranged from <4 to 127 pg/g wet weight, with a median of 26 pg/g wet weight), and T_4 in cord serum in 26 pregnant South Korean women. In an analysis of 289 births at Johns Hopkins Hospital in Maryland, PBDE in cord blood (median ∑PBDE=18.7 ng/g lipid) was compared to T_4, free T_4, and TSH in cord blood and T_4 from blood spots collected from newborns at 2 and 18 days of age (on average) (Herbstman et al. 2008). There were consistent negative associations between PBDEs and free and total T_4 in cord blood and/or spot samples, although these were primarily nonsignificant. Kim et al. (2011d, 2012b) analyzed blood samples collected from infants in neonatal screening tests. They found a positive relationship between PBDEs with TSH (BDE 197 and BDE 196 only), a negative association with T_3 (BDE 154 only) for control babies (for ∑PBDE, range=1.61–252.9 ng/g lipid, mean=56.70 ng/g lipid, n=12), and no significant relationships between PBDEs and thyroid hormones in babies with congenital

hypothyroidism (for ∑PBDE, range=2.22–861.0 ng/g lipid, mean=59.84 ng/g lipid, n=26). In another Korean birth cohort (n=104), significant positive associations were observed between neonatal serum TSH and cord BDE 99 levels and cord TSH and cord BDE 47 levels; no significant associations were observed for free or total T_3 or T_4 and ∑PBDE, BDE 47, or BDE 99 levels in cord blood (median ∑PBDE in cord=8.8 ng/g lipid) (Kim et al. 2015).

Immune System Development

A study of developmental immunity found reduced risk of atopic dermatitis in Japanese infants (diagnosed at 7 months of age by questionnaire) with higher concentrations of PBDE in umbilical cord blood (median ∑PBDE=41 pg/g wet weight for 27 cases and 54.5 pg/g wet weight for 54 controls) (Ochiai et al. 2014).

Animal Studies

Teratology, Fetotoxicity, and Physical Growth and Development

Lower-brominated PBDEs: No exposure-related developmental changes were observed following gestational exposure to pentaBDE in GD 12 rat embryos from dams exposed to doses up to 120 mg/kg/day via gavage from GD 6.5 to 11.5 (Ellis-Hutchings et al. 2009), in GD 20 rat fetuses from dams exposed to doses up to 120 mg/kg/day via gavage from GD 6.5 to 19.5 (Ellis-Hutchings et al. 2009), or in GD 20 rat fetuses from dams exposed to doses up to 200 mg/kg/day via gavage from GD 6 to 15 (Argus Research Laboratories 1985a). End points evaluated included fetal/embryo survival, resorptions, fetal weight and length, gross abnormalities, and skeletal and soft tissue abnormalities. In these studies, maternal toxicity (significantly decreased maternal weight gain) was observed at doses ≥100 mg/kg/day (Argus Research Laboratories 1985a; Ellis-Hutchings et al. 2009). Similarly, rat dams exposed to pentaBDE at doses up to 30.6 mg/kg/day from GD 6 to 21 did not show any exposure-related changes in pregnancy or birth indices (Branchi et al. 2001, 2002, 2005; Kodavanti et al. 2010; Zhou et al. 2002). Zhou et al. (2002) also reported no change in offspring viability and growth, as assessed by numbers of pups at birth and on PNDs 4–21, body weight of pups on PNDs 4–90, and eye opening status on PNDs 11–18; however, Kodavanti et al. (2010) observed significantly decreased body weight from PND 29 to 58 in female offspring at ≥10.2 mg/kg/day (8–10% reduction at PND 60). No exposure-related changes were observed in litter size, live births per litter, sex ratio, implantation sites, timing of eye opening, or body or organ weights (brain, liver, thymus) on PND 21 in offspring from rat dams fed

vanilla wafers dosed with commercial pentaBDE (DE-71) at doses up to 11.4 mg/kg/day from 28 days pre-mating through PND 21 (Poon et al. 2011). In a similar study, no exposure-related changes were observed in litter size, live pups per litter, sex ratio, offspring survival, or timing of eye opening or pinna detachment in offspring from rat dams fed cookies dosed with DE-71 at doses up to 30 mg/kg/day from GD 1 to PND 21; however, a significant decrease in offspring body weight was observed during early development (up through PND 30) at 30 mg/kg/day, but not at doses ≤3 mg/kg/day (Bowers et al. 2015).

Several studies examined developmental effects of very low doses of pentaBDE. Following maternal exposure to pentaBDE at doses of 0, 0.5, 1, or 2 mg/kg/day via gavage from GD 6 to 19, GD 20 rat fetuses showed delayed ossification and an increased incidence of internal variations at 2 mg/kg/day (Blanco et al. 2012). Significantly increased skeletal variations included delayed ossification of parietal and occipital bones, caudal vertebrae, and floating ribs. Soft tissue variations included significant increase in the size of the ventricles of the heart and liver enlargement. No significant changes were observed in the number of live fetuses, the sex ratio, the average fetal body weight/litter, or external malformations (Blanco et al. 2012). In another study, incisor eruption was delayed in offspring from rat dams exposed on GD 6 to a single gavage dose of pentaBDE at 0.3 mg/kg, but not 0.06 mg/kg (average age at eruption was not reported) (Kuriyama et al. 2005). No exposure-related delays were reported for fur development or eye opening (Kuriyama et al. 2005). Following single gavage doses of pentaBDE up to 0.3 mg/kg or tetraBDE up to 0.7 mg/kg/day in F0 rats on GD 6, no significant, exposure-related changes were observed in F1 body weights through PND 100 or F2 fetal end points (implantation sites, implantation sites/dam, number of live fetuses, fetuses/dam, mean fetal weight, resorption rate, or incidence of skeletal anomalies) on GD 21 (Talsness et al. 2005, 2008).

In several other studies assessing offspring body weight following developmental exposure to pentaBDE (without assessing any teratogenic or fetotoxic end points), no consistent body weight effects were found. No dose-related body weight changes were observed in offspring of male and female rats exposed to pentaBDE at doses up to 25 mg/kg/day via gavage for 70 days pre-mating through PND 42 (Bondy et al. 2011, 2013). No exposure-related body weight effects were observed in rat pups from dams exposed to pentaBDE at doses up to 30 mg/kg/day via gavage or pentaBDE-dosed cookies from GD 6 to PND 18 or 21 (Bansal et al. 2014; Cheng et al. 2009; Ellis-Hutchings et al. 2006; Miller et al. 2012; Zhao et al. 2014), or in mouse pups from dams exposed to pentaBDE at 452 mg/kg/day every third day from GD 4 to PND 17 via gavage (Skarman et al. 2005). A poorly-reported study indicated that pup weight was significantly decreased at PND 21 by 8, 16, and 15% following maternal exposure to pentaBDE at 50, 100, at 200 mg/kg/day, respectively, from GD 6 to PND 21 via gavage; by PND 63, no body weight

effects were observed (Hong et al. 2010). Another study reported significantly elevated pup body weight on PND 21 in rat offspring from dams exposed to pentaBDE at 2 mg/kg/day via gavage from GD 6 to PND 21; no changes were observed at 1 mg/kg/day (Blanco et al. 2014).

Three studies exposed rat dams to different commercial octaBDE mixtures at 0, 2.5, 10, or 25 mg/kg/day via gavage on GDs 6–15, including FR-1208 (Life Science Research Israel Ltd. 1987), Saytex 111 (Argus Research Laboratories 1985b), and DE-79 (WIL Research Laboratories 1986). Following exposure to FR-1208, postimplantation loss was significantly elevated at 10 and 25 mg/kg/day when Freeman-Tukey arcsine transformed values were tested as normally distributing data (Student's t-test); however, no statistical differences were observed with untransformed data and values were within the range of laboratory historical control values. There were no indications of skeletal malformation or variations or delayed or retarded ossification in any dose group (Life Science Research Israel Ltd. 1987). Following exposure to Saytex 111, the number of resorptions per litter was significantly increased by 8-fold and the number of live fetuses per litter was decreased 6.6% in the 25 mg/kg/day group (Argus Research Laboratories 1985b). Average fetal body weights were also significantly reduced at 25 mg/kg/day (Argus Research Laboratories 1985b). Following exposure to DE-79, effects observed at 50 mg/kg/day included significantly reduced mean maternal body weight gain during the post-treatment period (GDs 16–20) and fetotoxicity as indicated by increased postimplantation loss due to late resorptions (not significantly increased compared to control group but exceeded historical control range), 39% reduced mean fetal weight ($p<0.01$), skeletal variations (e.g., reduced ossification of the skull and various unossified bones) that were associated with the reduced fetal weights in this group, and single instances of malformations (fetal anasarca, bent limb bones, unilateral absence of 13^{th} rib) commonly associated with maternal toxicity (WIL Research Laboratories 1986).

In rabbit does exposed to octaBDE (Saytex 111) at 0, 2, 5, or 15 mg/kg/day on GDs 7–19 via gavage, the 15 mg/kg/day group showed slight fetotoxicity, as indicated by a significantly ($p\leq0.05$) increased incidence of delayed ossification of the sternebrae (Breslin et al. 1989). This finding was accompanied by evidence of slight maternal toxicity as indicated by decreased body weight gain during GDs 7–20 and 7–28 (not statistically identified), reduced body weight on GD 28 (7% less than controls, $p\leq0.05$), and significantly increased absolute and relative liver weights on GD 28 (Breslin et al. 1989).

Developmental effects were assessed in mice from dams fed cornflakes containing tetraBDE at doses of 0, 0.03, 0.1, or 1 mg/kg/day from 28 days premating to PND 21 (Ta et al. 2011). At PND 21, a significant decrease in crown-rump length of pups was observed in the 0.1 mg/kg/day group, compared

with controls; however, no other dose-group showed this effect and the ponderal index (weight/crown-rump length) was not statistically different among treatment groups. Similarly, body weight was significantly decreased by ~13–17% from PND 14 to 18 in the 0.1 mg/kg/day group, compared with controls, but not in the 0.03 or 1 mg/kg/day groups. No changes were observed in gestation length, litter size, or sex ratio (Ta et al. 2011). In another study using the same protocol, no changes were observed in the number of pups per litter, the sex ratio, or pup body weight (Koenig et al. 2012). Pre-weaning weights were significantly reduced by ~10% in female offspring of female mice exposed to tetraBDE at 0.03 mg/kg/day via gavage for 28 days premating through PND 21, but only in one of two experimental replicates (Woods et al. 2012). In a dietary study, no exposure-related changes were observed in pregnancy length, litter sizes, pup mortality, sex ratio, or pup weight in rats exposed to tetraBDE at doses up to 32 mg/kg/day from GD 1 to PND 14 (Wang et al. 2011a).

DecaBDE: Developmental effects were assessed in mice following maternal exposure to decaBDE at gavage doses of 0, 150, 750, 1,500, or 2,000 mg/kg/day from GD 7 to 9 (Chi et al. 2011). No gross external malformations were observed; however, significant exposure-related changes were observed in postimplantation loss, resorptions, number of live litters, and fetal body weight on GD 16. The percentage of postimplantation loss per litter was significantly increased by 3, 2.7, and 9.8% at 750, 1,500, and 2,000 mg/kg/day, respectively, compared with control. At 1,500 and 2,000 mg/kg/day, the percentage of resorptions per litter was also significantly increased by 2.7 and 8.6%, respectively. Additionally, the percentage of live fetuses per litter was significantly decreased by 10% in the high-dose group. Fetal body weight was significantly decreased by 10, 10, and 22% at 750, 1,500, and 2,000 mg/kg/day, respectively, compared with controls (Chi et al. 2011). A significant 15% reduction in pup body weight was observed in offspring of mouse dams fed dietary decaBDE at 260 mg/kg/day from GD 10 through PND 21 (Watanabe et al. 2008); however, another study using the same protocol did not observe body weight effects in PND 21 pups at doses up to 2,900 mg/kg/day (Watanabe et al. 2010b). No exposure-related changes were observed in the number of liters or survival rate of pups in either study at doses up to 3,100 mg/kg/day (Watanabe et al. 2008, 2010b). In other studies, no exposure-related teratogenic, fetotoxic, or body weight effects, and/or delays in attainment of developmental landmarks, were observed following decaBDE exposure in rat offspring from dams exposed to gavage doses up to 146 mg/kg/day from GD 10 to PND 20 or 21 (Fujimoto et al. 2011; Saegusa et al. 2012), in rat offspring from dams exposed to gavage doses up to 1,000 mg/kg/day from GD 0 to 19 or from GD 6 to PND 21 (Hardy et al. 2001, 2002; Biesemeier et al. 2011), in mouse offspring from dams exposed to gavage doses up to 1,500 mg/kg/day from GD 0 to 17 (Tseng et al. 2008, 2013), or in mouse offspring from dams exposed to doses up to 20 mg/kg/day via micropipette from PND 2 to 15 (Rice et al. 2007). In a poorly-

reported study, the study authors reported that pup weight was significantly decreased in mouse offspring at PND 21 following maternal exposure to decaBDE at 500, 2,500, and 12,500 mg/kg/day via gavage from GD 6 to PND 21; however, the included graph and table do not support that statement (Hong et al. 2010).

A lower purity commercial decaBDE product (77% decaBDE, 22% nonaBDE, 0.8% octaBDE) used in the 1970s was fetotoxic in rats at high, albeit not maternally toxic, dose levels. Developmental effects were investigated in GD 21 rat fetuses from dams exposed to decaBDE at doses of 10, 100, or 1,000 mg/kg/day by gavage on GDs 6–15 (Dow Chemical Co. 1985; Norris et al. 1975a). The numbers of fetuses with subcutaneous edema and delayed ossification of normally developed skull bones were significantly increased at 1,000 mg/kg/day. Resorptions were significantly increased at ≥10 mg/kg/day, but the increases were not dose-related and rates in the high dose group were comparable to historical control values. As discussed in Section 3.2.2.5 (Reproductive Effects), a one-generation study of the 77% commercial decaBDE mixture at ≤100 mg/kg/day in rats found no effects on numbers of live pups at birth or during lactation, body weights of pups at birth or weaning, or skeletal development or soft-tissue histology of pups at weaning (Dow Chemical Co. 1975; Norris et al. 1975a).

An additional study evaluated developmental effects in neonatal mice engineered to express neonatal human apolipoprotein E (three genotypes: apoE2, apoE3, and apoE4) exposed once to decaBDE at 0, 10, or 30 mg/kg via micropipette on PND 10 (Reverte et al. 2014). Investigators were assessing the potential effect of different human apoE genotypes on susceptibility to decaBDE exposure during development, as apolipoprotein is a genetic factor that is associated with varied vulnerability for the development of neurodegenerative disease. No exposure-related changes were observed in survival, body weight gain, ontogeny of reflexes, pinna detachment, or incisor eruption. However, eye opening was significantly delayed in apoE2 mice exposed to 30 mg/kg, compared with apoE2 controls.

Neurodevelopment

Lower-brominated PBDEs

Neurobehavior: In a series of one-day exposure neonatal gavage studies using similar experimental designs, mice exposed to pentaBDE at doses ≥0.8 mg/kg on PND 3 or PND 10 consistently showed alterations in open-field behavior at 2–8 months of age, characterized by decreased activity during the first 20-minute period followed by increased activity during the third 20-minute period; exposure-related

effects were not observed in any study at ≤0.4 mg/kg/day or following exposure to pentaBDE at 8 mg/kg on PND 19 (Eriksson et al. 2002b, 2006; Fischer et al. 2008; Hallgren et al. 2015; Sand et al. 2004; Viberg et al. 2002, 2004a, 2004b). These findings indicate an initial decrease in activity, but also a lack of habituation to new surroundings. The study authors noted that this nonhabituating behavior profile (i.e., decreased activity early in the test period and increased activity late in the test period) has also been reported in adult mice neonatally exposed to certain *ortho*-PCB congeners (Eriksson and Fredriksson 1996a, 1996b). Several other 1-day exposure studies report similar findings in rats and mice following exposure to various lower-brominated PBDEs. Decreased spontaneous activity and/or impaired habituation was observed in rats exposed to pentaBDE at 8 mg/kg on PND 10, mice exposed to hexaBDE at ≥0.45 mg/kg on PND 10, mice exposed to tetraBDE at 10.5 mg/kg on PND 10, mice exposed to heptaBDE at 15.2 mg/kg on PND 3, and mice exposed octaBDE at 16.8 mg/kg on PND 3 or 10 (Eriksson et al. 2001; Viberg et al. 2003a, 2005, 2006). Increased vertical activity was significantly increased at 4 months, but not 2 months, in mice exposed to tetraBDE at ≥1 mg/kg on PND 10; no changes were observed in horizontal activity or habituation (Gee and Moser 2008). No changes in open-field behavior were observed in mice exposed to heptaBDE at 15.2 mg/kg or nonaBDE at 18.5 on PND 10 (Viberg et al. 2006). The observed effects may be modulated by the cholinergic system, as mice exposed to pentaBDE at 8 mg/kg on PND 10 showed significantly altered responses in a nicotine-induced behavior task (decreased instead of increased activity) (Viberg et al. 2002).

Evidence for exposure-related changes in open-field behavior is less consistent in pre- and perinatal studies. Male offspring from mouse dams exposed to pentaBDE at 18 mg/kg/day via gavage or "self-administration" from a modified syringe from GD 6 to PND 21 showed significantly increased motor activity during the 3rd 10-minute block of an open field test on PND 34, indicating decreased habituation (female offspring not evaluated) (Branchi et al. 2005). This effect was transient, as it was no longer observed in male offspring at PND 60 to 120. No exposure related changes were observed in the amount of time spent in the center versus the middle of the open field (Branchi et al. 2005). However, male and female offspring from mouse dams exposed to pentaBDE at 0, 0.6, 6, or 30 mg/kg/day via gavage from GD 6 to PND 21 showed changes suggestive of an age-dependent alteration in activity at ≥6 mg/kg/day; effects included hyperactivity (increased locomotion and rearing) and impaired habituation at PNDs 34 and 60, altered thigmotaxis (reduced time near walls) at PND 60, and a tendency to hypoactivity (reduced locomotion) at PND 120 (Branchi et al. 2001, 2002). In 24-hour observations of open-field behavior, total activity, time spent active, duration of activity per active phase, and total activity per active phase were all significantly increased in PND 36 male rat offspring following a single maternal exposure to 0.3 mg/kg on GD 6 via gavage (Kuriyama et al. 2005). At PND 71, the increases in total activity and

time spent active persisted in the 0.3 mg/kg group, and were also significantly increased at 0.06 mg/kg (Kuriyama et al. 2005). Bowers et al. (2015) reported a significant increase in rearing behavior in rats at PND 110 following maternal exposure to pentaBDE at doses up to 30 mg/kg/day via dosed cookie intake from GD 1 to PND 21; however, rearing behavior did not differ from control on PND 16, 55, or 230, and no other changes in motor activity or habituation behavior were observed in open-field testing at any time-point. Kodavanti et al. (2010) also reported a lack of exposure-related changes in open-field behavior in rats at PND 100, 114, or 273 following maternal exposure to pentaBDE at doses up to 30.6 mg/kg/day via gavage from GD 6 to PND 21. Similarly, no exposure-related changes were observed in general motor activity in an open field in PND 22 male and female offspring of rat dams exposed to pentaBDE at doses up to 2 mg/kg/day via gavage from GD 6 to PND 21; however, the offspring exposed to 2 mg/kg/day spent a significantly greater percentage of time in the center of the open field, indicating decreased anxiety (anxiolytic effect) (Blanco et al. 2013). However, no effect on anxiety behavior was observed in the emergence latency assay in PND 35 or 80 rat offspring of dams fed pentaBDE-dosed cookies at intake levels up to 30 mg/kg/day from GD 1 to PND 21 (Bowers et al. 2015). In offspring of mouse dams fed cornflakes containing tetraBDE at doses up to 1 mg/kg/day from pre-mating day 28 through PND 21, no changes in locomotor activity were observed at PNW 8 or 17 (Koenig et al. 2012). In contrast, a second study using the same protocol reported significantly decreased locomotion and distance travelled in open-field testing of PND 60 females exposed to ≥0.1 mg/kg/day; at 0.03 mg/kg/day, PND 60 female mice showed decreased activity in the center of the open field (Ta et al. 2011). No exposure-related changes in open-field behavior were observed at PND 60 in males or PND 42 in either sex (Ta et al. 2011). Open field behavior was not significantly altered in PND 21 male offspring of mouse dams administered tetraBDE at 0.2 mg/kg/day from GD 8 to PND 21, compared with control (Kim et al. 2015).

In 1-day exposure neonatal gavage studies, significant impairments were also observed in learning and memory in the Morris water maze test in mice exposed to pentaBDE at 0.8 mg/kg on PND 10, mice exposed to hexaBDE at ≥0.9 mg/kg on PND 10, and mice exposed to octaBDE at 16.8 mg/kg on PND 10, or in rats exposed to tetraBDE at ≥1 mg/kg on PND 10 (Fischer et al. 2008; He et al. 2009, 2011; Viberg et al. 2003a, 2006). Observed changes included increased latencies to find a hidden platform during a 4-day training period and decreased distance travelled in the quadrant containing the hidden platform compared with controls; no changes were observed during a reversal phase on the 5th day (when the platform was moved to a new quadrant). Similarly, impairments in learning and memory were observed in the radial arm maze in mice exposed to pentaBDE at 0.8 mg/kg on PND 10, as evidence by the increased number of re-entries into maze arms from which the food pellet had already been eaten (Fischer

et al. 2008). No exposure-related effects on learning or memory were observed in the Morris water maze in mice exposed to octaBDE at 16.8 mg/kg on PND 3 or nonaBDE at 18.5 mg/kg on PND 10 (Viberg et al. 2006). Based on the observed deficits, some of the studies evaluated the density of nicotinic cholinergic receptors in the hippocampus. Significant decreases in receptor density of 7–31% were observed in mice exposed to penta- or hexaBDE at ≥9 mg/kg on PND 10 (Viberg et al. 2003a, 2004b, 2005). Another study reported a significant 23% decrease in cortical density of nicotinic cholinergic receptors in mice exposed to pentaBDE at 0.8 mg/kg on PND 10; hippocampal density was not altered at this dose (Fischer et al. 2008). The observed effects may be modulated by the cholinergic system, as mice exposed to pentaBDE at 8 mg/kg on PND 10 showed significantly altered responses in a nicotine-induced behavior task (decreased instead of increased activity) (Viberg et al. 2002).

Learning and memory impairments have also been reported following pre- and perinatal exposures. Following maternal exposure to pentaBDE at 0, 1, or 2 mg/kg/day via gavage from GD 6 to PND 21, a nonsignificant trend toward increased time to locate the hidden platform in the Morris water maze was observed on days 2–4 in PND 22 rat offspring from both dose groups; however, the increase was only significant on day 4 in the 2 mg/kg/day group (Blanco et al. 2013). In another study, significantly increased latency to find the escape platform was observed in the Morris water maze on training days 2–3 in PND 34 offspring of rat dams exposed to pentaBDE at 2 mg/kg/day from GD 6 to PND 21 (Cheng et al. 2009). In a low-dose study, maternal exposure to 0.2 mg/kg/day from GD 1 to PND 21 via gavage did not impair spatial learning in PND 34–36 offspring (Zhao et al. 2014). Effects observed at higher doses may be transient, as no exposure-related changes were observed in the Morris water maze in PND 235 rat offspring following maternal exposure to pentaBDE at doses up to 30 mg/kg/day via dosed cookie intake from GD 1 to PND 21 (Bowers et al. 2015). No exposure-related deficits in the Morris water maze were observed during PNW 7 or 11 in offspring of mouse dams exposed to tetraBDE at 0.03 mg/kg/day via gavage from pre-mating day 28 to PND 21 (Woods et al. 2012). Similarly, offspring of mouse dams fed cornflakes containing tetraBDE at 0, 0.03, 0.1, or 1 mg/kg/day from pre-mating day 28 through PND 21 did not show exposure-related impairments in the Morris water maze at PNW 8 (Ta et al. 2011). However, another study using the same protocol reported a significant increase in the latency to find a hidden escape hole in the Barnes maze on the first day of training at ≥0.03 mg/kg/day in PNW 8 offspring (Koenig et al. 2012). No exposure-related effects were observed during trial days 2–4 or during reversal learning on day 5 (escape hole placed in a different location) at doses up to 1 mg/kg/day (Koenig et al. 2012). Other studies assessed learning and attention using 5-choice visual learning and attention tasks conducted from PND 30 to 95 in offspring of rat dams exposed to pentaBDE via gavage from PND 6 to 12 (Driscoll et al. 2012; Dufault et al. 2005). Offspring exposed to 30 mg/kg/day required significantly

more trials to reach "passing" criterion in the visual discrimination task, and committed significantly more errors than controls prior to reaching the criterion (Dufault et al. 2005). The number of omission errors (no choice made) was also significantly increased in rats exposed to 30 mg/kg/day. No exposure-related impairments were observed in the visual discrimination task at doses ≤15 mg/kg/day, and no exposure-related impairments were observed in the sustained attention task at doses up to 30 mg/kg/day (Driscoll et al. 2012; Dufault et al. 2005).

In the three-chambered sociability task, general sociability (time spent in the chamber with a social target) was decreased in female offspring of mouse dams exposed to tetraBDE at 0.03 mg/kg/day via gavage from pre-mating day 28 to PND 21 (only dose evaluated); no exposure-related changes were observed in male offspring (Woods et al. 2012). No changes were observed in social novelty (time spent in the chamber with a new social target vs. a familiar social target) or barrier social interaction tests (time spent interacting with social target) in either sex (Woods et al. 2012). No exposure-related changes in social interaction were observed in offspring of mouse dams fed cornflakes containing tetraBDE at 0, 0.03, 0.1, or 1 mg/kg/day from pre-mating day 28 through PND 21 (Ta et al. 2011). No performance deficits were observed in additional neurobehavioral tests in these studies, including the elevated plus maze, acoustic startle and prepulse inhibition, and fear conditioning (Ta et al. 2011; Woods et al. 2012). Similarly, no significant, exposure-related changes were observed in social interaction or social novelty indices in PND 70 offspring of dams administered tetraBDE at 0 or 0.2 mg/kg/day via gavage from GD 8 to PND 21 (Kim et al. 2015). Additionally, no exposure-related effects were observed in social dominance testing (tube test, urine marking test).

Sensory and motor development. Sensory and motor development (righting reflex, forelimb stick grasping reflex, forelimb placing reflexes, negative geotaxis, screen grasping and climbing, pole grasping, ultrasonic vocalizations, homing test) were assessed in male and female offspring of mouse dams exposed to pentaBDE at doses of 0, 0.6, 6, or 30 mg/kg/day via gavage from GD 6 to PND 21 (Branchi et al. 2001, 2002). The screen climbing response was delayed by approximately 2 days in the 30 mg/kg/day group, compared with controls; no other exposure-related changes were observed in reflex development (Branchi et al. 2001, 2002). However, in rats, development of the cliff drop and negative geotaxis reflexes was significantly delayed in male pups following maternal exposure to pentaBDE at 2 mg/kg/day via gavage from GD 6 to PND 21; no delays were observed in the development of the righting reflex (Cheng et al. 2009). Similarly, development of the cliff drop reflex was significantly delayed in male rat pups following a single maternal exposure to pentaBDE at 0.3 mg/kg on GD 6, but not at 0.06 mg/kg (average age at which the reflex developed was not reported) (Kuriyama et al. 2005). However, no exposure-

related changes were observed in the ability of male offspring to stay on a rotating rod for 3 minutes at doses up to 0.3 mg/kg (Kuriyama et al. 2005). In a low-dose study, no exposure-related changes in reflex maturation or motor coordination were observed in PND 3–30 offspring of dams exposed to pentaBDE at 0.2 mg/kg/day from GD 1 to PND 21 via gavage (Zhao et al. 2014). Similarly, no changes in grip strength or motor coordination (beam test) were observed in PND 12–60 rat offspring of dams fed pentaBDE-dosed cookies at intake levels up to 30 mg/kg/day from GD 1 to PND 21 (Bowers et al. 2015). However, the acoustic startle response was significantly increased at the highest intensity levels in rats on PND 9, but not PND 20 (Bowers et al. 2015).

Sensory and motor development was also tested in offspring of mouse dams fed cornflakes containing tetraBDE at doses of 0, 0.03, 0.1, or 1 mg/kg/day from pre-mating day 28 to PND 21 (Ta et al. 2011). No significant exposure-related effects were found in the Wahlsten battery for sensory and motor development (righting reflex, cliff aversion, needle grasp, visual placing, vibrissa placing, eye opening, ear opening, ear twitch response, screen pull, screen cling/climb, startle reflex) on PNDs 8–18 or rotarod performance on PNDs 35–36; however, significant differences in ultrasonic pup vocalization (UPV) measures were observed between the 1 mg/kg/day group and control, including increased duration of UPVs on PND 13 and increased UPV bout duration on PND 9 and 13. A nonsignificant trend was also observed in the 1 mg/kg/day group in the number of UPVs on PNDs 13 and 17 (Ta et al. 2011). Similarly, female offspring of mouse dams exposed to tetraBDE at 0 or 0.03 mg/kg/day via gavage from pre-mating day 28 to PND 21 showed significantly decreased UPV between PND 8 and 16; no exposure-related deficits were observed in male or female offspring in sensory or motor test batteries from PND 8 to 21 or rotarod performance at PNDs 29–30 or 66–68 (Woods et al. 2012). Koenig et al. (2012) also reported a lack of exposure-related changes motor tests (grip strength, ladder walk, gait analysis) in PND 14–42 offspring of mouse dams fed cornflakes containing tetraBDE at doses up to 1 mg/kg/day from pre-mating day 28 through PND 21 (Koenig et al. 2012).

In other studies, no exposure-related changes were observed in functional observation batteries in male offspring of rat dams exposed to pentaBDE at doses up to 30.6 mg/kg/day via gavage from GD 6 to PND 21 (assessed at PND 24 or 60) or male mice exposed to single tetraBDE doses up to 30 mg/kg via gavage on PND 10 (assessed at PNDs 12–18 or at 1 or 3 months of age) (Gee and Moser 2008; Kodavanti et al. 2010).

Electrophysiology. Following a single exposure to tetraBDE at 0, 6.8, or 68 mg/kg via gavage on PND 10, hippocampal slices from PND 17 to 19 male mice were prepared for field-excitatory

postsynaptic potential (fEPSP) recordings (Dingemans et al. 2007). No exposure-related differences in the stimulus-response relation were seen in fEPSPs. However, post-tetanus potential (PTP) and long-term potential (LTP) were significantly decreased in the hippocampus of exposed mice, compared with controls. No exposure-related effects on paired-pulse inhibition were observed.

To assess auditory function, distortion product otoacoustic emissions (DPOAEs) were measured in adult offspring of rat dams fed vanilla wafers containing pentaBDE at doses of 0, 5.7, or 11.4 mg/kg/day from pre-mating day 28 to PND 21 (Poon et al. 2011). No exposure-related changes were observed in DPOAE amplitudes, frequencies, or thresholds.

Histology and organ weight. Ultrastructural changes were observed in the hippocampus of 2-month-old rats exposed once to tetraBDE on PND 10 at ≥5 mg/kg, but not at 1 mg/kg (He et al. 2009). At 5 mg/kg, the endoplasmic reticulum appeared increasing swollen and degranulated, and at 10 mg/kg, the neurons were acutely affected, with puffed periplast, dissolved cell organelles, and vacuolized mitochondria (no incidence data reported) (He et al. 2009). No exposure-related changes in hippocampal histology were observed in PND 70 offspring of mouse dams fed cornflakes containing tetraBDE at 0, 0.03, 0.1, or 1 mg/kg/day from pre-mating day 28 through PND 21 (Ta et al. 2011).

No exposure-related changes in brain weight were observed in neonatal, weanling, or adult offspring following maternal exposure to pentaBDE at 18 mg/kg/day via gavage on GD 6 to PND 21 (Ellis-Hutchings et al. 2006), maternal exposure to pentaBDE-dosed cookies at doses up to 30 mg/kg/day from GD 1 to PND 21 (Bowers et al. 2015), or maternal exposure to pentaBDE-dosed vanilla wafers at doses up to 11.4 mg/kg/day from pre-mating day 28 to PND 21 (Poon et al. 2011). Similarly, cerebrum weight was unaffected in 2-month-old rats exposed once to tetraBDE at doses up to 10 mg/kg via gavage on PND 10 (He et al. 2011).

Biochemical, proteomic, genomic, and epigenetic changes. Hippocampal and cortical tissues of rat pups were evaluated for mRNA and protein expression levels of several T_3-mediate proteins (BDNF, NCAM1, and GAP-43) following maternal exposure to tetraBDE at 0, 3.2, or 32 mg/kg/day via gavage from GD 1 to PND 14 (Wang et al. 2011a). At PNDs 1, 7, and 14, multiple alterations in mRNA and protein levels were observed; however, magnitude, direction, and significance of the changes were time- and region-dependent, with no clear exposure-related pattern (Wang et al. 2011a). In another study, hippocampal and cortical tissues were evaluated for gene expression levels of TRα1, TRα2, TRβ1, and BDNF in PND 21 offspring of rat dams exposed to pentaBDE at 0, 1, or 2 mg/kg/day via gavage from GD 6 to

PND 21 (Blanco et al. 2013). The only exposure-related change observed was a significant decrease in BDNF expression in the hippocampus at 2 mg/kg/day (Blanco et al. 2013).

In 2-month-old rats exposed once to tetraBDE at 0, 1, 5, or 10 mg/kg on PND 10, various dose-related changes were observed in the mRNA and protein expression levels of apoptotic proteins in the hippocampus, including induction of caspase3, caspase12, and cytochrome C (He et al. 2009). Costa et al. (2015) reported similar induction of caspase3 in mice sacrificed 24 hours following exposure to 20 mg/kg of tetraBDE on PND 10, compared with control. Markers of oxidative stress were also elevated in exposed mice, including malondialdehyde (MDA), 8-isoprostane, and reactive protein carbonyls, and tetraBDE-mediated induction of caspase3 was significantly greater in glutathione-deficient knockout mice (*Gclm* -/-) than in wild-type mice (Costa et al. 2015). In another 1-day neonatal exposure study, brain levels of calcium/calmodulin-dependent protein kinase II (CaMKII), NMDA interacting proteins PSD-95 and SAP97, AMPA receptor subunit GluR1, and NMDA receptor subunits NR1, NR2A, and NR2B were measured in PNDs 17–19 mice exposed to tetraBDE at 0, 6.8, or 68 mg/kg on PND 10 (Dingemans et al. 2007). Protein expression levels of NR2B, GluR1, and the autophosphorylated-active form of CaMKII were significantly decreased in exposed mice compared with control. No exposure-related changes were observed for total CaMKII, NR1, NR2A, PSD-95, or SAP97 protein expression levels. Additionally, K+-evoked catecholamine release was evaluated from chromaffin cells isolated from mice in the 0 and 68 mg/kg groups; no significant exposure-related effects were observed (Dingemans et al. 2007).

Hippocampal, cortical, and cerebellar tissues were evaluated for markers of oxidative stress in PND 37 male offspring of rat dams exposed to pentaBDE at 0 or 2 mg/kg/day via gavage from GD 6 to PND 21 (Cheng et al. 2009). In the hippocampus of offspring of exposed dams, the specific activities of SOD and GSH-Px were significantly decreased, lipid peroxidase, H_2O_2, and NO generation were significantly increased, and the number of free radicals was significantly increased, compared with controls. No significant changes were observed for these measures in the cerebral cortex or cerebellum, with the exception of significantly increased H_2O_2 generation in the cerebellum. No changes in brain GSH concentrations were observed (Cheng et al. 2009). Increased markers of apoptosis and oxidative stress were also observed in the hippocampus of offspring of rat dams exposed to the commercial pentaBDE mixture DE-71 at 30.6 mg/kg/day via gavage from GD 6 to PND 14 (Kodavanti et al. 2015). In a low-dose study, no exposure-related changes were observed in cortical, cerebellar, or hippocampal levels of SOD, GSH-Px, GSH, H_2O_2, NO, or lipid peroxidation in PND 37 male offspring of dams exposed to 0.2 mg/kg/day via gavage from GD 1 to PND 21, compared with controls (Zhao et al. 2014).

DNA methylation and mRNA levels of DNA methyltransferase (*Dmnt1*) were measured in adult offspring of mouse dams exposed to tetraBDE at 0 or 0.03 mg/kg/day via gavage from pre-mating day 28 to PND 21 (Woods et al. 2012). Global DNA methylation was significantly decreased in female, but not male, offspring; no changes were observed in *Dmct1* transcript levels.

Cortical and hippocampal cholinergic gene transcription was evaluated in 2-month-old mice exposed to pentaBDE at 12 mg/kg via gavage on PND 10 (Hallgren et al. 2015). Significant transcriptional findings included increased cortical nAchR-β2, AChR5, and nAChR-α4 in exposed mice, compared with controls; a near-significant increase in cortical AchE transcription was also observed. No exposure-related cholinergic gene transcription changes were observed in the hippocampus of 2-month-old mice. Additionally, no exposure-related cholinergic gene transcription changes were observed in the cortex or hippocampus of mice sacrificed 24 hours postexposure (i.e., PND 11). Cholinergic effects were also evaluated in offspring from a one-generation study in mink (Bull et al. 2007). F0 females were exposed to dietary pentaBDE at 0, 0.01, 0.05, or 0.25 mg/kg/day from pre-mating day 28 to PNW 6. No kits were born in the 0.25 mg/kg/day group; for the other groups, 6 kits/group were sacrificed at PNW 6 and 10 kits/group continued dietary exposure until PNW 27 and were sacrificed at PNW 45. In both PNW 6 and 45 kits, ChE was determined in blood plasma and cerebral cortex. In the cerebral cortex, ACh, mAChR, and nAChR binding were also measured. No exposure-related effects were observed in any cholinergic measures in 6-week-old kits or 27-week-old juveniles.

DecaBDE

Neurobehavior. As seen in the lower-brominated PBDE neurobehavioral section, decreased spontaneous activity and impaired habituation in open-field testing were observed at 2 and 4 months in mice exposed once to decaBDE on PND 3 at doses ≥2.22 mg/kg (Buratovic et al. 2014; Johansson et al. 2008; Viberg et al. 2003b, 2007). Also as observed with pentaBDE, decaBDE-exposed mice showed significantly altered responses in a cholinergic-induced behavior task (decreased instead of increased activity) at ≥5.76 mg/kg on PND 3 (Buratovic et al. 2014; Johansson et al. 2008). Following exposure on PND 10 or 19, however, no exposure-related changes in open-field behavior were observed in mice exposed to decaBDE at doses up to 20.1 mg/kg (Viberg et al. 2003b). In contrast, significantly increased locomotor activity during the first 1.5 hours of a 2-hour observation period was observed in PND 70 males following exposure to decaBDE at 20 mg/kg/day via micropipette from PND 2 to 15 (Rice et al. 2007). No changes in locomotor activity were observed at PND 70 in females or 1 year in either sex at doses up to 20 mg/kg/day (Rice et al. 2007). In a perinatal exposure study, no exposure-related changes in motor

activity were observed in neonatal, weanling, juvenile, or adult offspring of rat dams exposed to decaBDE at doses up to 1,000 mg/kg/day via gavage from GD 6 to PND 21 (Biesemeier et al. 2011).

Operant training and visual discrimination were assessed in young adult (3-month-old) and aging (16-month-old) mice following exposure to decaBDE at 0, 6, or 20 mg/kg/day via micropipette on PNDs 2–15 (Rice et al. 2009). Neurobehavioral tasks included lever-press training followed by a series of operant procedures, including a fixed-ratio (FR) schedule of reinforcement, a fixed-interval (FI) 2-minute schedule, and a light-dark visual discrimination. No significant, exposure-related effects were observed in the young adult cohort; however, learning impairment and impulsivity were observed in the aging cohort. In the FR task, exposure did not lead to impaired performance; however, there was a significant main effect of decaBDE exposure on the slope parameter for the number of earned food pellets. The control group earned the fewest reinforcers at the beginning of the task, and the high-dose group earned the most; by the end of the 10 sessions, all dose groups earned about the same number of reinforcers. In the FI task, there were significant main effects of decaBDE exposure on the fitted mean for the overall response rate, with the high-dose having a marginally higher response rate than the control group ($p=0.06$). This means that the exposed mice were emitting more responses for the same number of reinforcers. No significant exposure-related changes were observed for other parameters measured in the FI task (pause time, run rate, index of curvature, or number of responses during the feed cycle). A number of significantly altered parameters were observed during the visual discrimination task (41 trials). Significantly decreased number of first choice errors and shorter response latencies were observed in 6 and 20 mg/kg/day females and 20 mg/kg/day males; these findings were particularly pronounced in the earlier trials. However, mice in the 20 mg/kg/day group showed a significantly higher rate of error in the last 15 trials, compared with controls. Additionally, after an initial error, mice in the 20 mg/kg/day group made significantly more “perseverative” errors than controls.

Altered spatial learning and memory have been reported in the Morris water maze following prenatal or neonatal exposure to decaBDE. While initial spatial learning was not impaired in mice exposed to 5.76 or 13.4 mg/kg on PND 3, reversal learning (ability to find the escape platform in a new location after initial training) was significantly impaired at ≥5.76 mg/kg at 5 and 7 months (Buratovic et al. 2014). Following gestational exposure from GD 1 to 14, rat offspring showed significantly impaired spatial learning on PND 25 at ≥30 mg/kg/day, but not at 10 mg/kg/day, compared with controls; reversal learning was not assessed in this study (Chen et al. 2014). An additional study evaluated spatial learning and memory in neonatal mice engineered to express neonatal human apolipoprotein E (three genotypes: apoE2, apoE3, and apoE4) exposed once to decaBDE at 0, 10, or 30 mg/kg via micropipette on PND 10 (Reverte et al.

2013). Investigators were assessing the potential effect of different human apoE genotypes on susceptibility to decaBDE exposure during development, as apolipoprotein is a genetic factor that is associated with varied vulnerability for the development of neurodegenerative disease. Impaired learning and memory were observed at 4 months in apoE3 and apoE4 male mice at ≥10 mg/kg/day and at 12 months in apoE3 females exposed to 30 mg/kg (lack of preference for target quadrant). No wild-type mice were evaluated.

In other behavioral tests, no exposure-related changes were observed in auditory startle responses, or learning and memory in the water-filled T-maze in weanling, juvenile, or adult offspring from rat dams exposed to decaBDE at doses up to 1,000 mg/kg/day via gavage from GD 6 to PND 21 (Biesemeier et al. 2011) or in the elevated plus maze in 4-month-old mice exposed once to decaBDE at doses up to 20.1 mg/kg via gavage on PND 3 (Johansson et al. 2008). No changes in were observed in surface-righting or geotaxis reflexes or motor function assays (tail pull, cling and climb test) at PNDs 12–16 in mice engineered to express neonatal human apolipoprotein E (three genotypes: apoE2, apoE3, and apoE4) exposed once to decaBDE at 0, 10, or 30 mg/kg via micropipette on PND 10 (Reverte et al. 2014).

Sensory and motor development. A comprehensive functional observation battery was conducted every other day from PND 2 to 20 in mice exposed to decaBDE at 0, 6, or 20 mg/kg/day via micropipette from PND 2 to 15 (Rice et al. 2007). The only exposure-related changes observed were a significant reduction in the number of male and female pups performing the palpebral reflex on PND 14 and a significant reduction in the number of male pups performing an effective forelimb grip on PNDs 14 and 16 in the 20 mg/kg/day group.

Electrophysiology. Five groups of developing mice were exposed to decaBDE at 0 or 20.1 mg/kg/day via gavage during the following periods: gestational (GDs 1–21, via dam), lactational (PNDs 1–21, via dam), neonatal (PNDs 3–21, direct), post-weaning (PNDs 22–41), or gestational, lactational, and post-weaning (GD 1–PND 21, via dam, and PNDs 22–41, direct) (Xing et al. 2009). In the control group, dams were administered the vehicle only from GD 1 to PND 21 and offspring were administered the vehicle from PND 22 to 41. The dams and pups in all exposure groups were administered the vehicle during non-exposure periods (e.g., the group exposed to decaBDE during gestation only was administered the vehicle daily from PND 1 to 41). In all groups, *in vivo* extracellular recording of synaptic transmission in the hippocampus was measured on PND 60 by placing the anesthetized mice in a stereotaxic head holder. Significantly decreased synaptic potency, short-term plasticity, and long-term potentiation were observed in exposed mice from the neonatal, post-weaning, and gestation+lactation+post-weaning groups. In the

lactation-only group, long-term potentiation was significantly decreased, but no exposure-related changes were observed in synaptic potency or short-term plasticity. No exposure-related changes were observed in the gestation-only exposure group.

Histology and organ weight. No exposure-related changes were observed in brain weight, histology, or morphometry in weanling or juvenile offspring from rat dams exposed to decaBDE at doses up to 1,000 mg/kg/day via gavage from GD 6 to PND 21 or PND 10 to 21 (Biesemeier et al. 2011; Fujimoto et al. 2011; Saegusa et al. 2012) or juvenile offspring from rat dams exposed to decaBDE at doses up to 1,500 mg/kg/day via gavage from GD 0 to 17 (Tseng et al. 2008). Absolute brain weight was significantly decreased in GD 16 fetuses following maternal exposure to decaBDE at 2,000 mg/kg/day via gavage on GDs 7–9; however, the difference was no longer significant once brain weights were adjusted for body weight (Chi et al. 2011).

Biochemical, proteomic, and genomic changes. Seven months following exposure to decaBDE at 0 or 13.4 mg/kg on PND 3, the cortical and hippocampal expression of CaMKII, Gap-43, Tau, and synaptophysin were evaluated in male and female mice (Buratovic et al. 2014). Significant increases in protein levels of CaMKII, Gap-43, and Tau were observed in the cortex and hippocampus in exposed male mice and increased levels of Tau were observed in the cortex and hippocampus of exposed female mice, compared with control. No changes in synaptophysin were observed.

Neonatal mice engineered to express neonatal human apolipoprotein E (three genotypes: apoE2, apoE3, apoE4) were exposed once to decaBDE at 0, 10, or 30 mg/kg via micropipette on PND 10 and evaluated for BDNF levels in the hippocampus (Reverte et al. 2013). When all genotypes were combined for analysis, hippocampal BDNF levels were significantly elevated in males and females (combined) in the 30 mg/kg group. No wild-type mice were evaluated.

Following exposure to decaBDE at 0, 2, 15, or 146 mg/kg/day from GD 10 to PND 21, brains from offspring sacrificed on PND 20 and 77 were fixed for hippocampal immunohistochemistry (reelin, flutamic acid decarboxylase 67 [GAD67], EphA5, Tacr3, and neuron-specific nuclear protein [NeuN]) and cresyl violet staining of apoptotic bodies (Saegusa et al. 2012). Significant, exposure-related findings included an increase in the number of reelin-immunoreactive cells in the dentate hilus in groups exposed to ≥15 mg/kg/day on PND 20, an increase in the number of EphA5-postive cells in the CA1 layer on PND 20, and a minimal increase in the number NeuN-immunoreactive cells in the hilus in the 146 mg/kg/day group on PND 77.

Reproductive System Development

Lower-brominated PBDEs: Reproductive performance was assessed in F1 male and female offspring from rat dams exposed to single pentaBDE doses of 0, 0.06, or 0.3 mg/kg or tetraBDE doses of 0, 0.14, or 0.7 mg/kg on GD 6 via gavage (Kuriyama et al. 2005; Talsness et al. 2005, 2008). Following pentaBDE exposure, no significant exposure-related effects were observed in F1 male fertility or F2 litter parameters when exposed males were mated with unexposed females (Kuriyama et al. 2005). Additionally, ejaculatory and mounting latencies, intromission frequency and latency, and number of penetrations were not altered in F1 exposed mice, compared with controls; however, the percent of males with two or more ejaculations was significantly decreased by 32% in the F1 males from the 0.3 mg/kg group (Kuriyama et al. 2005). In pentaBDE-exposed F1 females mated to unexposed males, there were no exposure-related changes in female pregnancy rate, total implantation sites, implantation sites/dam, F2 fetuses/gravid dam, or total number of live F2 fetuses (Talsness et al. 2005). However, the resorption rate was 12 and 15% in the 0.06 and 0.03 mg/kg groups, respectively, compared with the control rate of 9%, and the percentage of litters with resorptions was 69 and 72% in the 0.06 and 0.3 mg/kg groups, respectively, compared with the control percentage of 47% (Talsness et al. 2005). Following tetraBDE exposure, reproductive performance of F1 females was unaltered by developmental tetraBDE exposure (Talsness et al. 2008). No exposure-related changes were observed for the following F2 litter parameters: total number of implantation sites, implantation sites/dam, number of live fetuses, fetuses/dam, mean fetal weight, or resorption rate. In the 0.7 mg/kg group, the sex ratio was significantly altered; however, comparison of the altered sex ratio with controls from two different historical experiments (n=24 and 43 litters) revealed no differences (Talsness et al. 2008). F1 male reproductive performance was not assessed following tetraBDE exposure.

Male offspring of rat dams exposed to pentaBDE at 0, 1.7, 10.2, or 30.6 mg/kg/day via gavage from GD 6 to PND 21 showed a significant 1.8-day delay in PPS (an external sign of pubertal development), compared with controls (Kodavanti et al. 2010). A 5.5% decrease in AGD was also observed at PND 7 in the 30.6 mg/kg/day group; although not statistically significant, the study authors argue that this finding may be biologically relevant, as the findings were not confounded by body weight effects and were accompanied by the delay in PPS and a 20% decrease in mean testosterone concentration on PND 60 (Kodavanti et al. 2010). After maternal exposure to a lower pentaBDE dose (2 mg/kg/day) from GD 6 to PND 21 via gavage, no exposure-related changes in AGD were observed in male offspring on PND 1 (Cheng et al. 2009). Female offspring of rat dams exposed to pentaBDE at 0, 1.7, 10.2, or

30.6 mg/kg/day via gavage from GD 6 to PND 21 showed a significant reduction in mammary gland development on PND 21 at 10.2 and 30.6 mg/kg/day, showing lack of outgrowth, fewer lateral branches and limited terminal end bud development, compared with controls (Kodavanti et al. 2010). Vaginal opening was not assessed.

As discussed in Section 3.2.2.5 (Reproductive Effects), delays in reproductive development also occurred in male and female rats that were exposed to pentaBDE at 0, 3, 30, or 60 mg/kg/day via gavage during pubertal development (PNDs 23–53 in males or PNDs 22–41 in females) (Stoker et al. 2004). PPS was significantly delayed by 1.7 and 2.1 days in the 30 and 60 mg/kg/day groups, respectively, and vaginal opening was significantly delayed by 1.8 days in the 60 mg/kg/day group. However, no changes were observed in estrous cycling at doses up to 60 mg/kg/day (Stoker et al. 2004).

Following a single gavage administration of pentaBDE at 0, 0.06 or 0.3 mg/kg on GD 6 to rat dams, various exposure-related sperm effects were observed in male offspring on PND 140 in both dose groups (Kuriyama et al. 2005). Spermatid number and daily sperm production were significantly decreased by 31 and 34%, and sperm number was significantly decreased by 29 and 18%, at 0.06 and 0.3 mg/kg, respectively (Kuriyama et al. 2005).

Following a single gavage administration of pentaBDE at 0, 0.06 or 0.3 mg/kg on GD 6 to rat dams, multiple ultrastructural changes were noted in the ovaries of female offspring at PND 90 in both exposure groups, including destruction of the surface of the serosal epithelial cells, necrosis, and numerous vesicular structures with dense granular material within the cytoplasm (Talsness et al. 2005). Additional changes observed in the 0.3 mg/kg group included degenerative changes and aggregates of small and large vesicles filled with homogeneously dense granular material in the cytoplasm and clumped chromatin within the condensed nucleus. No statistically significant, exposure-related histological changes were observed at the light microscopic level in the ovary, uterus, or vagina of female offspring, and no exposure-related effects were observed on the number of ovarian follicles (Talsness et al. 2005). Following a single gavage administration of tetraBDE at 0, 0.14, or 0.7 mg/kg on GD 6 to rat dams, the mean number of secondary follicles in the ovaries of female offspring was significantly decreased by 43% in both exposure groups at PND 38, and the mean number of tertiary follicles was significantly decreased by 38% in the 0.7 mg/kg group, compared with controls (Talsness et al. 2008). No exposure-related changes were observed in the number of primordial, primary, or atretic follicles. No histopathological lesions or organ weight changes were observed in the ovary, uterus, or vagina at PND 38 or 100 (Talsness et al. 2008). However, ultrastructural changes of the ovaries were observed on PND 200 in F1 females

from both exposure groups, including an accumulation of vesicular structures with homogeneously dense granular material in the cytoplasm of the stromal cells, which appeared to fuse together to form large vacuoles (Talsness et al. 2008). No exposure-related histopathological changes were observed in the uteri or ovaries from female rats exposed to pentaBDE at gavage doses up to 60 mg/kg/day for 20 days during pubertal development (PNDs 22–41) (Stoker et al. 2004).

In 2-month-old females exposed to tetraBDE on PND 10, relative uterine weights were significantly decreased by 23–36% at doses ≥1 mg/kg and relative ovary weights were significantly increased by 27–35% at doses ≥5 mg/kg (He et al. 2011). In other studies, no exposure-related changes were observed in ovary or uterus weights in PND 100 offspring of rat dams exposed to tetraBDE at doses up to 0.7 mg/kg via gavage on GD 6 (Talsness et al. 2008), in PND 31 offspring of rat dams exposed to pentaBDE at 18 mg/kg/day from GD 6 to PND 18 via gavage (Ellis-Hutchings et al. 2006), in PND 43 offspring of rat dams exposed to pentaBDE at doses up to 25 mg/kg/day from pre-mating day 70 to PND 42 (Bondy et al. 2013), or in PND 42 rats exposed to pentaBDE at doses up to 60 mg/kg/day for 20 days during pubertal development (PNDs 22–41) (Stoker et al. 2004).

No exposure-related histopathological changes were observed in the epididymides or left testis from male rats exposed to pentaBDE at gavage doses up to 60 mg/kg/day for 31 days during pubertal development (PNDs 23–53) (Stoker et al. 2004). No other developmental studies examined male reproductive histology following exposure to lower-brominated PBDEs.

Relative testes weights were significantly increased by 1.3-fold in PND 31 male offspring of rat dams exposed to pentaBDE at 18 mg/kg/day from GD 6 to PND 18 via gavage (absolute weights not reported); no exposure-related changes were observed on PND 12 and 18 (Ellis-Hutchings et al. 2006). In contrast, following a single maternal exposure to pentaBDE on GD 6, adult male rat offspring showed significant 10 and 11% decreases in relative testes weights at 0.06 and 0.3 mg/kg, respectively, as well as a significant 5% decrease in relative epididymis weight at 0.3 mg/kg (Kuriyama et al. 2005). Neither absolute organ weights nor body weight were significantly altered (Kuriyama et al. 2005). In other studies, no exposure-related weight effects were observed in male reproductive organs (seminal vesicles, prostate, epididymides, or testes) in PND 60 offspring of rat dams exposed to pentaBDE at doses up to 30.6 mg/kg/day from GD 5 to PND 21 (Kodavanti et al. 2010), in 2-month-old rats exposed to tetraBDE at doses up to 10 mg/kg on PND 10 (He et al. 2011), in PND 43 offspring of rat dams exposed to pentaBDE from pre-mating day 70 to PND 42 at doses up to 25 mg/kg/day (Bondy et al. 2013), or in

PND 53 rats exposed to pentaBDE at doses up to 60 mg/kg/day for 31 days during pubertal development (PNDs 23–53) (Stoker et al. 2004).

After a single maternal gavage exposure to tetraBDE on GD 6, serum E2 levels in female rat offspring were significantly decreased on PND 28 by ~38% at 0.7 mg/kg; no change was observed in the 0.14 mg/kg group (Talsness et al. 2008). No exposure-related changes in serum testosterone or LH were observed in adult F1 males after a single exposure to pentaBDE at doses up to 0.3 mg/kg via gavage on GD 6 (Kuriyama et al. 2005). Exposure-related effects on serum testosterone levels were also not observed in male offspring of rat dams on PND 60 following exposure to pentaBDE at doses up to 30.6 mg/kg/day from GD 6 to PND 21 (Kodavanti et al. 2010). In male rats exposed to pentaBDE at 0, 3, 30, or 60 mg/kg/day via gavage during pubertal development (PNDs 23–53), serum prolactin was increased 2-fold in the 60 mg/kg/day group approximately 2 hours after the final exposure on PND 53; however, no exposure-related changes were observed in serum testosterone, serum or pituitary luteinizing, or pituitary prolactin levels (Stoker et al. 2004).

DecaBDE: Male offspring of mouse dams exposed to decaBDE at 0, 10, 500, or 1,500 mg/kg/day via gavage from GD 0 to 17 were assessed for reproductive system effects on PND 71 (Tseng et al. 2013). The mean AGD and AGI (anogenital index; corrected for body weight) were significantly reduced in the 1,500 mg/kg/day group, compared with control. No exposure-related changes were observed in testicular index ([testicular length x testicular width]/body weight) or male reproductive organ weights (testis, epididymis, cauda epididymis, or seminal vesicles). However, increased incidences of testicular lesions were observed in male offspring, with increased incidence of slight/moderate vacuolization in interstitial cells in all treated groups (0/5, 4/5, 3/5, or 5/5 at 0, 10, 500, or 1,500 mg/kg/day, respectively) and increased incidence of slight-severe vacuolization in seminiferous tubules at 1500 mg/kg/day (4/5; control incidence 0/5). Additionally, in the 1,500 mg/kg/day group, seminiferous tubules had lost almost all spermatozoa and spermatids. Analysis of male offspring sperm parameters (from the seminiferous tubules) showed a significant increase in percentage of abnormal sperm heads in the 1,500 mg/kg/day group (18.2%) compared with controls (10.3%). No changes were observed in abnormal sperm heads at lower doses, and no changes were observed in sperm count, motility, or velocity at any dose. However, evidence of sperm damage was observed in all exposed groups. The DNA fragmentation index (DFI) and level of sperm with DNA damage (X αT) were significantly elevated in all exposed groups in a dose-related manner. Sperm H_2O_2 generation was significantly elevated in a dose-related manner; however, only the values in the 10 and 1,500 mg/kg/day groups reached statistical significance in pairwise

comparisons with controls. No changes were observed in sperm O_{2-} generation. No changes in serum testosterone levels were observed.

In other studies, no exposure-related changes were observed in AGD, onset of puberty (PPS or vaginal opening), estrous parameters, and/or reproductive organ weight and histology in offspring of rat dams exposed to dietary decaBDE at doses up to 146 mg/kg/day from GD 10 to PND 21 (Fujimoto et al. 2011) or gavage doses up to 1,000 mg/kg/day from GD 6 to PND 21 (Biesemeier et al. 2011). Similarly, no exposure-related changes were observed in AGD or the onset of puberty (vaginal opening or descent of the testes) in mice exposed to decaBDE at doses up to 20 mg/kg/day via micropipette from PND 2 to 15 (Rice et al. 2007). No changes in were observed in vaginal opening or testicle descent in mice engineered to express neonatal human apolipoprotein E (three genotypes: apoE2, apoE3, and apoE4) exposed once to decaBDE at 0, 10, or 30 mg/kg via micropipette on PND 10 (Reverte et al. 2014).

Endocrine System Development

Lower-brominated PBDEs: Histological, ultrastructural, and morphometric changes of the thyroid were observed at PND 100 in female offspring of dams exposed once to tetraBDE via gavage on GD 6 at 0, 0.14, or 0.7 mg/kg; however, a clear dose-response pattern cannot be determined from the available data (Talsness et al. 2008). The study authors reported "occasional" follicular cyst formation in the 0.14 mg/kg group with multiple areas of degenerated follicular epithelium. In the 0.7 mg/kg group, only mild cyst formation was observed. Ultrastructural changes observed in both exposure groups included irregular, non-typical follicular shape and detached and swollen follicular cells. Incidence data were not reported for any of these end points. Morphometric analysis showed that the colloid area of the thyroid was also significantly increased in offspring, but only in the 0.14 mg/kg group (Talsness et al. 2008). In mink, no exposure-related changes were observed in thyroid histology in PNW 6 offspring of sows exposed to pentaBDE at doses up to 0.06 mg/kg/day from pre-mating week 4 to PNW 6 (Zhang et al. 2009).

In rats exposed once to tetraBDE via gavage on PND 10 at doses of 0, 1, 5, or 10 mg/kg, relative thyroid weights were significantly decreased by 11% in the 10 mg/kg group at 2 months of age (He et al. 2011). In other studies, no exposure-related changes in thyroid weight were observed in rat offspring of dams exposed once to tetraBDE at gavage doses up to 0.7 mg/kg on GD 6 (Talsness et al. 2008) or in mink offspring of sows exposed to pentaBDE at doses up to 0.06 mg/kg/day from pre-mating week 4 to PNW 6 (Zhang et al. 2009).

Significant reductions in serum T_4 ranging from 12 to 90% were observed in male and female offspring of rat dams exposed once to pentaBDE on GD 6 at 0.3 mg/kg (Kuriyama et al. 2007), exposed to pentaBDE or commercial pentaBDE mixtures from GD 6 to PND 18 or 21 via gavage at doses as low as 2 mg/kg/day (Blanco et al. 2013; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Miller et al. 2012; Shah et al. 2011; Szabo et al. 2009; Zhou et al. 2002), exposed to pentaBDE from GD 1 or 6 to PND 21 via dosed cookies at intake levels ≥3 mg/kg/day (Bansal et al. 2014; Bowers et al. 2015), or exposed to dietary tetraBDE from GD 1 to PND 14 at doses ≥3.2 mg/kg/day (Wang et al. 2011a). These reductions were observed in offspring between PND 7 and 22. In studies described above that also evaluated offspring at older ages, it was found that the effects were no longer observed at PNDs 31–60 (Bowers et al. 2015; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Szabo et al. 2009; Zhou et al. 2002), indicating that serum T_4 changes in offspring may be transient. In one-generation studies, offspring from rat dams fed pentaBDE-dosed vanilla wafers from pre-mating day 28 to PND 21 showed significant 43–55% reductions in serum T_4 on PND 21 at ≥5.7 mg/kg/day (Poon et al. 2011) and male and female offspring from rat dams exposed to pentaBDE via gavage from pre-mating day 70 to PND 42 showed significant 65–70% reductions in serum T_4 on PND 21 at 25 mg/kg/day (but not ≤5 mg/kg/day) (Bondy et al. 2011, 2013). In rats and mice exposed once to tetraBDE via gavage on PND 10 at doses up to 10 or 20 mg/kg, respectively, no exposure-related changes were observed in serum T_4 levels (Costa et al. 2015; Gee et al. 2008; He et al. 2011). In other mouse studies, maternal exposure to the pure pentaBDE congener BDE 99 at doses up to 452 mg/kg/day via gavage from GD 6 to PND 21 or from GD 4 to PND 17 did not lead to altered serum T_4 levels in offspring at PNDs 11–37 (Branchi et al. 2005; Skarman et al. 2005). In contrast, maternal exposure to the commercial pentaBDE mixture Bromkal 70-5DE at 452 mg/kg/day via gavage from GD 4 to PND 17 caused a significant 29–32% reduction in serum T_4 in PND 11 mouse offspring (Skarman et al. 2005). This effect was transient, as it was no longer observed at PND 18 (Skarman et al. 2005). In mink, no exposure-related changes were observed in serum T_4 levels in PNW 6 offspring of sows exposed to dietary pentaBDE at doses up to 0.06 mg/kg/day from pre-mating week 4 to PNW 6 (Zhang et al. 2009). In mink offspring that continued exposure through PNW 33, serum T_4 levels were significantly increased by 31% compared with control; however, this response was entirely attributable to the females, which were significantly elevated by 71% compared to males at the same dose (change compared with female controls was not reported) (Zhang et al. 2009).

Evidence for exposure-related serum T_3 changes is less consistent. In a one-generation study, male and female offspring from rat dams exposed to pentaBDE via gavage from pre-mating day 70 to PND 42 showed significant 16–27% reductions in serum T_3 on PND 21 at 25 mg/kg/day (but not ≤5 mg/kg/day)

(Bondy et al. 2013). Similarly, offspring of rat dams exposed to pentaBDE at ≥2 mg/kg/day via gavage from GD 6 to PND 21 showed a significant 19–25% reduction in serum T_3 levels on PNDs 21–23 and offspring from dams fed cookies dosed with ≥3 mg/kg/day pentaBDE from GD 1 to PND 21 showed a significant 5–40% reduction in serum T_3 levels on PND 21; no exposure-related effect was observed at doses ≤1.7 mg/kg/day (Blanco et al. 2013; Bowers et al. 2015; Shah et al. 2011). This effect was transient, as it was no longer observed at PND 50 or later (Bowers et al. 2015; Shah et al. 2011). In contrast, exposure-related changes in serum T_3 levels were not observed in offspring of rat dams exposed to pentaBDE at doses up to 30.6 mg/kg/day via gavage or pentaBDE-dosed cookies from GD 6 to PND 18 or 21 (Bansal et al. 2014; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Szabo et al. 2009) or offspring of rat dams exposed to a single pentaBDE dose up to 0.3 mg/kg on GD 6 via gavage (Kuriyama et al. 2007). In rats and mice exposed once to tetraBDE via gavage on PND 10 at doses up to 10 or 20 mg/kg, respectively, no exposure-related changes were observed in serum T_3 levels (Costa et al. 2015; Gee et al. 2008; He et al. 2011). In mink, no exposure-related changes were observed in serum T_3 levels in PNW 6 offspring of sows exposed to pentaBDE at doses up to 0.06 mg/kg/day from pre-mating week 4 to PNW 6; however, in offspring that continued exposure through PNW 33, serum T_3 levels were significantly reduced by ~31% at 0.06 mg/kg/day (Zhang et al. 2009).

No exposure-related changes in serum TSH were observed in offspring of rat dams exposed to a single pentaBDE dose up to 0.3 mg/kg on GD 6 via gavage (Kuriyama et al. 2005), offspring of rat dams exposed to pentaBDE at doses up to 30.6 mg/kg/day via gavage or pentaBDE-dosed cookies from GD 6 to PND 21 (Bansal et al. 2014; Kodavanti et al. 2010), or rats exposed once to tetraBDE via gavage on PND 10 at doses up to 10 mg/kg (He et al. 2011).

DecaBDE: Following maternal exposure to decaBDE at 0, 2, 15, or 146 mg/kg/day via gavage from GD 6 to PND 21, the incidences of diffuse follicular cell hypertrophy in the thyroid of rat offspring on PND 21 were 0/10, 1/10, 3/10, and 9/10 in males and 0/10, 3/10, 2/10, and 4/10 in females, respectively (Fujimoto et al. 2011). No change was observed in thyroid weight (Fujimoto et al. 2011). Following maternal exposure to decaBDE at 0, 10, 500, or 1,500 mg/kg/day via gavage on GDs 0–17, histological evaluation of the thyroid glands in male offspring at PND 71 showed that a few acini were slightly enlarged in the 1,500 mg/kg/day group, compared to the controls (female offspring were not evaluated) (Tseng et al. 2008). The normal cuboidal epithelium had dose-dependently transformed into squamous epithelium, with the most notable change found in the 1,500 mg/kg/day group. Incidence data for histological lesions were not reported (Tseng et al. 2008).

Serum T_3 levels were significantly reduced by 16% on PND 21 in male offspring of rat dams exposed to decaBDE at 146 mg/kg/day via gavage from GD 6 to PND 21; no change was observed in serum T_3 levels in female offspring or serum T_4 or TSH levels in either sex at doses ≤146 mg/kg/day (Fujimoto et al. 2011). Following maternal exposure to decaBDE at 0, 10, 500, or 1,500 mg/kg/day via gavage on GDs 0–17, serum T_3 levels were significantly decreased by 21% in the 10 and 1,500 mg/kg/day groups in male mouse offspring examined on PND 71 (female offspring not examined); serum T_3 levels were not significantly altered in the 500 mg/kg/day group and serum T_4 levels were not altered in any group (Tseng et al. 2008). In neonatal male mice exposed to 0, 6, or 20 mg/kg/day from PND 2 to 15, serum T_4 was reduced by ~8 and 22% at 6 and 20 mg/kg/day, respectively (Rice et al. 2007). This finding was reported as a dose-related trend; however, pair-wise statistics were not reported. No exposure-related changes in serum T_4 levels were observed in similarly exposed neonatal female mice (Rice et al. 2007). Serum T_3 levels were not examined by Rice et al. (2007).

Immune System Development

Lower-brominated PBDEs: In a one-generation study, F0 rats were exposed to pentaBDE at 0, 0.5, 5, or 25 mg/kg/day via gavage for 70 days prior to mating, through mating, gestation, and lactation (PND 21) (Bondy et al. 2013). F1 rats continued exposure to their respective doses from PND 22 to 42. Half of the F1 rats were sacrificed on PND 43 and assessed for serum immunoglobin levels, B and T lymphocyte quantification in the spleen, spleen cell proliferation *in vitro*, and immune organ weight and histology. The remaining F1 rats were assessed for immune function at PND 56 using the KLH antigen immune challenge. Serum IgE and IgG1 levels were significantly reduced by 77 and 53%, respectively, in females at 25 mg/kg/day; no changes were observed in serum IgE or IgG1 levels in males or serum IgM, IgA, IgG2a, IgG2b, or IgGc levels in either sex. All exposed groups showed a significant, dose-related reduction in the proportion of B cells and a significant concomitant increase in the proportion of T cells in the spleen (7–18%). *In vitro*, increased proliferation of unstimulated spleen cells was observed in cells harvested from F1 males and females from the 25 mg/kg/day group; however, the proliferative response to ConA or lipopolysaccharide (LPS) stimulation was not affected by pentaBDE exposure. In the thymic cortex from F1 rats, mild increases in apoptotic lymphocytes and tingible macrophages were observed in F1 males (0/14, 1/19, 3/13, and 3/13) and F1 females (0/13, 3/17, 0/13, and 4/14) in control, 0.5, 5, and 25 mg/kg/day groups, respectively. Trend test analysis indicated that the increase was significantly dose-related in males, but not females. No treatment-related histopathological changes were observed in the Peyer's patches, mesenteric lymph nodes, or spleen of F1 rats. Absolute thymus weights were significantly increased in the 5 mg/kg/day males and females and relative thymus weight was only

increased in the 5 mg/kg/day females; no changes were observed in thymus weights at 25 mg/kg/day. These organ weight changes reflect observed body weight changes (significantly increased in the 5 mg/kg/day group). In the immune challenged rats, no exposure-related changes were observed in KLH-specific IgG levels or changes in delayed-type hypersensitivity responses to KLH injections (Bondy et al. 2013). In another one-generation study (pre-mating day 28 to PND 21), maternal exposure to pentaBDE-dose vanilla wafers at doses up to 11.4 mg/kg/day had no effect on thymus weight in PND 21 offspring (Poon et al. 2011).

In a poorly-reported study, mouse dams were exposed to pentaBDE at 0, 50, 100, or 200 mg/kg/day via gavage from GD 6 to PND 21 (Hong et al. 2010). In PND 21 offspring, study authors report exposure-related decreases in serum IgM and IgG1, decreased absolute and relative spleen weights at ≥100 mg/kg/day, and reduced cellularity levels at ≥100 mg/kg/day. No statistically significant increases in T- or B-cell lymphocyte proliferation were observed *in vitro*. The only significant effect observed in PND 63 offspring was increased T-cell proliferation following *in vitro* exposure to ConA at 200 mg/kg/day.

In another study, absolute spleen weight was significantly increased by 9% in PND 140 male offspring of rat dams exposed to single pentaBDE doses of 0.06 and 0.3 mg/kg on GD 6; relative spleen weight was only significantly increased in the 0.06 mg/kg group (12%) (Kuriyama et al. 2005). No organ weight changes were observed in the thymus of PND 140 male rats (Kuriyama et al. 2005). Following maternal exposure to pentaBDE at 0 or 18 mg/kg/day via gavage from GD 6 to PND 18, no exposure-related changes were observed in spleen or thymus weights measured in rat offspring on PNDs 3, 12, 18, and 31 (Ellis-Hutchings et al. 2006).

DecaBDE: Immune function in PND 28 mice was assessed using the RSV intranasal infection test following maternal exposure to decaBDE from GD 10 to PND 21 at doses of 0, 3.3, 34, 260, or 3,100 mg/kg/day (Watanabe et al. 2008). Typical features of pneumonia due to RSV infection were observed in all RSV-infected mice; however, exacerbation of histopathological changes in the lung was observed in 50% of mice exposed to 3,100 mg/kg/day, including hypertrophy and/or hyperplasia. Five days after the RSV infection, pulmonary viral titers of RSV and bronchoalveolar lavage fluid (BALF) levels of IFN-γ were significantly increased in the 260 mg/kg/day group (titers and BALF fluid not assessed in the 3,100 mg/kg/day group). Additionally, mRNA expression of RANTES (a characteristic marker of severity of inflammation in the lungs due to an RSV infection) was significantly elevated at 34 and 260 mg/kg/day (Watanabe et al. 2008). In a second study, immune function in PND 28 mice was

also assessed using the RSV infection test following maternal exposure to decaBDE from GD 10 to PND 21 at doses of 0, 290, or 2,900 mg/kg/day (Watanabe et al. 2010b). In this study, pulmonary viral titers of RSV were significantly increased in the 2,900 mg/kg/day group 1 and 5 days post-infection. BALF levels of TNF-α, IL-6, and IL1β were significantly decreased one day post-infection (cytokine levels at 5 days postexposure were not reported). No exposure-related changes were observed in BALF cell TNF-α production *in vitro* in response to LPS.

In a poorly-reported study, mouse dams were exposed to decaBDE at 0, 500, 2,500, or 12,500 mg/kg/day via gavage from GD 6 to PND 21 (Hong et al. 2010). Absolute and relative thymus weights were significantly increased in offspring the 2,500 mg/kg/day group at PND 21, but not the 500 or 12,500 mg/kg/day groups. At PND 21, no exposure-related changes were reported for spleen weight, spleen, or thymus cellularity, serum IgM or IgG1 levels, or T- or B-cell lymphocyte proliferation *in vitro*. The study authors report an increase in the relative B cell population and a decrease in the relative distribution of macrophage cells in spleens from pups exposed to decaBDE (no statistics provided). No exposure-related effects were observed at PND 63. In another study, no exposure-related changes in spleen weight were observed in PND 71 male offspring of mouse dams exposed to decaBDE at doses up to 1,500 mg/kg/day from GD 0 to 17 (Tseng et al. 2008).

Summary

Teratology, fetotoxicity, and physical growth and development: No human studies have evaluated associations between embryotoxicity or fetotoxicity and PBDE exposure. Evidence for altered physical grown and development from human studies is inconsistent. Available data from animal studies do not indicate that PBDEs are embryotoxic or fetotoxic at PBDE doses below doses that elicited maternal toxicity, although occasional observations of reduced pup weight were reported. Taken together, it is unlikely that oral PBDE exposure will cause embryotoxicity or fetoxicity in humans; however, data indicate that PBDE exposure could potentially lead to low birth weight.

Neurodevelopment: Evidence from both human and animal studies indicates that oral PBDE exposure can lead to adverse effects in neurodevelopment, leading to altered neurobehavior later in life.

Reproductive system development: Based on limited human and adequate animal data, it is possible that that oral PBDE exposure during development may adversely affect the developing reproductive system,

particularly the male reproductive system. However, data are too limited to adequately determine whether or not PBDE exposure in infants and children will lead to altered reproductive performance.

Endocrine system development: While human data are inconsistent, they suggest that PBDEs can interact with thyroid hormone homeostasis in infants and children. These data, along with available animal studies, indicate that the thyroid is a target of concern for PBDE exposure, especially lower-brominated PBDEs.

Immune system development: Animal data suggest that oral PBDE exposure during development may lead to immunosuppression; however, data are too limited to adequately assess the immunotoxic potential of PBDE exposure in infants and children.

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

3.2.2.7 Cancer

Human Studies. There was no clear association between risk of non-Hodgkin's lymphoma (NHL) and exposure to 2,2'4,4'-tetraBDE in a case-control study of 77 Swedish men and women who were recruited in 1995–1997 and ranged in age from 28 to 85 years (Hardell et al. 1998; Lindstrom et al. 1998). Adipose tissue concentrations of 2,2',4,4'-tetraBDE (BDE 47) (used as a marker for total PBDE exposure) were compared in 19 patients with NHL, 23 patients with malignant melanoma, 8 patients with other cancers or *in situ* changes, and 27 persons with no cancer diagnosis. The highest concentrations were seen in the patients with NHL. The mean concentration of BDE 47 was 13.0 ng/g (ppb) lipid (range 1.0–98.2 ppb) in the 19 NHL patients and 5.1 ppb (range 0.6–27.5 ppb) in the 27 persons without known malignancies. Logistic regression, adjusted for age, gender, sum of PCBs, and sum of chlordanes, was performed on cases and controls in three concentration groups (<2.05, 2.05–<5.43, and ≥5.43 ppb). A nonsignificantly elevated risk with a suggestive dose-response was found for NHL in the two highest concentration groups compared with the lowest group; the ORs and 95% CIs were 1.9 (0.3–14) and 3.8 (0.7–26) in the middle and high groups, respectively. Although the risk was highest in the group with the highest concentration of 2,2'4,4'-tetraBDE (p=0.09 for trend), there was no significant difference between cases and controls (p=0.14). The results for patients with malignant melanoma did not differ from controls.

Hardell et al. (2006) found no association between testicular cancer risk and serum PBDE (sum of congeners 47, 99, and 153, but concentrations not reported) in a study of 58 cases recruited from hospitals in Sweden and age-matched controls. Blood was also collected from the mothers of the cases and controls (44 of the case mothers and 45 of the control mothers agreed to participate). There was a marginally significant relationship between maternal PBDE and the risk of testicular cancer in sons (OR 2.5, 95% CI 1.02–6.0 using median concentration in mothers of controls as a cut-off) and some evidence of a dose-response (OR 3.2, 95% CI 1.1–11 for those with high concentrations of PBDE in blood [>75th percentile] and OR 1.8, 95% CI 0.6–7.9 for those with low concentrations of PBDE in blood [median–75th percentile]). The relevance of this finding is uncertain, as it is unclear the extent to which the case mothers' body burden of PBDE at the time of the study might relate to body burden when giving birth to the cases (approximately 30 years previously, as median age of the cases was 30 years). A case-control study of Singaporean males found no significant association between serum levels of BDE 47 and risk of prostate cancer (Pi et al. 2016). The study included 240 prostate cancer incident cases and 268 controls. Serum concentrations of BDE 47 were 37 ng/g lipid in cases and 58 ng/g lipid in controls. Other BDEs analyzed in serum included BDE 99, BDE 100, BDE 153, BDE 154, and BDE 183, but the concentrations were below the limit of detection of the analytical method (0.3–20 pg/g lipid).

PBDE concentrations in adipose tissue (sum of congeners 28, 47, 66, 100, 99, 85, 154, 153, 138, and 183) were significantly higher in 21 cases with exocrine pancreatic cancer recruited in Sweden 1996–1999 (median 3.1 ng/g lipid) than in 59 controls comprising 20 males undergoing transurethral resection for benign prostate hyperplasia and 39 females undergoing hysterectomy 1997–1998 in the same geographical area (median 1.6 ng/g lipid) (Hardell et al. 2007). Case-control analysis found that the risk of pancreatic cancer was not significantly increased with lipid PBDE (OR 3.90, 95% CI 0.93–16.3) using median concentration in controls as a cut-off after adjustment for age, sex, and BMI at tissue sampling, but that the increase in risk was significant when the BMI adjustment was performed for the year before tissue sampling (OR 7.67, 95% CI 1.53–38.5, body weight 1 year before tissue sampling obtained by questionnaire).

Serum concentrations of PBDEs (10 tri- to hepta-BDEs) were not associated with risk of thyroid cancer in a nested case-control study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a large multicenter clinical trial in the United States (Aschebrook-Kilfoy et al. 2015). The study included 104 case of thyroid cancer and 208 controls matched to cases by race, sex, birth date, center, and blood collection date. Median lipid adjusted concentrations of ΣPBDEs (sum of BDE 47, 99, 100, and 153) were 12.8 ng/g for cases and 19.4 ng/g for controls. For ΣPBDEs, the OR for the fourth versus the first

quartile was 0.62 (95% CI 0.29–1.30). Restricting the analyses to cases with the papillary subtype (75% of the cases) did not alter the findings.

A case-control study found no evidence of an association between adipose concentrations of PBDE (BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and their sum) and breast cancer risk in women from the San Francisco Bay area of California (Hurley et al. 2011). The study population included 78 cases with histologically confirmed invasive breast cancer and 56 controls with benign histological changes undergoing surgical breast biopsies. PBDE concentrations in both cases and controls were relatively high (median values of 56.32 and 72.25 ng/g lipid in cases and controls, respectively, for total BDE). Another case-control study of 170 native Alaskan women reported that cases (n=75) had significantly higher serum levels of BDE 47 (38.8 ng/g lipid) than controls (n=95, 25.1 ng/g lipid) (Holmes et al. 2014). The result of univariate logistic regression analysis showed increase risk that approached statistical significance (OR 1.79, 95% CI 0.97–3.32); no statistical significance was apparent in multivariable analysis (OR 1.58, 95% CI 0.75–3.33).

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

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

this is a poorly defined and understood term that is no longer used by NTP to characterize hepatoproliferative lesions in rats. A dose-related trend for mononuclear cell leukemia was observed in treated male rats but was not considered to be biologically significant because of a high incidence in control animals.

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

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

Summary. With the exception of one small case-control study reporting possible associations between adipose PBDE concentrations and risk of pancreatic cancer, there is no evidence for carcinogenicity of PBDEs in human studies. There is limited evidence of carcinogenicity in animals in a NTP bioassay with decaBDE (significantly increased incidences of neoplastic liver nodules in rats and combined

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

3.2.3 Dermal Exposure

A few studies have examined groups of chemical workers involved in the manufacture and distribution of PBDEs (Bahn et al. 1980; Brown et al. 1981; Chanda et al. 1982; Landrigan et al. 1979; Rosenman et al. 1979; Stross et al. 1981). Although the route of exposure (inhalation relative to dermal) of these workers has not been well defined, they appear to have had a high potential for dermal exposure (Anderson et al. 1978). Results from these studies are discussed in this section, as well as in Section 3.2.1. Dermal exposure may not be an important route of concern for PBDEs because dermal absorption is likely to be low, particularly for the highly brominated congeners, based on *in vitro* dermal absorption assays (Hughes et al. 2001; Roper et al. 2006).

3.2.3.1 Death

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

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

3.2.3.2 Systemic Effects

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

Systemic effects that have been observed in humans and animals following dermal exposure to PBDEs are described below. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 3-4.

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

Table 3-4 Levels of Significant Exposure to Lower Brominated Diphenyl Ethers - Dermal

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

Note on chemical form: The chemical forms included technical octaBDE and pentaBDE mixtures (exact compositions were not reported).

Bd Wt = body weight; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

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

Dermal Effects. No studies evaluating dermal exposure of PBDEs were located.

There was no evidence of primary irritation in intact skin of rabbits that were dermally exposed to a former commercial decaBDE mixture (500 mg as dry solid was applied to clipped skin and occluded for 24 hours) (IRDC 1974). A similar application of 77.4% decaBDE (containing 21.8% nonaBDE and 0.8% octaBDE) (dry solid, amount not reported), octaBDE (500 mg as dry solid), or pentaBDE (0.5 mL as a viscous liquid) was also non-irritating to intact rabbit skin (IRDC 1975a, 1975b).

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

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

Ocular Effects. No studies were located regarding ocular effects in animals after dermal exposure to PBDEs.

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

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to PBDEs.

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

No studies were located regarding the following effects in humans or animals after dermal exposure to PBDEs:

3.2.3.3 Immunological and Lymphoreticular Effects
3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

Limited information exists regarding the *in vivo* genotoxicity of PBDEs. The frequency of micronuclei in peripheral lymphocytes was significantly higher in 23 Chinese workers who dismantled electronic waste (median PBDE serum concentrations 382 ng/g lipid weight) compared with 26 unexposed workers (median PBDE serum concentrations 158 ng/g lipid weight) (Yuan et al. 2008). Multivariate logistic regression analysis of several risk factors showed that only history of engaging in dismantling electronic waste was a significant predictor of micronuclei frequencies. The investigators also noted that pollutants other than PBDEs also may have played a role in the increased frequency of micronuclei. No evidence of oxidative DNA damage was found in peripheral lymphocytes from exposed workers. A study of 84 healthy Korean subjects from the general population reported that serum concentrations of BDE 47 and BDE 99 were not associated with telomere length in peripheral lymphocytes (Shin et al. 2010); actual concentrations of PBDEs were not provided. Telomers are complex structures consisting of repeat DNA sequences and associated proteins located at the end of chromosomes which protect chromosomes from end-to-end fusions.

Dosing of mice with up to 1,250 mg/kg/day pentaBDE (mixed congeners) by gavage once per day for 3 consecutive days did not increase the frequency of micronuclei in blood or bone marrow cells (Witt et al. 2008). In another gavage study, dosing of pregnant mice with ≥10 mg/kg/day decaBDE (the lowest dose

tested) on GDs 0–17 resulted in significant sperm chromatin DNA damage in male offspring examined at 71 days of age, as indicated by DNA denaturation induction and increased DNA fragmentation index in the sperm chromatin structure analysis (Tseng et al. 2013). The investigators suggested that hydrogen peroxide, which was increased in sperm cells, may have been involved in induction of oxidative DNA damage. A summary of *in vivo* genotoxicity studies of PBDEs is presented in Table 3-5.

Results from *in vitro* assays for gene mutation in various *Salmonella typhimurium* strains and in *Escherichia coli* WP2 *uvr*A conducted with 2,2',4,4',5-pentaBDE and decaBDE yielded negative results in the presence or absence of metabolic activation (Evandri et al. 2003; NTP 1986). Assays conducted in mammalian cells yielded mixed results. Tests of decaBDE (BDE 209) for sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells were negative and the same was reported for gene mutation in mouse lymphoma L5178Y cells (NTP 1986). These tests were conducted with and without metabolic activation. However, decaBDE induced DNA damage (Comet assay) in human SK^{-}N-MC neuroblastoma cells (Pellacani et al. 2012) and SW 480 colon carcinoma cells (Curcic et al. 2014). Several congeners (BDE 47, 99, 253, 183, and 209) induced micronuclei in human mammary carcinoma cells (Barber et al. 2006). Both BDE 32 and BDE 47 caused DNA damage (Comet assay) in HepG2 hepatocellular carcinoma cells (Saquib et al. 2016). The congener 2,2',4,4'-tetraBDE (BDE 47) also induced micronuclei formation and DNA damage (Comet assay) in human neuroblastoma cells (Gao et al. 2009; He et al. 2008a; Pellacani et al. 2012) and DNA damage (Comet assay) in rat primary hippocampal neurons (He et al. 2008b). However, BDE 47 did not cause DNA damage in normal human hepatocytes, as assessed by the Comet assay (An et al. 2011). BDE 47 also induced gene recombination in Chinese hamster SPD8/V79 cells, but not Sp5/V79 cells (Helleday et al. 1999). In the same study, 3,4-diBDE (BDE 12) and 2-monoBDE (BDE 1) produced positive results for gene recombination in both Chinese hamster SPD8/V79 cells and Sp5/V79 cells (Helleday et al. 1999). Experiments conducted by Ji et al. (2011) in chicken DT40 cell lines showed that BDE 47 and 2,2,4',5-tetraBDE (BDE 49) could induce DNA damage (double strand breaks; identified by γ-H2AX focus formation) and that BDE 47 could also induce chromosomal aberration. Ji et al. (2011) also reported that tetraBDEs had a greater genotoxic potential than PBDEs with a higher number of bromine substitutes and that hydroxylated analogs of tetraBDEs were more genotoxic than tetraBDEs. These investigators suggested that DNA damage caused by tetraBDEs and hydroxylated analogs is mediated through ROS, which leads to replication blockage and subsequent chromosomal breaks. However, Song et al. (2009) did not find evidence of DNA damage (Comet assay) in human adreno cortical carcinoma cells exposed to the hydroxylated metabolite OH-BDE-47 or OH-BDE-85. DNA damage by PBDEs could be mediated via covalent binding of PBDE quinone metabolites, as both Lai et al. (2011) and Huang et al. (2015) have

Table 3-5. Genotoxicity of Polybrominated Diphenyl Ethers (PBDEs) *In Vivo*

Species (test system)	Compound	End point	Results	Reference
Human peripheral lymphocytes	Total PBDEs	Micronucleous assay	±	Yuan et al. 2008
Human peripheral lymphocytes	Total PBDEs	Oxidative DNA damage	−	Yuan et al. 2008
Human peripheral lymphocytes	BDE 47	Telomere length	−	Shin et al. 2010
Human peripheral lymphocytes	BDE 99	Telomere length	−	Shin et al. 2010
Mouse blood and bone marrow	PentaBDE (unspecified)	Micronucleous assay	−	Witt et al. 2008
Mouse sperm	BDE 209	DNA damage (sperm chromatin structure analysis)	+	Tseng et al. 2013

+ = positive result; – = negative result; ± = inconclusive result; BDE = brominated diphenyl ether

reported that PBDE quinone metabolites covalently bind to DNA *in vitro* to form DNA adducts. These metabolites would result from oxidation of hydroxylated metabolites to dihydroxylated metabolites by microsomal cytochrome P450s. A summary of the *in vitro* genotoxicity data for PBDEs is presented in Table 3-6.

Overall, the information available from *in vivo* and *in vitro* studies with a few PBDE congeners is insufficient to make generalizations regarding the genotoxicity of PBDEs.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption of PBDEs in humans after inhalation exposure.

Evidence for the inhalation absorption of lower-brominated PBDEs in animals was provided by observations of systemic toxicity in rats that were intermittently exposed to a commercial octaBDE product (bromine content 78.7%) as dust aerosol for 13 weeks (Great Lakes Chemical Corporation 2000). The absorption of the lower-brominated BDE congeners was indicated by the occurrence of hepatic, thyroid, and ovarian effects in rats following exposure to 16 or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks.

No studies were located that quantified absorption of inhaled PBDEs, but Staskal et al. (2005) reported absorption efficiencies of 91% in mice given single intratracheal doses of ^{14}C-BDE 47 in corn oil. This estimate was derived by comparing the radioactivity profiles in urine, feces, and tissues 5 days after intratracheal or intravenous administration of 1 mg/kg doses of ^{14}C-BDE 47.

3.4.1.2 Oral Exposure

Human Data. No information was located regarding absorption of PBDEs in humans following controlled oral exposure.

Table 3-6. Genotoxicity of Polybrominated Diphenyl Ethers (PBDEs) *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms:					
Salmonella typhimurium, TA98, TA100, TA1535, TA1537	BDE 209	Gene mutation	–	–	NTP 1986
S. typhimurium, TA98, TA100	BDE 99	Gene mutation	–	–	Evandri et al. 2003
Escherichia coli, WP2 uvrA	BDE 99	Gene mutation	–	–	Evandri et al. 2003
Mammalian cells:					
Human L02 normal hepatocytes	BDE 47	DNA damage (Comet assay)	No data	–	An et al. 2011
Human MCF-7 mammary carcinoma cells	BDE 47, 99, 153, 183, 209	Micronuclei	No data	+	Barber et al. 2006
Human SW 480 colon carcinoma cells	BDE 209	DNA damage (Comet assay)	No data	+	Curcic et al. 2014
Human SH-SY5Y neuroblastoma cells	BDE 47	DNA damage (Comet assay)	No data	+	Gao et al. 2009
Human SH-SY5Y neuroblastoma cells	BDE 47	Micronuclei	No data	+	He et al. 2008a
Human SH-SY5Y neuroblastoma cells	BDE 47	DNA damage (Comet assay)	No data	+	He et al. 2008a
Human SK-N-MC neuroblastoma cells	BDE 47	DNA damage (Comet assay)	No data	+	Pellacani et al. 2012
Human SK-N-MC neuroblastoma cells	BDE 209	DNA damage (Comet assay)	No data	+	Pellacani et al. 2012
Human HepG2 hepatocellular carcinoma cells	BDE 32, 47	DNA damage (Comet assay)	No data	+	Saquib et al. 2016
Human H295R adrenocortical carcinoma cells	OH-BDE-47 OH-BDE-85	DNA damage (Comet assay)	NA	–	Song et al. 2009
Rat primary hippocampal neurons	BDE 47	DNA damage (Comet assay)	No data	+	He et al. 2008b
Mouse lymphoma L5178Y cells	BDE 209	Gene mutation	–	–	NTP 1986
Chinese hamster Sp5/V79 cells	BDE 47	Gene recombination	No data	–	Helleday et al. 1999
Chinese hamster SPD8/V79 cells	BDE 47	Gene recombination	No data	+	Helleday et al. 1999
Chinese hamster Sp5/V79 cells	BDE 12	Gene recombination	No data	+	Helleday et al. 1999

Table 3-6. Genotoxicity of Polybrominated Diphenyl Ethers (PBDEs) *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Chinese hamster SPD8/V79 cells	BDE 12	Gene recombination	No data	+	Helleday et al. 1999
Chinese hamster Sp5/V79 cells	BDE 1	Gene recombination	No data	+	Helleday et al. 1999
Chinese hamster SPD8/V79 cells	BDE 1	Gene recombination	No data	+	Helleday et al. 1999
Chinese hamster ovary cells	BDE 209	Sister chromatid exchange	–	–	NTP 1986
Chinese hamster ovary cells	BDE 209	Chromosomal aberrations	–	–	NTP 1986
Other cells					
Chicken DT40 cell line	BDE 47	DNA damage (γ-H2AX focus formation)	No data	+	Ji et al. 2011
	BDE 49	DNA damage (γ-H2AX focus formation)	No data	+	Ji et al. 2011
	BDE 47	Chromosomal aberrations	No data	+	Ji et al. 2011

+ = positive result; — = negative result; BDE = brominated diphenyl ether; DNA = deoxyribonucleic acid; NA = not applicable

Animal Data

Overview: Information regarding oral absorption in animals is available from studies of commercial PBDE mixtures and individual ^{14}C-labeled tetra-, penta-, hexa-, and decaBDE congeners. As summarized below, the most recent and best available estimates of oral absorption efficiencies following gavage administration in lipophilic vehicles indicate a range of 70–85% for tetra- (BDE 47), penta- (BDE 99, BDE 100), and hexa- (BDE 153, BDE 154) congeners, and 10–26% for decaBDE (BDE 209).

Information on oral absorption of the commercial pentaBDE mixture DE-71 and the commercial octaBDE mixture DE-79 is available from studies in which male Sprague-Dawley rats were fed diets containing 0 or approximately 32–33 ng/day (≈120 ng/kg/day) of either mixture in peanut oil for 21 days (Hakk et al. 2001; Huwe et al. 2002b, 2007). The doses were designed to mimic environmental exposure concentrations. Liver, carcass, and feces were analyzed for major congeners in the penta- and octaBDE formulations 24 hours after the final feeding; urine was not evaluated. The study of the pentaBDE mixture (DE-71) assessed the following six congeners: BDE 47, BDE 85, BDE 99, BDE 100, BDE 153, and BDE 154 (Hakk et al. 2001; Huwe et al. 2007). Based on liver, carcass, and unrecovered concentrations of congeners, and assuming that excretion in the urine was negligible, absorption is estimated to have been 44.3% for penta congener BDE 85 and 84.3–92.4% for the other tetra- to hexaBDE congeners. The study of the octaBDE mixture (DE-79) assessed the following eight congeners: BDE 153, BDE 154, BDE 183, BDE 190, an unknown heptaBDE, and three unknown octaBDEs (Huwe et al. 2002b). Based on liver, carcass, and unrecovered concentrations of congeners, and assuming that excretion in the urine was negligible, absorption is estimated to have been 84.2–95.1% for the hexaBDEs, 68.5–79.1% for the heptaBDEs, and 55.7–83.3% for the octaBDEs.

Early studies with ^{14}C-decaBDE (BDE 209) indicated that gastrointestinal absorption efficiency was low (~9 or <1%) in rats (El Dareer et al. 1987; Norris et al. 1973, 1975b; NTP 1986). Following treatment with a single 1 mg/kg dose of ^{14}C-decaBDE in corn oil, administered as a low purity commercial mixture (77.4% decaBDE, 21.8% nonaBDE, 0.8% octaBDE) by gavage, 90.6 and >99% of the dose was eliminated in the feces within 24 and 72 hours post-dosing, respectively (Norris et al. 1973, 1975a). An oral absorption efficiency estimate of about 9% is indicated, assuming that fecal radioactivity excreted in 24 hours was nonabsorbed, and fecal radioactivity excreted between 24 and 72 hours was from biliary excretion of absorbed material. Two feeding studies were conducted in which rats were exposed to a commercial mixture as unlabeled decaBDE (92% pure) on days 1–7 and ^{14}C-decaBDE (98.9% pure) on day 8, followed by unlabelled decaBDE on days 9, 9–10, or 9–11 (El Dareer et al. 1987; NTP 1986). In

the first study, dietary concentrations ranged from 238 to 51,100 ppm (six levels) (≈20–4,500 mg/kg/day). Recovery of radioactivity in the feces ranged from 91.3±4.0 to 101±4% of the administered dose and was not related to dose level. In the second study, rats were exposed to dietary concentrations of 277 or 48,000 ppm (≈20 or 4,300 mg/kg/day). Recovery of radioactivity in the feces ranged from 82.5±4.7 to 86.4±8.5% of the dose and was not related to dose level or time of sacrifice (24, 48, or 72 hours after ^{14}C-decaBDE intake). For both dose levels, the percent of ^{14}C dose remaining in the gut contents (<4%) and gut tissue (<0.04%) decreased with time. Of the radioactivity recovered, >99% was in the feces and gut contents. Based on a comparison of average tissue concentrations following intravenous and oral administration, NTP (1986) estimated that oral absorption was 0.33±0.19% at the highest dietary level (50,000 ppm).

More recent studies indicated that absorption efficiency of ^{14}C-decaBDE (BDE 209) in rats can be influenced by vehicle and have reported absorption efficiencies in the 10–26% range using lipophilic vehicles (Hakk et al. 2002b; Morck and Klasson Wehler 2001; Morck et al. 2003; Riu et al. 2008; Sandholm et al. 2003). In normal and bile duct-cannulated male Sprague-Dawley rats administered single 3-µmol/kg (≈3 mg/kg) doses of ^{14}C-decaBDE (>98% pure) in Lutrol F127/soya phospholipone (34:16, w/w)/water, radioactivity in feces collected for 72 hours accounted for about 90% of the administered dose in conventional rats (Morck and Klasson Wehler 2001; Morck et al. 2003). In bile duct-cannulated rats, averages of 88 and 9.5% of the dose were recovered in feces and bile, respectively, within 3 days. Radioactivity recovered in urine was <0.1% of the dose in normal and bile-duct cannulated rats. The radioactivity in bile indicates that at least 10% of the dose was absorbed (Morck and Klasson Wehler 2001; Morck et al. 2003). Hakk et al. (2002b) reported similar results in another study in which four bile duct-cannulated male Sprague-Dawley rats were orally administered single 3-µmol/kg doses of ^{14}C-decaBDE (>98% pure) in Lutrol 127, soyaphospholipone, and water. Radioactivity in bile and urine collected for 72 hours accounted for 9.2 and <0.1% of the administered dose, respectively. Sandholm et al. (2003) reported an oral bioavailability of 26% for decaBDE from plasma concentration-time curves for 144 hours following gavage and intravenous administration of single 2-µmol/kg doses of unlabeled decaBDE (purity >98%) in a DMA/polyethylene glycol/water vehicle (4:4:1) to Sprague-Dawley rats. DecaBDE concentrations in plasma samples were quantified by gas chromatography/mass spectrometry (GC/MS). Oral bioavailability was calculated by dividing the area under the plasma concentration-time curve for oral exposure (AUC_{oral}) by the $AUC_{i.v.}$. Qualitative analysis by GC/MS of pooled plasma samples determined 3 major metabolites among 13 hydroxylated metabolites: a hydoxy-octaDDE, a hydroxyl-nonaBDE and a hydoxy-methoxy-hexaBDE. The presence of these phenolic metabolites in the plasma samples indicates that the oral bioavailability (and hence oral absorption efficiency) of decaBDE

may have been higher than the calculated value of 26% based on parent-compound plasma concentration-time curves (Sandholm et al. 2003). Riu et al. (2008) reported that >19% of administered radioactivity was recovered in tissues (including fetuses) and carcasses, 24 hours after oral administration of 2-mg/kg doses of ^{14}C-labeled decaBDE (>99.8% radiopurity) dissolved in peanut oil to pregnant Wistar rats on GDs 16, 17, 18, and 19. This finding indicates an absorption efficiency of about 20%, assuming that radioactivity recovered in the feces (about 66% of the administered dose) was not absorbed. Because biliary excretion of decaBDE has been demonstrated in rats, this value may underestimate the actual oral absorption that occurred in this study. However, the aqueous fraction (which would contain hydroxylated metabolites and conjugates) accounted for only 4% of the radioactivity in the collected feces, and 97% of the radioactivity in the organic-solvent fraction of the feces was determined by high-performance liquid chromatography (HPLC) to be unchanged decaBDE.

Estimates of oral absorption efficiencies for BDE 47 in rats and mice have ranged from about 75 to 95%, depending on species and employed measurement techniques (Örn and Klasson-Wehler 1998; Sanders et al. 2006a; Staskal et al. 2005). A single 14.5-mg/kg (30-µmol/kg) gavage dose of ^{14}C-BDE 47 in corn oil was well absorbed by male Sprague-Dawley rats and male C57Bl mice (Örn and Klasson-Wehler 1998). Approximately 5% of the dose in rats and 7% of the dose in mice was excreted as parent congener in the feces in 24 hours. The investigators concluded that these values represented the non-absorbed doses, indicating that absorption of BDE 47 was 93–95%. Later studies with male F344 rats and male B6C3F1 mice reported oral absorption efficiency estimates for BDE 47 of 75% in rats and 85% in mice (Sanders et al. 2006a). Sanders et al. (2006a) used a more refined technique that compared profiles of radioactivity in urine, feces, and tissues 24 hours after gavage and intravenous administration of single 1-µmol/kg doses of ^{14}C-BDE 47 in corn oil. Using a similar technique comparing radioactivity profiles in excreta and tissues 5 days after gavage and intravenous administration of single 1-mg/kg doses of ^{14}C-BDE 47 in corn oil, Staskal et al. (2005) reported that oral absorption efficiency was approximately 82% in female C57BL/6J mice.

Evidence for extensive oral absorption of pentaBDE congeners (BDE 99 and BDE 100) in rats and mice comes from studies that administered single oral doses of about ~28 µmol/kg ^{14}C-BDE 100 (~98% pure) in peanut oil to male Sprague-Dawley rats (Hakk et al. 2006), about 2.2 mg/rat (~15 µmol/kg) of ^{14}C-BDE 99 (~98% pure) in corn oil to male Sprague-Dawley rats (Hakk et al. 2002a), or 1 µmol/kg body weight of ^{14}C-BDE 99 (~96% pure) in corn oil to male F344 rats and male B6C3F1 mice (Chen et al. 2006). Seventy-two hours after administration of BDE 100, about 73 and 41% of the administered radioactivity remained in tissues of conventional and bile-duct cannulated rats, respectively; fecal

radioactivity accounted for about 20 and 26% of administered radioactivity in conventional and bile-duct cannulated rats, respectively (Hakk et al. 2006). Assuming that radioactivity excreted in feces within 24 hours was non-absorbed, reported values of 11.5% in conventional rats and 16.8% in bile duct-cannulated rats indicate oral absorption for BDE 100 of about 89 and 84%, respectively. In the studies with BDE 99, radioactivity in 24-hour feces accounted for 22.3 and 52.5% of administered radioactivity in conventional and bile-cannulated rats, respectively, indicating absorption efficiencies for BDE 99 of at least 78 and 48% (Hakk et al. 2002a). Chen et al. (2006) compared radioactivity profiles in 24-hour excreta and tissues after gavage and intravenous administration of ^{14}C-BDE 99 to arrive at estimated oral absorption efficiencies of approximately 85% in both male rats and male mice.

Results from rat and mouse studies with ^{14}C-labeled hexaBDEs (BDE 153 and BDE 154) administered as single doses in oil vehicles also indicate extensive oral absorption (Hakk et al. 2009; Sanders et al. 2006b). Hakk et al. (2009) estimated an oral absorption efficiency for BDE 154 of about 77% in male Sprague-Dawley rats, based on radioactivity profiles in 72-hour excreta and tissues after gavage administration of single 11.3-µmol/kg ^{14}C-BDE 154 (>98% pure) to conventional and bile duct-cannulated rats. Sanders et al. (2006b) estimated oral absorption efficiencies for BDE 153 of about 70% in male F344 rats and male B6C3F1 mice, based on comparison of radioactivity profiles in 24-hour excreta and tissues after gavage and intravenous administration of single 1-µmol/kg doses ^{14}C-BDE 153 (96% pure).

3.4.1.3 Dermal Exposure

No information was located regarding dermal absorption of PBDEs in humans.

A dermal absorption efficiency of 62% was reported for female mice exposed to an occluded dermal dose of 1 mg/kg ^{14}C-BDE 47) (Staskal et al. 2005). Profiles of radioactivity in urine, feces, and tissues 5 days after dermal or intravenous administration were compared to estimate dermal absorption efficiency. Approximately 15% of the administered dose remained at the site of application 5 days after application. No other *in vivo* studies of dermal absorption with PBDE congeners or mixtures were located.

In *in vitro* studies with human breast skin and mouse dorsal skin samples exposed to ^{14}C-BDE 147 (radiochemical purity=96.5%) for 24 hours in a flow-through diffusion cell apparatus, reported mean absorption efficiencies (percent of applied radioactivity collected in receptor compartment) were 1.88% for human skin (n=10) and 14.58% for rat skin (n=12) (Roper et al. 2006).

Limited dermal absorption of ^{14}C-decaBDE by mouse skin was indicated in an *in vitro* study in which ^{14}C-decaBDE dissolved in tetrahydrofuran was applied (three dose levels) to dorsal skin excised from adult hairless female mice, and fractions of receptor fluid were collected over a 24-hour period (Hughes et al. 2001). Transfer of radioactivity to the receptor fluid was minimal, accounting for only 0.07–0.34% of the applied radioactivity. Two to 20% of the radioactivity was found in the skin. The highest percentage of the dose in the skin was associated with application of the lowest dose. Washing the skin with solvent 24 hours after application removed 77–92% of the applied dose.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No information was located regarding distribution of PBDEs in humans following controlled inhalation exposure.

The distribution of bromine was examined in tissues of rats after inhalation exposure to octaBDE (Great Lakes Chemical Corporation 1978). Groups of rats were exposed to 0, 1.2, 12, 120, or 1,200 mg/m^3 of dusts of octaBDE 8 hours/day for 14 days. At necropsy, sections of the lungs, adipose tissue, and liver were collected for bromine analysis using a neutron activation technique. The results showed concentrations of bromine in the lungs and adipose tissue significantly higher in all groups relative to controls; the amounts of bromine detected were concentration-related. In the liver, the concentration of bromine was also elevated in all groups relative to controls except in the 1.2 mg/m^3 exposure group; the elevated concentrations in the liver were not as marked as in the lungs or in adipose tissue.

3.4.2.2 Oral Exposure

Human Studies.

Overview: No studies were located that examined tissue distribution of PBDEs in humans following controlled oral exposure. Evidence for the transfer of PBDEs from pregnant mothers to the developing fetus and for the transfer of PBDEs from maternal blood to breast milk and then to nursing infants comes from a number of studies of PBDE concentrations in maternal and cord serum samples and breast milk samples from groups of non-occupationally exposed women. Although the contributions of different possible exposure routes experienced by these women are uncertain, it is thought that ingestion of PBDEs

in dust and food represented a significant exposure route. In general, the tetra- and penta-brominated PBDEs have been the predominant congeners detected in maternal and cord serum samples and breast milk samples, but some recent studies assaying for a wider range of PBDE congeners have found evidence for distribution of hepta-, octa-, or decaBDEs into cord serum and breast milk. In evaluation of these studies, the location where the study was performed (e.g., Asia, Europe or North America) is very important, as the patterns of exposure to various congeners were different due to different usage patterns of commercial mixtures (see Section 6.5, General Population and Occupational Exposure, for more information).

A number of studies have examined concentrations of PBDEs or hydroxylated PBDEs in maternal and cord blood samples in non-occupationally exposed groups of women from the United States (Chen et al. 2013; Mazdai et al. 2003; Qiu et al. 2009), France (Antignac et al. 2009, 2008), China (Li et al. 2013a), Japan (Kawashiro et al. 2008), Spain (Vizcaino et al. 2011), the Netherlands (Meijer et al. 2008), and Korea (Wan et al. 2010). In the most recent of the U.S. studies, BDE 28, BDE 47, BDE 99, BDE 100, and BDE 153 were detected in 90, 90, 95, 85, and 100% of 20 maternal and 65, 65, 80, 90, and 85% of 20 matched cord serum samples, respectively (Chen et al. 2013). Percentages of samples above the limit of detection were lower for BDE 209 (55% maternal and 40% cord) and BDE 154 (25% maternal and 5% cord). Chemical analyses for other PBDE congeners were not conducted in this study. Median concentrations of congeners in maternal serum samples (ng/g lipid) were in the following order: BDE 47 > BDE 153 > BDE 209 > BDE 99 > BDE 100 > BDE 28 > BDE 154. In cord serum samples, the order was: BDE 47 > BDE 99 > BDE 209 > BDE 28 > BDE 153 > BDE 100 > BDE 154. Concentrations of four hydoxylated PBDEs (6-OH-BDE-47, 5-OH-BDE-47, 4'-OH-BDE-49 and 6'-OH-BDE-99) were also determined. Geometric mean concentrations (ng/g lipid) of total BDEs and total OH-BDEs in cord samples were higher than those in maternal serum samples (~52% and 42 higher for OH-BDEs and BDEs, respectively). Equal or higher concentrations of total OH-BDEs or total BDEs in cord serum, compared with maternal serum, were found in 85 and 80% of the matched mother-neonate pairs. The results suggest that each of the seven BDEs and four OH-BDEs can cross the placenta and distribute to the fetus, and that internal exposure via blood is equal to or higher in fetuses, compared with their mothers. In contrast, BDE 209 was the most abundant congener detected in both maternal and cord blood samples from China, where industrial production of BDE 209 may result in exposure (Li et al. 2013a).

Similar evidence for transplacental transfer of a set of PBDE congeners more enriched in higher-brominated PBDEs was reported in a recent study that measured concentrations of 19 PBDE congeners in maternal and cord serum samples from 29 mother-neonate pairs from a Wenzhou region of China that is

the major region for electronics dismantling and recycling in China (Li et al. 2013a). In both maternal and cord serum samples, the congeners with the highest geometric mean concentrations (ranging from 3.32 to 1.78 ng/g lipid in maternal samples) were BDE 207 > BDE 208 > BDE 209 > BDE 28. Geometric means for total cord serum concentrations of lower-brominated congeners (BDE 17 to BDE 154), higher-brominated congeners (BDE 183 to BDE 209), and all BDEs were higher than respective concentrations in maternal blood by about 15, 47, and 41%, respectively (Li et al. 2013a).

Frederiksen et al. (2010) utilized a human *ex vivo* placenta perfusion system to study the kinetics of placental transfer of BDE 47, BDE 99, and BDE 209 to the fetus. Placentas were perfused for 4 hours with 1 ng/mL concentrations of the non-labeled congeners. Samples of maternal and fetal compartments were taken during the perfusion, and concentrations in samples were determined by GC/MS. Placental transfer of BDE 47 and BDE 99 was demonstrated, and transfer of BDE 47 was faster and more extensive than BDE 99. Transfer of BDE 209 across the placenta to the fetal compartment was not demonstrated with the detection limits of the techniques employed. Frederiksen et al. (2010) proposed that future perfusion studies with BDE 209 should use ^{14}C-labeled BDE 209 to increase sensitivity.

Evidence for the transfer of PBDEs from maternal blood to breast milk and hence to nursing infants comes from a number of studies examining PBDE concentrations in breast milk samples. Most studies of PBDEs in breast milk samples through 2002 measured concentrations of only lower-brominated congeners (tetra, penta and hexaBDEs) used in many commercial products up to that time: BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 (Hites 2004). Additionally, higher brominated PBDEs (e.g., decaBDE; BDE 209) were often omitted from early human biomonitoring due to the inability to accurately measure them at that time. In these early studies, BDE 47 was the congener detected at the highest concentration. A number of more recent studies have included chemical analysis for a greater number of PBDE congeners (including hepta-, octa- and deca-brominated congeners) in breast milk samples collected in the United States (Daniels et al. 2010; Park et al. 2011; Schecter et al. 2010, 2006), France (Antignac et al. 2009, 2008), and Philippines (Malarvannan et al. 2013). The detection of higher-brominated congeners in some of these recent studies indicates that both lower and higher-brominated congeners can be distributed to breast milk (Antignac et al. 2008, 2009; Malarvannan et al. 2013; Park et al. 2011; Schecter et al. 2010).

Further support for the transfer of PBDEs from mothers to nursing children comes from a report that average concentrations of BDE 47 and BDE 99 were statistically significantly ($p < 0.05$) increased by ~5-fold in serum samples from 4-year-old Spanish children (n=202) who had been breastfed, compared

with formula-fed 4-year-old children (n=42) (Carrizzo et al. 2007). This study analyzed serum samples for 13 PBDE congeners including tri- (BDE 17, BDE 28), tetra- (BDE 47, BDE 66, BDE 71), penta- (BDE 85, BDE 99, BDE 100), hexa- (BDE 138, BDE 153, BDE 154), and hepta-brominated congeners (BDE 183, BDE 190). BDE 47 and BDE 99 were the predominant congeners detected in both breastfed and formula-fed children; concentrations of BDE 47 and BDE 99 in breastfed children were about 16 and 6 times higher than the congener with the next highest concentration, BDE 100. The following congeners were not detected in the collected serum samples: BDE 17, BDE 28, BDE 66, BDE 71, BDE 85, BDE 183, and BDE 190. This study did not control for potential differences in other PBDE exposure pathways, such as ingestion of contaminated dusts or food.

Animal Studies.

Overview: Tissue distribution studies in animals orally exposed to ^{14}C-labeled BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 209 indicate that decaBDE is distributed among tissues somewhat differently than tetra-, penta- and hexaBDEs. While lower-brominated BDE congeners, following absorption and an initial wide distribution, are preferentially accumulated in adipose tissues, absorbed decaBDE is less readily distributed to adipose tissues and appears to preferentially distribute to highly perfused tissues. Although less likely to partition to adipose tissues, decaBDE was still found in low quantities in adipose tissues in these studies, and has been shown to transfer from dams to fetuses and neonates from exposure during gestational and nursing periods. Two studies with female Sprague-Dawley rats given oral doses of nonlabeled BDE 209 in corn oil from GD 7 to postpartum day (PPD) 4 or 8 demonstrated maternal transfer to developing fetuses and neonates by examining whole-body BDE 209 concentrations in offspring, but another study with similarly exposed Sprague-Dawley rats found no clear evidence for maternal transfer by examining BDE 209 concentrations in blood from dams and offspring.

Results from studies of rats or mice orally exposed to ^{14}C-labeled decaBDE (BDE 209) indicate that decaBDE is not as readily distributed to adipose tissues as the lower-brominated BDEs and more readily distributed to highly perfused tissues (El Dareer et al. 1987; Morck and Klasson-Wehler 2001; Morck et al. 2003; Norris et al. 1975a; NTP 1986; Riu et al. 2008). In male rats administered single gavage doses of 1 mg/kg of a ^{14}C-labeled commercial decaBDE mixture (77.4% pure containing 21.8% nonaBDE and 0.8% octaBDE), radioactivity could be detected on day 1 in all sampled tissues (adipose, skin, liver, heart, adrenals, spleen, pancreas) (Norris et al. 1975a). On day 16 after dosing, radioactivity was only detected in adrenals and spleen (0.01 and 0.06% of the administered dose per gram of tissue, respectively). In F344 rats fed diets containing a commercial mixture as unlabeled decaBDE (92% pure) on days 1–7,

^{14}C-decaBDE (98.9% pure) on day 8, and unlabelled decaBDE on days 9, or 9–10, or 9–11, the levels of radioactivity remaining in tissues 72 hours after the exposure period ended had the following order: gastrointestinal tract > liver > kidney > lung > skin > adipose (El Dareer et al. 1987; NTP 1986). In Sprague-Dawley rats given single 3-µmol/kg (≈3 mg/kg) gavage doses of ^{14}C-decaBDE (>98% pure) in Lutrol F127/soya phospholipone (34:16, w/w)/water, concentrations of radioactivity remaining in tissues 3 days after dose administration had the following order (^{14}C nmol equivalents/g lipid concentrations in parentheses): plasma (22 nmol/g) > liver (14.9 nmol/g) > heart ~ small intestine wall ~ adrenal (ranging from 5.6 to 4.0 nmol/g) > lung ~thymus ~ kidney (ranging from 2.1 to 1.8 nmol/g) > adipose (0.17 nmol/g) (Morck and Klasson-Wehler 2001; Morck et al. 2003). In pregnant Wistar rats given single 2-mg/kg doses of ^{14}C-decaBDE (>99.8% pure) in peanut oil daily on GDs 16–19, concentrations of radioactivity on a wet weight basis (µg ^{14}C-decaBDE equivalents/g tissue) were highest in adrenals (33 µg/g), ovaries (16 µg/g), and liver (11 µg/g); intermediate in kidneys > stomach > heart ~ placentas > lung > spleen > plasma > uterus > carcass (ranging from 3.90 to 1.11 µg/g); and lowest in adipose tissue (0.79 µg/g), fetuses (0.46 µg/g), brain (0.11 µg/g), and amniotic fluid (0.11 µg/g) (Riu et al. 2008).

Results from studies of rats and mice exposed to oral doses of ^{14}C-labeled BDE 47 indicate wide distribution to tissues following absorption with preferential accumulation in fatty tissues, contrasting the preferential distribution of decaBDE to highly perfused tissues (Örn and Klasson-Wehler 1998; Sanders et al. 2006a; Staskal et al. 2005, 2006a). Five days after gavage administration of single 30-µmol/kg doses of ^{14}C-BDE 47 in corn oil to male Sprague-Dawley rats, concentrations of radioactivity had the following order (^{14}C-BDE 47 equivalent nmol/g wet tissue): adipose (706) > lung (12) > kidney (11) > liver (5) > brain (1.9) > plasma (0.76) (Örn and Klasson-Wehler 1998). A similar order of wet tissue concentrations (nmol/g wet tissue) was observed in male C57Bl mice exposed to ^{14}C-BDE 47: adipose (79) > liver (7) > lung (5) > kidney (3) > brain (1) > plasma (not detected) (Örn and Klasson-Wehler 1998). In another study that gave single 1-µmol/kg doses of ^{14}C-BDE 47 to male and female F344 rats in corn oil, the following order of amounts of radioactivity remaining in tissues was observed 24 hours after dose administration (percentages of administered dose for male rats): adipose (24.6%) > skin (13.0%) > muscle (3.0%) > liver (1.3%) > blood (0.2%) > brain ~ kidney ~ lung (0.1% each) (Sanders et al. 2006a). A similar order was observed in female rats, but the amount of radioactivity in adipose in females (37%) was higher than in male rats (24.6%) (Sanders et al. 2006a). Tissue distribution in male and female B6C3F1 mice exposed to ^{14}C-BDE 47 was similar to distribution in F344 rats, with females showing higher accumulation of radioactivity in adipose than male mice (Sanders et al. 2006a). Staskal et al. (2005) reported similar patterns for tissue distribution in female C57BL/6J mice 5 days after administration of single oral doses of 0.1, 1.0, 10, or 100 mg/kg ^{14}C-BDE 47 in corn oil. For all doses,

the reported order of remaining radioactivity in tissues was: adipose (8–14% of administered dose) > skin and muscle (~2–3%) > liver (~1%) > brain ~ kidneys ~ lungs (<0.05% each) (Staskal et al. 2005). The same tissue distribution pattern was also observed in female C57BL/6J mice given nine 1-mg/kg/day doses of unlabeled BDE 47 in corn oil followed by single 1-mg/kg doses of ^{14}C-BDE 47 (Staskal et al. 2006a). Using percent of dose/g of tissue as the dose metric to compare single-dose levels in rats reported by Staskal et al. (2005) with repeated-dose levels in tissues, the tissue concentrations from the repeated-dose scenario with 1 mg/kg were comparable to tissue concentrations from single 10-mg/kg doses and about 2 times greater than concentrations from single 1-mg/kg doses (Staskal et al. 2006a). The results indicate the potential for incremental accumulation of BDE 47 in fat with continued exposure.

Results from studies of ^{14}C-BDE 99 (Chen et al. 2006; Hakk et al. 2002a) and ^{14}C-BDE 100 (Hakk et al. 2006) indicate an initial wide distribution of penta-brominated congeners to tissues following absorption with preferential accumulation in fatty tissues, similar to results from studies with BDE 47. In male F344 rats given single doses of 0.1 µmol/kg ^{14}C-BDE 99 (~96% pure) in corn oil, levels of radioactivity remaining in tissues 24 hours after dose administration had the following order (percent of administered dose): adipose (20.8%) > skin (7.0%) > muscle (5.2%) > liver (2.1%) > blood = brain (0.3% each) > lung = brain (0.1% each) (Chen et al. 2006). Similar orders of tissue concentrations were seen 24 hours after oral administration in male rats given single 1, 10, 100, or 1,000 µmol/kg doses, and in female F344 rats and male and female B6C3F1 mice given single 1 µmol/kg doses (Chen et al. 2006). Preferential accumulation in adipose also was found in male Sprague-Dawley rats 24 hours after administration of 14.5 µmol/kg doses of ^{14}C-BDE 99 (>98% pure) in corn oil (Hakk et al. 2002a). In male Sprague-Dawley rats 72 hours after administration of single 25.2 µmol/kg doses of ^{14}C-BDE 100 (>95% pure) in peanut oil, the adipose, gastrointestinal tract, and skin had the highest concentrations of radioactivity (>35 nmol/g fresh tissue weight), liver and lung had intermediate concentrations (~10–15 nmol/g), and other tissues, including lung, adrenals, testes, and muscle, had the lowest concentrations (<10 nmol/g) (Hakk et al. 2006).

Preferential distribution and accumulation in adipose also has been found for hexa-brominated BDEs in studies with rats or mice exposed orally to ^{14}C-BDE 153 (Sanders et al. 2006b) and ^{14}C-BDE 154 (Hakk et al. 2009). In male F344 rats given single doses of 1 µmol/kg ^{14}C-BDE 153 (~96% pure) in corn oil, levels of radioactivity remaining in tissues 24 hours after dose administration had the following order of percent of administered dose: adipose (16.7%) > muscle (13.4%) > skin (8.3%) > liver (5.8%) > blood (0.9%) > kidney (0.4%) > lung = brain (0.2% each) (Sanders et al. 2006b). Similar orders of tissue concentrations were observed in similarly exposed female F344 rats and male and female B6C3F1 mice

(Sanders et al. 2006b). During repeated daily applications of 1-µmol/kg ^{14}C-BDE 153 doses to male rats, supralinear increases in concentrations of radioactivity (nmol ^{14}C equivalents/g wet tissue) were observed in adipose and skin (e.g., average concentrations in adipose after 1, 3, and 10 consecutive doses were 1.57, 9.21, and 30.38 nmol/g, respectively) (Sanders et al. 2006b). This observation suggests that adipose and skin serve as sinks for radioactivity initially distributed to other tissues. In male Sprague-Dawley rats sampled 72 hours after administration of single 12.3 µmol/kg doses of ^{14}C-BDE 154 (>95% pure) in peanut oil, levels of radioactivity remaining in tissues had the following order (percent of administered dose): carcass (24.3%) > gastrointestinal tract (3.77%) > adipose (1.82%) > liver (0.68) > thymus ~ testis ~ lung ~ adrenal ~ kidney ~ plasma ~ heart ~ spleen (≤0.1% each) (Hakk et al. 2009). Expression of the data on a concentration basis (nmol ^{14}C equivalents/g wet tissue weight) showed the highest concentrations in lipid rich tissues: adrenals (29.56 nmol/g), adipose (21.79 nmol/g), skin (7.55 nmol/g), gastrointestinal tract (4.58 nmol/g), and thymus (4.48 nmol/g). Concentrations in carcass, lung, and liver were intermediate (3.58, 2.26, and 1.80 nmol/g), and concentrations in testis, kidney, heart, spleen, and muscle ranged from 1.01 to 0.45 nmol/g. The concentration in plasma was very low (0.04 nmol/g) (Hakk et al. 2009).

Maternal transfer of decaBDE (BDE 209) has been demonstrated in female Sprague-Dawley rats given oral 5 µmol/kg/day doses of nonlabeled BDE 209 in peanut oil from GD 7 to PPD 4 (Cai et al. 2011). BDE 209 concentrations in blood of dams increased with duration of exposure: mean concentrations (standard error [SE]) were 358.17 (210.49) and 701.17 (63.43) µg/g lipid weight on GD 15 and PPD 4, respectively (Cai et al. 2011). Whole-body concentrations of BDE 209 in fetuses and neonates also increased with duration: mean BDE 209 concentrations (and SE) were 20.53 (7.9), 28.95 (3.57), and 45.04 (10.23) µg/g lipid on GD 15, GD 21, and PPD 4, respectively (Cai et al. 2011). Nona-brominated congeners (BDE 208, BDE 207, and BDE 206) were detected in dam blood samples and whole-bodies of fetuses and neonates at lower concentrations than BDE 209 and higher concentrations than octa-brominated BDEs (BDE 196, 197/204, 198/203). In a related study by the same group of investigators, female Sprague-Dawley rats were exposed to 5 µmol/kg/day doses of nonlabeled BDE 209 from GD 7 to PPD 8 and from PPD 1 to 8 (Zhang et al. 2011). Whole-body BDE 209 concentrations in pups exposed during gestation and lactation were about 2 times greater than concentrations of pup exposed only during lactation, suggesting that BDE 209 exposure and accumulation can occur during gestational and nursing periods (Zhang et al. 2011).

In another study with female Sprague-Dawley rats given 1, 10, 100, 300 or 1,000 mg/kg/day of nonlabeled BDE 209 in corn oil from GD 7 to PPD 4, measurements of BDE 209 concentrations in blood

samples of dams and offspring gave no clear evidence of maternal transfer, but whole-body concentrations in offspring were not measured (Biesemeier et al. 2010). BDE 209 concentrations in blood (reported as ng/mL blood) collected on GD 20 were generally higher in exposed dams than in exposed fetuses, but mean concentrations of dams and fetuses in the 100-, 300-, and 1,000-mg/kg groups did not increase with increasing dose. Mean BDE 209 concentrations in maternal or offspring blood collected on PPD 4 also did not increase with increasing dose levels, but mean BDE 209 concentrations in exposed groups of PPD 4 pups were mostly higher than mean concentrations in dams from the same exposed groups (Biesemeier et al. 2010).

Further evidence for different tissue distributions of decaBDE and lower-brominated congeners comes from a study in which neonatal NMRI mice were given single 0.7 mg/kg doses of ^{14}C-decaBDE or 0.8 mg/kg doses of ^{14}C-BDE 99 in a 20% fat emulsion to simulate milk on PND 3, 10, or 19 (Eriksson et al. 2002b; Viberg et al. 2003a). Neonatal mice exposed to ^{14}C-BDE 209 on PND 3, 10, or 19 had about 0.48, 0.40, and 0.06% of the total administered radioactivity in the brain, 24 hours after dose administration (Viberg et al. 2003a). Seven days after exposure, radioactivity in the brain had increased approximately 2-fold in mice exposed on PND 3 or 10 (to 0.74 and 1.05% of the administered dose), but remained the same as previously measured in mice exposed on PND 19 (0.06% of administered dose). Mice exposed to ^{14}C-BDE 99 on PND 3, 10, or 19 had about 0.37, 0.51, and 0.51% of the administered dose in the brain, 24 hours after dose administration; 7 days after dose administration, decreased levels in brains were seen in mice exposed on PNDs 3, 10, and 19 (about 0.18, 0.28, and 0.15% of the administered dose) (Eriksson et al. 2002b).

3.4.2.3 Dermal Exposure

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

3.4.3 Metabolism

Oxidative hydroxylation of PBDEs is a principal metabolic transformation that occurs in humans and laboratory animals. Hydroxylated PBDEs have been identified in samples of human biological fluids, including blood (Athanasiadou et al. 2008; Hovander et al. 2002; Lacorte and Ikonomou 2009; Qiu et al. 2009; Rydén et al. 2012; Wan et al. 2009, 2010; Wang et al. 2012; Yu et al. 2010a) and breast milk (Lacorte and Ikonomou 2009). Hydroxylated PBDEs also have been identified in feces or bile of laboratory rodents exposed to ^{14}C-labeled tetra-, penta-, hexa- or decaBDEs, including:

- rats orally exposed to BDE 47 (Marsh et al. 2006; Orn and Klasson-Wehler 1998; Sanders et al. 2006a);
- female mice given single intravenous doses of BDE 47, BDE 99, BDE 100, or BDE 153 (Staskal et al. 2006b)
- conventional or bile-duct cannulated male rats given oral or intravenous doses of BDE 99 (Chen et al. 2006; Hakk et al. 2002a);
- conventional or bile-duct cannulated rats given oral doses of BDE 154 (Hakk et al. 2009); and
- conventional or bile-duct cannulated rats given oral doses of BDE 209 (Morck et al. 2003; Riu et al. 2008).

Hydroxylated metabolites have also been identified in feces and carcasses of male rats fed a commercial pentaBDE mixture (DE-71) for 21 days (Huwe et al. 2007), in plasma of rats given single intraperitoneal injections of an equimolar mixture of BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 183 (Malmberg et al. 2005), and in plasma of mice after oral and subcutaneous exposure to DE-71 for 34 days (Qiu et al. 2007). Oxidative hydroxylation of PBDEs also has been demonstrated and studied in *in vitro* metabolic systems with human liver microsomes or primary hepatocytes (Cheng et al. 2008; Erratico et al. 2012, 2013; Feo et al. 2013; Lupton et al. 2009; Stapleton et al. 2009) and rat liver microsomes or primary hepatocytes (Dong et al. 2010; Erratico et al. 2011).

Metabolic cleavage of the ether bond in PBDEs to form brominated phenols and debromination to form lower-brominated PBDEs are other metabolic fates of PBDEs in mammals. Evidence for cleavage of the ether bond includes the identification of:

- glucuronide- and sulfate-conjugates of 2,4-dibromophenol in male rats given single oral doses of ^{14}C-BDE 47 (2,2',4,4'-tetraBDE) (Sanders et al. 2006a);
- unconjugated 2,4,5-tribromophenol in feces and urine and glucuronide-, sulfate-, and glutathionyl-conjugates of 2,4,5-tribromophenol in bile and urine in conventional and bile duct-cannulated male rats given single oral doses of ^{14}C-BDE 99 (2,2',4,4',5-pentaBDE) (Chen et al. 2006); and
- 2,4-dibromophenol and 2,4,5-tribromophenol as metabolites of BDE 47 and BDE 99 following in vitro incubation with human liver microsomes (Erratico et al. 2013, 2012).

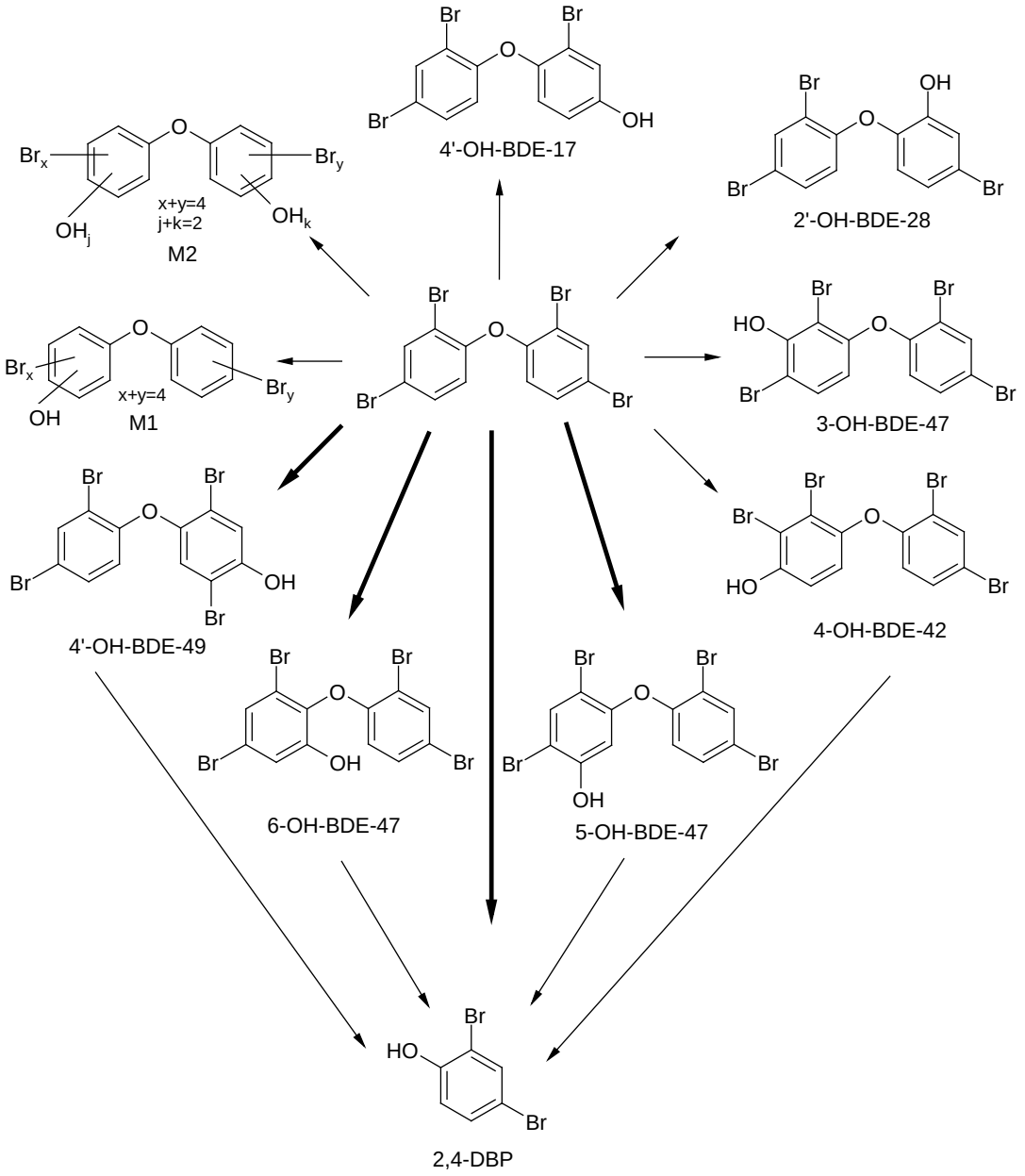
Evidence for debromination includes the identification of:

- hydroxylated triBDEs in feces of rats given single oral doses of ^{14}C-BDE 47 (2,2',4,4'-tetraBDE) (Marsh et al. 2006);
- hydroxylated tetraBDEs in feces of male rats given single oral doses of ^{14}C-BDE 99 (2,2',4,4',5-pentaBDE) (Hakk et al. 2002a);
- mono- and di-hydroxylated tetraBDEs in feces of rats given single oral doses of ^{14}C-BDE 100 (2,2',4,4',6-pentaBDE) (Hakk et al. 2006);
- hydroxylated tetra- and pentaBDEs in feces of rats given single oral doses of ^{14}C-BDE 154 (2,2',4,4',5,6'-hexaBDE) (Hakk et al. 2009);
- several hydroxylated BDEs with five to seven bromines per molecule in feces of rats given single doses of ^{14}C-BDE 209 (Morck et al. 2003); and
- several hydroxylated BDEs with eight or nine bromines per molecule in male rats given single doses of ^{14}C-BDE 209 (Sandholm et al. 2003).

Information from *in vivo* toxicokinetic studies with rodents exposed to the best studied congeners (i.e., BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 209) is inadequate to describe detailed metabolic pathways, but is adequate to propose that cytochrome P450s are likely to be involved in the formation of hydroxylated metabolites and hydoxylated debrominated metabolites of BDE 47 (Sanders et al. 2006a), BDE 99 (Chen et al. 2006), BDE 100 and BDE 154 (Hakk et al. 2006, 2009), and BDE 209 (Morck et al. 2003; Sandholm et al. 2003). Recent *in vitro* studies with human or rat liver microsomes or hepatocytes, and human or rat recombinant CYPs, provide more detailed information adequate for proposing metabolic pathways for BDE 47, BDE 99, and BDE 100 in humans showing CYP2B6 mediation for hydroxylation, debromination, and ether bond cleavage for BDE 47, hydroxylation and ether bond cleavage for BDE 99, and hydroxylation for BDE 100 (see Figures 3-4, 3-5, and 3-6); however, no clear metabolic pathways were identified for BDE 153 or BDE 209 using these methods.

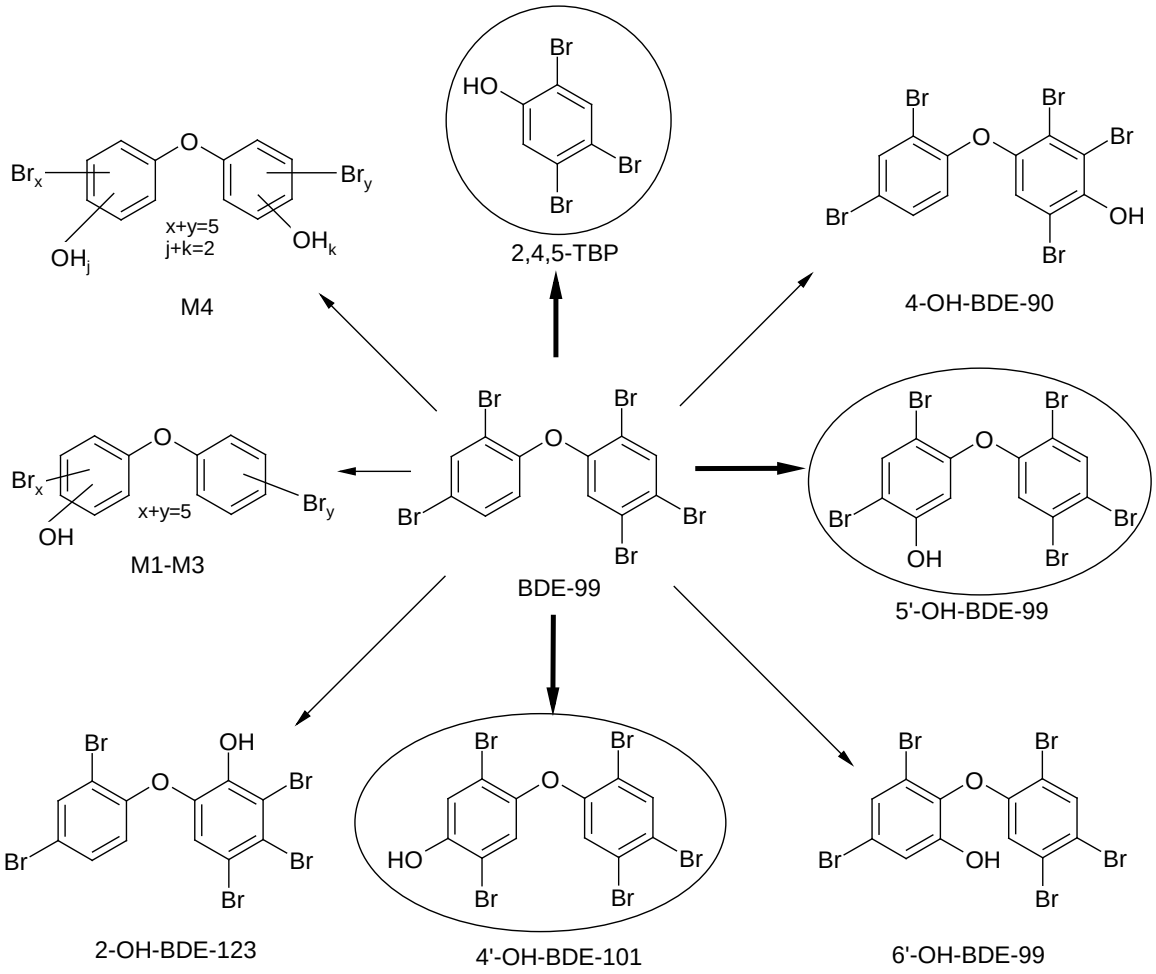
- BDE 47 was metabolized, principally by CYP2B6, in human liver microsomes (Erratico et al. 2013; Feo et al. 2013; Lupton et al. 2009), producing 5-OH-BDE-47, 6-OH-BDE-47, an unidentified dihydroxylated tetrabrominated BDE and 2,4-dibromophenol as major metabolites, and several minor metabolites including three other hydroxylated tetrabrominated BDEs and two hydroxylated tribrominated BDEs (Erratico et al. 2013; see Figure 3-4). The predominance of CYP2B6 involvement was demonstrated by inhibition of the production of all metabolites by a specific antibody to CYP2B6 (Erratico et al. 2013) and comparison of capabilities of 11 or 12 recombinant human CYPs (Erratico et al. 2013; Feo et al. 2013).

Figure 3-4. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE 47 Produced by Human Liver Microsomes*



*M1 and M2 refer to general structures of unidentified hydroxylated and dihydroxylated tetrabrominated BDEs. Structures of other metabolites were determined with authentic chemical standards and ultra-performance liquid chromatography-mass spectrometry techniques. Bold arrows indicate major metabolites. CYP2B6 is proposed to be involved in production of all metabolites, based on inhibition of BDE 47 metabolism by a specific antibody to CYP2B6, and higher rates of BDE 47 metabolism in human liver microsomes incubated with specific human recombinant CYP2B6, compared with 11 other human recombinant CYPs.

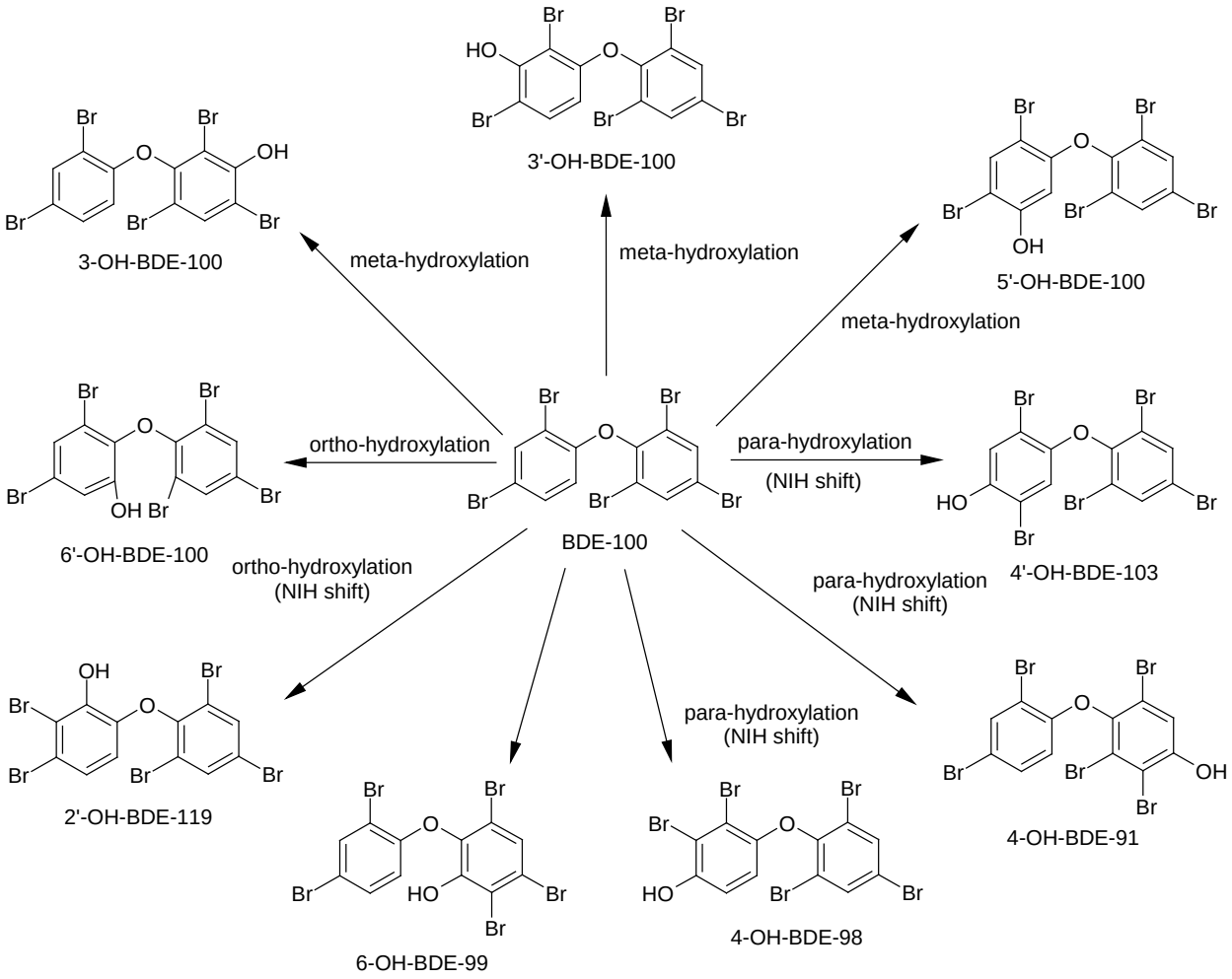
Figure 3-5. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE 99 Produced by Human Liver Microsomes*



*M1-3 and M4 refer to general structures of unidentified hydroxylated and dihydroxylated pentabrominated BDEs. Structures of other metabolites were determined with authentic chemical standards and ultra-performance liquid chromatography-mass spectrometry techniques. CYP2B6 is proposed to be involved in production of all metabolites, based on inhibition of BDE 99 metabolism by a specific antibody to CYP2B6, and higher rates of BDE 99 metabolism in human liver microsomes incubated with human recombinant CYP2B6, compared with11 other human recombinant CYPs.

Source: Erratico et al. 2012

Figure 3-6. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE 100 Produced by Human Liver Microsomes and Human CYP2B6*



*Structures of 3-OH-BDE-100, 5'-OH-BDE-100, 6'OH-BDE-100, and 4'-OH-BDE-103 were determined using commercial reference standards and ultra-performance liquid chromatography-mass spectrometry techniques. The two remaining mono-OH-pentaBDE metabolites were hypothesized using mass spectral fragmentation characteristics of derivatized OH-BDEs. Additional information based on theoretical boiling point calculations using COnductor-like Screening MOdel for Realistic Solvents (COSMO-RS) and experimental chromatographicretention times were used to identify the hypothesized metabolites as 2′-hydroxy-2,3′,4,4′,6-pentabromodiphenyl ether (2′-OHBDE-119) and 4-hydroxy-2,2′,4′,5,6-penta-bromodiphenyl ether (4-OH-BDE-91), respectively. CYP2B6 is proposed to be involved in production of all metabolites, based on inhibition of BDE 99 metabolism by a specific antibody to CYP2B6, and higher rates of BDE 100 metabolism in human liver microsomes incubated with human recombinant CYP2B6, compared with nine other human recombinant CYPs.

Source: Gross et al. 2015

- BDE 47 was metabolized by liver microsomes from phenobarbital (PB)-induced and dexamethasone (DEX)-induced rats, producing five hydroxylated tetrabrominated BDEs with PB-induction and two hydroxylated tetrabrominated BDEs with DEX induction (Erratico et al. 2011). The major metabolites identified were 4'-OH-BDE-49 and 3-OH-BDE-47 (with PB or DEX induction), and 4-OH-BDE-42 (PB induction only). No evidence for debromination or ether bond cleavage was found. These data and a comparison of metabolic capabilities of 14 recombinant rat CYP enzymes indicate that rat liver metabolism of BDE 47 involves CYP1A1, CYP2A2, and CYP3A1 (Erratico et al. 2011),

- BDE 99 was metabolized, principally by CYP2B6, in human liver microsomes (Erratico et al. 2012; Lupton et al. 2009; Stapleton et al. 2009), producing 2,4,5-tribromophenol, 5'-OH-BDE-99 and 4'-OH-BDE-101 as major metabolites and seven minor hydroxylated pentaBDEs (4-OH-BDE-90, 6'-OH-BDE-99, and 2-OH-BDE-123, three unidentified monohydroxy pentabrominated BDEs, and one dihydroxy pentabrominated BDE) (Erratico et al. 2012; see Figure 3-5). No evidence for debromination of BDE 99 was found. CYP2B6 was the only CYP among a panel of 12 human recombinant CYPs showing metabolic activity with BDE 99, and a specific antibody to CYP2B6 inhibited the production of all BDE 99 metabolites by human liver microsomes (Erratico et al. 2012).

- BDE 99 was metabolized to hydroxylated metabolites in primary rat hepatocytes (Dong et al. 2010) and in liver microsomes from DEX- and PB-induced rats (Erratico et al. 2011). Liver microsomes from DEX- and PB-induced rats produced 4-OH-BDE-99 as the major metabolite and lesser amounts (in decreasing order) of 5'-OH-BDE-99, 6'-OH-BDE-99, 2,4,5-tribromo-phenol, 4'-OH-BDE-101, and 2-OH-BDE-123. No evidence for debromination was found. These data and a comparison of metabolic capabilities of 14 recombinant rat CYP enzymes indicated that rat liver metabolism of BDE 99 involves CYP1A1, CYP2A2, CYP2B1, and CYP3A1 (Erratico et al. 2011).

- BDE 100 was metabolized by recombinant human P450s and pooled human liver microsomes (Gross et al. 2015). As with BDE 47 and BDE 99, human CYP2B6 was found to be the predominant enzyme responsible for nearly all formation of six mono-OH-pentaBDE and two di-OH-pentaBDE metabolites. Four metabolites were identified as 3-hydroxy-2,2′,4,4′,6-pentabromodiphenyl ether (3-OH-BDE-100), 5′-hydroxy-2,2′,4,4′,6-pentabromodiphenyl ether (5′-OHBDE-100), 6′-hydroxy-2,2′,4,4′,6-penta-bromodiphenyl ether (6′-OH-BDE-100), and 4′-hydroxy-2,2′,4,5′,6-pentabromodiphenyl ether (4′-OH-BDE-103) through use of reference standards (see Figure 3-6). The two remaining mono-OH-pentaBDE metabolites were hypothesized using mass spectral fragmentation characteristics of derivatized OH-BDEs, which allowed prediction of an ortho-OH-pentaBDE and a para-OH-pentaBDE positional isomer. Additional information based on theoretical boiling point calculations using COnductor-like Screening MOdel for Realistic Solvents (COSMO-RS) and experimental chromatographic retention times were used to identify the hypothesized metabolites as 2′-hydroxy-2,3′,4,4′,6-penta-bromodiphenyl ether (2′-OHBDE-119) and 4-hydroxy-2,2′,4′,5,6-pentabromodiphenyl ether (4-OH-BDE-91), respectively (Simpson et al. 2015). Kinetic studies of BDE 100 metabolism using P450 2B6 and HLMs revealed K_m values ranging from 4.9 to 7.0 μM and 6−10 μM, respectively, suggesting a high affinity toward the formation of OH-BDEs. Compared to the metabolism of BDE 47 and BDE 99 reported in previous studies, BDE 100 appears to be more slowly metabolized by P450s due to the presence of a third ortho-substituted bromine atom.

- BDE 153 was not metabolized by human liver microsomes under conditions that produced hydroxylated metabolites from BDE 47 (a dihydroxylated BDE 47 and 2,4-dibromophenol), and BDE 99 (2,4,5- tribromophenol, a dihydroxlated BDE 99, and 1,3-dibromo benzene) (Lupton et al. 2009).

- BDE 209 was not metabolized by human primary liver hepatocytes under conditions that produced 2,3,5-tribromophenol, two hydroxylated pentabrominated BDE metabolites and an unidentified hydroxylated tetrabrominated metabolite from BDE 99 (Stapleton et al. 2009).

In summary, Feo et al. (2013) and Gross et al. (2015) characterized the in vitro metabolism of BDE 47 and BDE 100 by pooled human liver microsomes and recombinant human CYPs, identifying a number of hydroxylated BDE metabolites; however, no brominated phenols were detected by the methods utilized by these investigators. In other studies, CYP2B6-mediated metabolism of BDE 47 and BDE 99 produces multiple hydroxylated metabolites via hydroxylation and ether bond cleavage, based on *in vitro* studies with human liver microsomes or hepatocytes and human recombinant CYPs (Erratico et al. 2012, 2013). The major metabolites of BDE 47 and BDE 99 formed by human liver microsomes were not the same as those identified using rat liver microsomes (Erratico et al. 2013, 2012, 2011). It is important to note that all studies consistently identified CYP2B6 as the primary human CYP responsible for the formation of hydroxylated metabolites of BDE 47, BDE 99, and BDE 100 (Erratico et al. 2012, 2013; Feo et al. 2013; Gross et al. 2015), while different classes of CYP enzymes appear to be involved in *in vitro* rat liver metabolism of BDE 47 and BDE 99: CYP1A1, CYP2A2, and CYP3A1 for BDE 47 and CYP1A1, CYP2A2, CYP2B1, and CYP3A1 for BDE 99 (Erratico et al. 2011). Production of hydroxylated metabolites of BDE 153 (Lupton et al. 2009) and BDE 209 (Stapleton et al. 2009) has not been demonstrated with human liver microsomes or hepatocytes, respectively. It is uncertain if these latter findings are reflective of a limited *in vivo* capacity of humans to metabolize these BDE congeners or because the proper *in vitro* conditions for metabolizing these congeners were not provided. Currently, studies of metabolism of BDE 47 and BDE 99 with *in vitro* human and rat systems have found evidence of metabolic oxidative debromination only with BDE 47 in human liver microsomes. In contrast, a number of *in vivo* studies have found evidence for oxidative debromination in feces collected from rats exposed to BDE 47 (Marsh et al. 2006), BDE 99 (Hakk et al. 2002a), BDE 100 (Hakk et al. 2006), BDE 154 (Hakk et al. 2009), and BDE 209 (Morck et al. 2003; Sandholm et al. 2003).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

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

3.4.4.2 Oral Exposure

Oral Exposure Elimination Overview. Apparent half-lives of PBDE congeners in blood of PBDE-exposed workers during non-exposed vacation periods ranged from 15 days for BDE 209, 18–39 days for nonabrominated congeners, and 37–94 days for octabrominated congeners. The detection of PBDEs in human breast milk samples indicates that elimination via milk is an elimination route for women, but several studies examining PBDE concentrations during lactation do not provide a clear account of the degree to which PBDEs are cleared from the body during lactation. Results from animal studies given single oral doses of ^{14}C-labeled PBDE congeners or PBDE mixtures indicate that biliary excretion into the feces is the principal route of elimination in rats, and that the urine and feces are principal routes of elimination of orally absorbed PBDEs in mice.

No studies were located regarding excretion of PBDEs in humans after controlled oral exposure.

Apparent half-lives of several PBDEs in blood were estimated for eight PBDE-exposed workers (four electronics dismantlers and four workers in a factory making flame-retarded rubber) from measurements of hepta-, octa-, nona- and decaBDE concentrations in blood collected during 28–29-day vacation periods without occupational exposure (Thuresson et al. 2006). After fitting the data to a single-phase exponential model, calculated apparent half-lives were: 15 days for BDE 209; 28, 39, and 18 days for nonabrominated congeners BDE 208, BDE 207, and BDE 206; 37, 72, 85, and 91 days for BDE 203 and three other octabrominated congeners of uncertain chemical structure; and 94 days for BDE 183.

The detection of PBDEs in human breast milk samples suggests that breast milk represents an elimination route of absorbed PBDEs in women (see Jakobsson et al. 2012 and Frederiksen et al. 2009 for reviews of PBDE levels in breast milk). Several studies have examined changes in PBDE concentrations (and other persistent lipophilic chemicals) in breast milk during lactation, but the results do not provide a clear account of the degree to which PBDEs are cleared from the body during breast feeding (Hooper et al. 2007; Jakobsson et al. 2012; LaKind et al. 2009; Thomsen et al. 2010).

Studies with rats given single oral doses of ^{14}C-labeled PBDE congeners or PBDE mixtures indicate that ingested PBDEs are principally excreted in the feces with <2% of administered radioactivity excreted in the urine within 3 days of dose administration. This pattern has been observed in male and female rats exposed to BDE 47 (Orn and Klasson-Wehler 1998; Sanders et al. 2006a), male and female rats exposed

to BDE 99 (Chen et al. 2006; Hakk et al. 2002a), male rats exposed to BDE 100 (Hakk et al. 2006), male and female rats exposed to BDE 153 (Sanders et al. 2006), male rats exposed to BDE 154 (Hakk et al. 2009), pregnant female and male rats exposed to BDE 209 (Morck et al. 2003; Riu et al. 2008), and male and female rats exposed to a mixture with 77.4% ^{14}C-BDE 209, 21.8% nonabrominated BDE, and 0.8% octabrominated (Norris et al. 1973, 1975b). Studies with bile duct-cannulated male rats indicated that radioactivity excreted in feces of conventional rats included bile duct-delivered metabolites (i.e., absorbed material) and unabsorbed compound. Cumulative biliary excretion represented about 3.9% of administered dose with BDE 99 (Hakk et al. 2002a), 1.7% with BDE 100 (Hakk et al. 2006), 1.3% with BDE 154, and about 10% with BDE 209 (Morck et al. 2003).

A different elimination pattern has been observed in mice, especially with BDE 47. In mice given single oral doses of ^{14}C-labeled PBDE congeners, fecal and urinary elimination were principal routes of elimination for BDE 47 (Orn and Klasson-Wehler 1998; Sanders et al. 2006a), whereas fecal elimination appeared to be more important than urinary elimination with BDE 99 (Chen et al. 2006) and BDE 153 (Sanders et al. 2006b). Male C57Bl mice excreted 20% of administered radioactivity in feces and 33% in urine within 5 days of administration of ^{14}C-BDE 47 (Orn and Klasson-Wehler 1998). Male and female B6C3F1 mice excreted about 30 and 20% of administered ^{14}C-BDE 47 dose in urine and about 22% and 25% in feces, within 24 hours (Sanders et al. 2006a). In B6C3F1 mice given ^{14}C-BDE 99, males excreted 7.8% in urine and 27.1% in feces within 24 hours, and females excreted 4.1% in urine and 32.4% in feces (Chen et al. 2006). Twenty-four hours after administration of ^{14}C-BDE 153, male B6C3F1 mice excreted 1% of administered dose in urine and 31.5% in feces, and females excreted 0.3% in urine and 26.0% in feces (Sanders et al. 2006b).

Complementary studies with female C57BL/6J given single intravenous 1-mg/kg doses of ^{14}C-labeled BDE 47, BDE 99, BDE 100, or BDE 153 also indicate that the degree of urinary excretion in mice is congener specific (Staskal et al. 2006b). Cumulative percentages of administered radioactivity excreted in urine within 5 days were 40, 16, 6, and 2% for BDE 47, BDE 99, BDE 100, and BDE 153, respectively. Relatively greater amounts of parent compound were found in urine from BDE 47-exposed mice, compared with mice exposed to the other congeners. Ratios of cumulative percentage dose excreted as parent compound or metabolite in urine were 1.5, 0.5, 0.4, and 0.2 for BDE 47, BDE 99, BDE 100, and BDE 153, respectively. In feces, respective ratios of parent compound:metabolite were 0.7, 0.2, 0.2, and 0.3 for these congeners, respectively.

The mechanism for the relatively high elimination of BDE 47 in the urine of mice is unknown, but has been hypothesized to involve binding to mouse major urinary protein (m-MUP) in the blood (Sanders et al. 2006a; Staskal et al. 2006b) and other membrane transporting polypeptides (Emond et al. 2013; Pacyniak et al. 2010, 2011).

3.4.4.3 Dermal Exposure

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

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The

numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

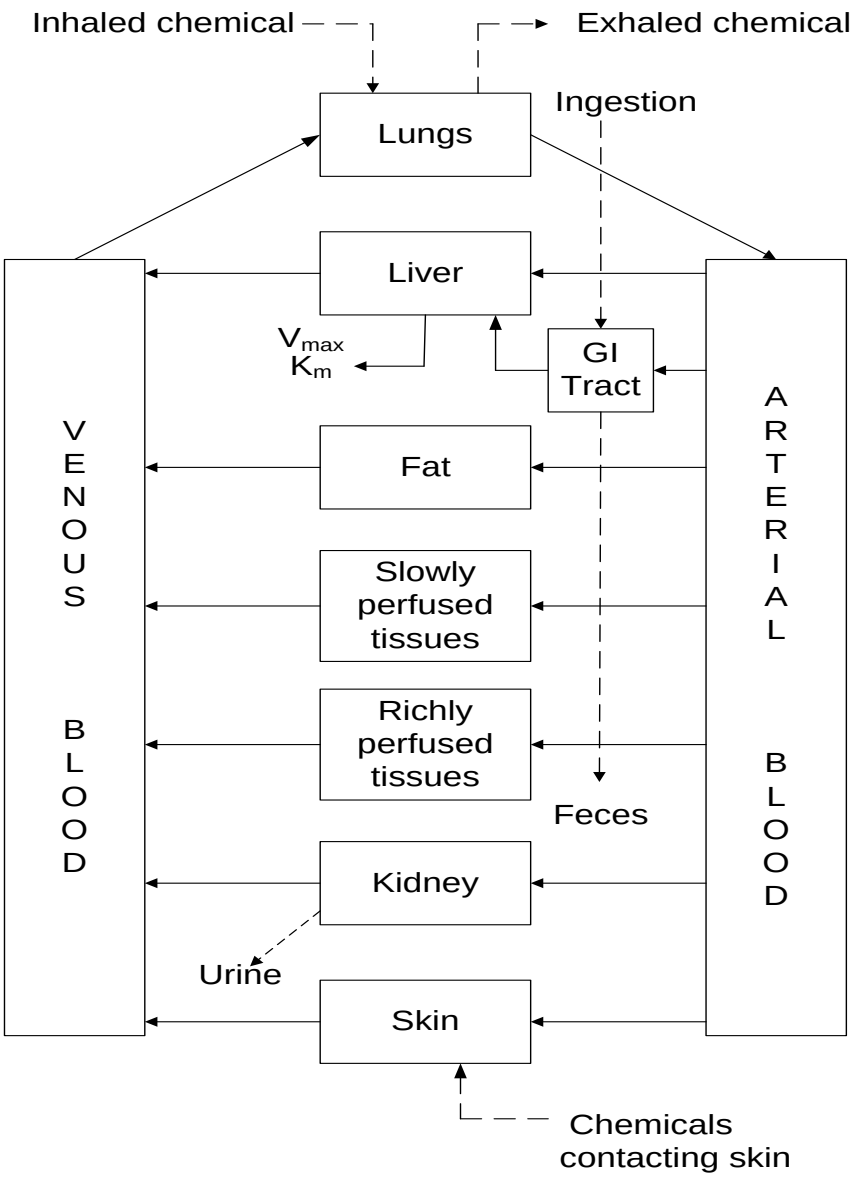
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-7 shows a conceptualized representation of a PBPK model.

If PBPK models for PBDEs exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Emond et al. (2010) developed a PBPK model for BDE 47 in male and female (nonpregnant and pregnant) adult rats. The model included eight compartments: liver, brain, adipose tissue, kidney, placenta, fetus, blood, and the remaining body. The model was calibrated with tissue concentration data from adult male and maternal-fetal toxicokinetic studies. Other data sets were then used to evaluate the model's performance. Model evaluations indicated that simulated BDE 47 tissue concentrations in adult male, adult female, and fetal compartments were within the standard deviations of the empirical data.

Emond et al. (2013) developed a PBPK model for BDE 47 in adult mice to describe the distribution of BDE 47 in tissues and its elimination in feces and urine, and to evaluate the role of transporters in elimination of BDE 47. The structure of the model was similar to the rat model developed by Emond et al. (2010), without the gestational submodel. In addition, binding to transporters proposed to facilitate

Figure 3-7. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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.

Source: Krishnan and Andersen 1994

urinary excretion in mice were added: mouse major urinary protein (m-MUP) in blood and P-glycoprotein, a membrane transporter in brain, liver, and kidneys. The model was used to investigate the roles that m-MUP and P-glycoprotein may play in BDE 47 elimination in mice.

No reports were located on the development of PBPK models for PBDEs in humans.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Information regarding oral absorption in animals is available from studies of commercial PBDE mixtures and individual ^{14}C-labeled tetra-, penta-, hexa-, and decaBDE congeners. The most recent and best available estimates of oral absorption efficiencies following gavage administration in lipophilic vehicles indicate a range of 70–85% for tetraBDE (BDE 47), pentaBDE (BDE 99, BDE 100), and hexaBDE (BDE 153, BDE 154) congeners, and 10–26% for decaBDE (BDE 209) (Hakk et al. 2001, 2002b, 2006, 2009; Huwe et al. 2002b, 2007; Morck and Klasson Wehler 2001; Morck et al. 2003; Örn and Klasson-Wehler 1998; Riu et al. 2008; Sanders et al. 2006a, 2006b; Sandholm et al. 2003; Staskal et al. 2005). Underlying mechanisms for oral absorption (e.g., active transport, diffusion, protein binding) have not been described.

Studies using *in vitro* gastrointestinal digestion models have evaluated bioaccessibility of PBDEs in environmentally relevant sources. In a study by Yu et al. (2010b), the bioaccessibility of lower-brominated PBDEs in 13 types of food (fish, meat, rice, flour, and vegetables) ranged from 2.6 to 41.3% in food. Dietary fat was the most important factor affecting the bioaccessibility of PBDEs, with bioavailability increasing with increased fat content, likely due to the lipophilic nature of PBDEs (Yu et al. 2010b). Bioavailability was also increased with increasing carbohydrate content, potentially due to the formation of micelles (Yu et al. 2010b). However, bioavailability decreased with increasing protein and fiber content, potentially due to adsorption to dietary fiber and ionic strength effect of amino acids leading to decreased partition of PBDEs in the aqueous phase (Yu et al. 2010b). Lepom et al. (2010) evaluated the bioaccessibility of PBDEs in ingested dust, which is expected to be the predominant source of human exposure in the United States (EPA 2010). In this study, the bioavailability of PBDEs in ingested dust was <50%, with higher bioavailability for the lower-brominated PBDEs (27–42%) compared with BDE 209 (10%) (Lepom et al. 2010). A similar study by Abdallah et al. (2012) showed comparable results for the bioaccessibility of PBDEs in ingested dust, with higher bioavailability for the lower-brominated PBDEs (32–58%) compared with BDE 209 (14%).

A dermal absorption efficiency of 62% was reported for female mice exposed to an occluded dermal dose of 1 mg/kg ^{14}C-BDE 47) (Staskal et al. 2005). *In vitro* studies have evaluated diffusion of PBDEs across human, rat, and mouse skin. For ^{14}C-BDE 47, the mean absorption efficiencies (percent of applied radioactivity collected in receptor compartment) were 1.88% for human skin and 14.58% for rat skin (Roper et al. 2006). For ^{14}C-decaBDE, mean absorption efficiency for mouse skin *in vitro* was reported to be only 0.07–0.34% of the applied dose (Hughes et al. 2001). Underlying mechanisms for dermal absorption (e.g., active transport, diffusion, protein binding) specific to PBDEs have not been described.

Distribution. Evidence for the transfer of PBDEs from pregnant mothers to the developing fetus and for the transfer of PBDEs from maternal blood to breast milk and then to nursing infants comes from a number of studies of PBDE concentrations in maternal and cord serum samples and breast milk samples from groups of non-occupationally exposed women (Antignac et al. 2009, 2008; Chen et al. 2013; Kawashiro et al. 2008; Li et al. 2013b; Malarvannan et al. 2013; Mazdai et al. 2003; Meijer et al. 2008; Park et al. 2011; Qiu et al. 2009; Schecter et al. 2010; Vizcaino et al. 2011; Wan et al. 2010). In general, the tetra- and penta-brominated PBDEs have been the predominant congeners detected in maternal and cord serum samples and breast milk samples, but some recent studies analyzing a wider range of PBDE congeners have found evidence for distribution of hepta-, octa-, or decaBDEs into cord serum and breast milk. Frederiksen et al. (2010) utilized a human *ex vivo* placenta perfusion system to study the kinetics of placental transfer of BDE 47, BDE 99, and BDE 209 to the fetus. Placentas were perfused for 4 hours with 1 ng/mL concentrations of the nonlabeled congeners. Samples of maternal and fetal compartments were taken during the perfusion, and concentrations in samples were determined by GC/MS. Placental transfer of BDE 47 and BDE 99 was demonstrated, and transfer of BDE 47 was faster and more extensive than BDE 99. Transfer of BDE 209 across the placenta to the fetal compartment was not demonstrated with the detection limits of the techniques employed. Frederiksen et al. (2010) proposed that future perfusion studies with BDE 209 should use ^{14}C-labeled BDE 209 to increase sensitivity.

Tissue distribution studies in animals orally exposed to ^{14}C-labeled BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 209 indicate that decaBDE is distributed among tissues somewhat differently than tetra-, penta- and hexaBDEs. While lower-brominated BDE congeners, following absorption and an initial wide distribution, are preferentially accumulated in adipose tissues, absorbed decaBDE is less readily distributed to adipose tissues and appears to preferentially distribute to highly perfused tissues (Chen et al. 2006; El Dareer et al. 1987; Eriksson et al. 2002b; Hakk et al. 2002a, 2006; Morck and Klasson-Wehler 2001; Morck et al. 2003; Norris et al. 1975a; NTP 1986; Örn and Klasson-

Wehler 1998; Riu et al. 2008; Sanders et al. 2006a, 2006b; Staskal et al. 2005, 2006a; Viberg et al. 2003a). Although less likely to partition to adipose tissues, decaBDE was still found in low quantities in adipose tissues in these studies, and has been shown to transfer from dams to fetuses and neonates from exposure during gestational and nursing periods (Cai et al. 2011; Zhang et al. 2011).

Metabolism. Oxidative hydroxylation of PBDEs is a principal metabolic transformation that is thought to occur in humans and laboratory animals. Hydroxylated PBDEs have been identified in samples of human biological fluids including blood (Athanasiadou et al. 2008; Hovander et al. 2002; Lacorte and Ikonomou 2009; Qiu et al. 2009; Rydén et al. 2012; Wan et al. 2009, 2010; Wang et al. 2012; Yu et al. 2010a) and breast milk (Lacorte and Ikonomou 2009). Hydroxylated PBDEs also have been identified in feces or bile of laboratory rodents exposed to ^{14}C-labeled tetra-, penta-, hexa- or decaBDEs (Chen et al. 2006; Hakk et al. 2002a, 2009; Marsh et al. 2006; Morck et al. 2003; Orn and Klasson-Wehler 1998; Riu et al. 2008; Sanders et al. 2006a; Staskal et al. 2006b). Oxidative hydroxylation of PBDEs also has been demonstrated and studied in *in vitro* metabolic systems with human liver microsomes or primary hepatocytes (Cheng et al. 2008; Erratico et al. 2012, 2013; Feo et al. 2013; Lupton et al. 2009; Stapleton et al. 2009) and rat liver microsomes or primary hepatocytes (Dong et al. 2010; Erratico et al. 2011). Metabolic cleavage of the ether bond in PBDEs to form brominated phenols and debromination to form lower-brominated PBDEs are other metabolic fate processes for PBDEs in mammals (Chen et al. 2006; Erratico et al. 2013, 2012; Hakk et al. 2002a, 2006, 2009; Marsh et al. 2006; Morck et al. 2003; Sanders et al. 2006a; Sandholm et al. 2003).

Information from *in vivo* toxicokinetic studies with rodents exposed to the best studied congeners (i.e., BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 209) is inadequate to describe detailed metabolic pathways, but is adequate to propose that cytochrome P450s are likely to be involved in the formation of hydroxylated metabolites and hydoxylated debrominated metabolites. *In vitro* studies with human liver microsomes or hepatocytes and human recombinant CYPs indicate that CYP2B6-mediated metabolism of BDE 47, BDE 99, and BDE 100 produced multiple metabolites via hydroxylation (Erratico et al. 2012, 2013; Feo et al. 2013; Gross et al. 2015) and ether bond cleavage (Erratico et al. 2012, 2013). The major metabolites of BDE 47 and BDE 99 formed by human liver microsomes were not the same as those identified using rat liver microsomes (Erratico et al. 2011, 2012, 2013). Different sets of CYP enzymes appear to be involved in *in vitro* rat liver metabolism of BDE 47 and BDE 99: CYP1A1, CYP2A2, and CYP3A1 for BDE 47 and CYP1A1, CYP2A2, CYP2B1, and CYP3A1 for BDE 99 (Erratico et al. 2011). Production of hydroxylated metabolites of BDE 153 (Lupton et al. 2009) and BDE 209 (Stapleton et al. 2009) has not been demonstrated with human liver microsomes or hepatocytes. It is

uncertain if these latter findings are reflective of a limited *in vivo* capacity of humans to metabolize these BDE congeners or because the proper *in vitro* conditions for metabolizing these congeners were not provided. While rat studies provide evidence for metabolic oxidative debromination of BDE 47, BDE 99, BDE 100, BDE 154, and BDE 209, studies with human liver microsomes only found evidence supporting the oxidative debromination of BDE 47.

Elimination. Apparent half-lives of PBDE congeners in blood of PBDE-exposed workers during non-exposed vacation periods ranged from 15 days for BDE 209, 18–39 days for nonabrominated congeners, and 37–94 days for octabrominated congeners (Thuresson et al. 2006). The detection of PBDEs in human breast milk samples indicates that elimination via milk is an elimination route for women, but several studies examining PBDE concentrations during lactation do not provide a clear account of the degree to which PBDEs are cleared from the body during lactation (Hooper et al. 2007; Jakobsson et al. 2012; LaKind et al. 2009; Thomsen et al. 2010). Results from animal studies given single oral doses of ^{14}C-labeled PBDE congeners or PBDE mixtures indicate that biliary excretion into the feces is the principal route of elimination in rats (Chen et al. 2006; Hakk et al. 2002a, 2006; Morck et al. 2003; Norris et al. 1973, 1975b; Orn and Klasson-Wehler 1998; Riu et al. 2008; Sanders et al. 2006a), and that the urine and feces are principal routes of elimination of orally absorbed PBDEs in mice (Chen et al. 2006; Orn and Klasson-Wehler 1998; Sanders et al. 2006a). In mice, the importance of urinary excretion is congener-specific, with BDE 47 showing the greatest ratio of cumulative percentage dose excreted as parent compound or metabolite (Staskal et al. 2006b). The mechanism for the relatively high elimination of BDE 47 in the urine of mice is unknown, but has been hypothesized to involve binding to mouse major urinary protein (m-MUP) in the blood (Sanders et al. 2006a; Staskal et al. 2006b) and other membrane transporting polypeptides (Emond et al. 2013; Pacyniak et al. 2010, 2011).

3.5.2 Mechanisms of Toxicity

Overview. As summarized in Section 2.2 (Summary of Health Effects) and detailed in Chapter 3 (Health Effects), the main targets of concern following PBDE exposure in humans are the developing nervous and reproductive systems, the developing and mature endocrine system, the liver, and the male reproductive system. Other potential targets are the female reproductive system, the adult nervous system, and the developing and adult immune system; however, evidence for these end points is limited. Numerous studies have been conducted to identify potential mechanisms of toxicity for PBDE exposure. These studies include evaluations of general mechanisms (e.g., hepatic enzyme induction, AhR-mediated effects) as well as target-specific mechanisms. For specific targets, the majority of mechanistic studies

have focused on endocrine disruption and neurological effects; however, definitive mechanisms underlying these effects have not been elucidated. For other effects, including reproductive toxicity, immunotoxicity, and hepatotoxicity, only limited mechanistic data are available. Mechanistic data relevant to toxic effects of PBDEs are reviewed below.

General Mechanisms of Toxicity. PBDEs share some toxicological properties with other structurally similar polyhalogenated aromatic compounds, particularly PBBs, PCBs, PCDDs, and PCDFs (ATSDR 1994, 1998, 2000). Although these chemicals are structurally similar in two dimensions, PBDEs (and polychlorinated diphenyl ethers or PCDEs) differ from the other classes on a three-dimensional basis. In particular, the oxygen bridge of the ether linkage in the diphenyl ether molecule increases the distance between the biphenyl rings, introduces a 120° bend in the alignment of the biphenyl rings, and serves as a barrier to rotation that inhibits the two aromatic rings from assuming a coplanar configuration (Hardy 2002a; Howie et al. 1990). Furthermore, halogen substitution of the *ortho* positions in the diphenylether molecule, as occurs for some congeners, pushes the aromatic rings to be orthoganol to each other (i.e., offset by 90°) (Hardy 2002a). Because the toxicity of TCDD and related compounds is related to their ability to assume a coplanar configuration for binding to AhR, this suggests that PBDEs are unlikely to display similar toxic potency (Hardy 2002a). Assays conducted by Chen et al. (2001) to compare AhR binding affinity and EROD activity of PBDE congeners and mixtures found that activities were very low relative to TCDD and related compounds, but also that, unlike for PCBs, AhR binding affinity was not correlated with planarization energies of the congeners (the calculated energy needed to force coplanarity of the PBDE molecule). The researchers speculated that the large size of the bromine atoms may distort the AhR binding site so that coplanar configuration is not required. However, even in studies of chlorinated analogs (PCDEs), it was found that increasing *ortho* substitution is less effective in decreasing the activity of these congeners than for PCBs (Howie et al. 1990). The authors attributed this difference to the increased bond length between the phenyl rings in PCDEs relative to PCBs.

In other words, the ether bridge makes PBDEs more non-coplanar in nature, which reduces AhR binding affinity relative to similar compounds, but also less sensitive to the influence of *ortho* substitutions that inhibit AhR binding of PBBs or PCBs. This has implications not only for dioxin-type toxicities, which are mediated by the AhR pathway, but also for non-dioxin-type effects. For example, Chen et al. (2001) found that the induction of CYP1A1 by PBDEs is AhR-mediated, as it is for numerous organochlorines, even though PBDEs do not readily adopt the coplanar conformation usually considered characteristic of AhR ligands. Structure-activity relationships have been incompletely elucidated for non-dioxin-like effects of PBDEs such as neurotoxicity. However, based on limited available data, it can be speculated

that di-*ortho*-substituted PBDEs might follow the neurotoxic potency of *ortho*-PCBs (Eriksson et al. 2002b; Kodavanti and Derr-Yellin 2002; Mariussen and Fonnum 2002, 2003).

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

The enzyme induction properties of PBDEs have been studied to a lesser extent than the enzyme induction properties of other structurally similar chemicals. Existing information suggests that PBDEs can be classified as mixed-type inducers of hepatic microsomal monooxygenases, although the mixed induction properties of the commercial mixtures are likely due to contamination with polybrominated-*p*-dibenzodioxins (PBDDs) and polybrominated dibenzofurans (PBDFs) (Darnerud et al. 2001; de Wit 2002; Hardy 2002b). Few studies have examined the structure-induction relationships for PBDEs. Chen et al. (2001) examined the ability of 12 PBDE congeners and 3 commercial mixtures to induce EROD activity in chick and rat hepatocytes, in liver cell lines from rainbow trout, rat, and human, and in a human intestinal cell line. The number of bromine substitutions in the congeners tested ranged from 3 to 7. In all cell types, BDE 77, 2,2',4,4',6-pentaBDE, BDE 66, and BDE 126 were the strongest inducers. BDE 153 and 2,2',3,4,4',5',6-heptaBDE were weak inducers in all cell types, whereas BDE 66 and BDE 85 were very weak inducers in rat hepatocytes and inactive in the other cells. BDE 47 and 2,2'4,4',5-pentaBDE, which are prominent in the environment, were not inducers in any cell line, and neither were BDE 28, 2,2',4,4',5,6'-hexaBDE, or the penta-, octa-, or decaBDE mixtures. For those congeners that had measurable EROD induction activity, their relative potencies were 10^{-3}–10^{-6} that of 2,3,7,8-TCDD. In general, the EROD induction activity paralleled the strength of the AhR binding with the notable exception of BDE 85, which despite its relatively strong AhR binding affinity (see above), showed no evidence of activating the AhR to its DRE binding form and was only a weak EROD inducer.

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

For example, Meerts et al. (1998) indirectly examined the AhR-mediated (dioxin-like) properties of 17 PBDE congeners in a recombinant H4II rat hepatoma cell line showing AhR-mediated expression of a luciferase reporter gene. The tested congeners varied from dibromo- to heptabromo- substituted compounds, and with the exception of BDE 15 and BDE 77, all had at least one *ortho* substitution. Seven of the congeners showed luciferase expression, indicating their ability to activate the AhR. The only discernable pattern of receptor activation that appeared to emerge from these results was that greater receptor activation was obtained with the penta- and hexaBDEs than with tri- and tetraBDEs.

Another study also examined the AhR induction potency of PBDE congeners using the *in vitro* luciferase assay with H4IIE-luc recombinant rat hepatoma cells (Villeneuve et al. 2002). Only 1 of 10 tested congeners (BDE 126) induced a significant response for AhR-mediated gene expression in the H4IIE-luc cells, but the magnitude of induction was 87% less compared with the response induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). With the exception of BDE 105, which induced a response of 1.7% of the TCDD maximum, no other congener, including the environmentally prominent congeners, BDE 47, BDE 99, and BDE 153, yielded a response greater than 1% of TCDD. Overall, the tested PBDE congeners were at least 200,000 times less potent than TCDD for inducing AhR-mediated gene expression in this test system. Using the same test system (H4IIE-luc recombinant rat hepatoma cells), Behnisch et al. (2003) reported AhR activities 5–6 orders of magnitude lower than TCDD for BDE 77, BDE 105, BDE 126, BDE 119, BDE 190, and BDE 209; BDE 47, BDE 66, BDE 85, BDE 99, BDE 100, BDE 153, and BDE 183 were inactive. Similarly, Hamers et al. (2006) reported AhR activities 6 orders of magnitude lower than TCDD for 7/19 PBDE congeners tested (BDE 38, BDE 49, BDE 79, BDE 99, BDE 181, BDE 183, and BDE 190), as well as the hydroxylated metabolite, 6OH-BDE-47. In another study, several hydroxylated and methoxylated PBDEs (19 out of 34 tested) were also shown to activate the AhR receptor in the H4IIE-luc assay, with potencies 4–12 orders of magnitude less than TCDD (Su et al. 2012).

Chen et al. (2001) studied the affinities of a series of 18 PBDE congeners and 3 commercial PBDE mixtures for rat hepatic AhR by using competitive AhR-ligand and EROD induction assays. The analysis

showed that both the congeners and octa- and pentaBDE commercial mixtures had binding affinities of 10^{-2}–10^{-5} times that of 2,3,7,8-TCDD. The congener with the highest affinity among the tested congeners was BDE 85, although its relative binding affinity was only 2% that of 2,3,7,8-TCDD. No binding activity could be determined for the decaBDE mixture. In contrast with PCBs, the binding affinities did not appear to relate to the planarity of the molecule, which according to Chen et al. (2001), was possibly due to the fact that the large size of bromine atoms expands the receptor binding site. The dioxin-like activity of the PBDE congeners and commercial mixtures was subsequently more completely characterized, by determining whether they act as AhR agonists or antagonists at sequential stages of the AhR signal transduction pathway leading to CYP1A1 expression in rat hepatocytes (Chen and Bunce 2001). BDE 77, BDE 119, and BDE 126 were moderately active towards dioxin-response element (DRE) binding and induced responses of both CYP1A1 mRNA and CYP1A1 protein analogous to the maximal response of TCDD, although at concentrations 3–5 orders of magnitude greater than TCDD. These congeners showed additive behavior towards DRE binding with TCDD (i.e., an increased response compared to TCDD alone), whereas most of the other congeners antagonized the action of TCDD. BDE 100, BDE 153, and BDE 183 were very weak activators of DRE binding, and other congeners and the three commercial BDE mixtures were inactive. In particular, the environmentally prominent congeners BDE 47 and BDE 99 were among the least active with respect to dioxin-like behavior (i.e., were inactive at all stages of signal transduction), and the commercial pentaBDE mixture had negligible EROD induction activity. The PBDE congeners that bound most strongly to the AhR were also the strongest inducers of CYP1A1 mRNA and CYP1A1 protein, indicating that the induction of CYP1A1 was AhR-mediated. Considering all of the end points evaluated in the Chen et al. (2001) and Chen and Bunce (2001) studies, it was concluded that the relative induction potencies (REPs) of the most active PBDEs toward CYP1A1 are $\approx 10^{-4}$ that of TCDD, which is similar to some mono-*ortho*-PCBs and two orders of magnitude less than those of coplanar PCBs, but the REPs for the environmentally prominent congeners are essentially zero. Consistent with these findings, Behnisch et al. (2003) also reported REPs of 10^{-4}–10^{-6} that of TCDD for BDE 25, BDE 77, BDE 100, BDE 126, and BDE 183 in the H4IIE-EROD bioassay, while BDE 154, BDE 99, BDE 47, and BDE 28 were inactive.

Mechanism of Endocrine Disruption. PBDE-induced endocrine disruption is likely to involve multiple mechanisms, including altered synthesis/clearance, transport, and/or receptor binding of endocrine hormones.

The apparent lack of effect of PBDEs on serum TSH suggests that direct effects on the thyroid leading to inhibition of T_4 synthesis are unlikely. However, Wu et al. (2016) present *in vitro* data that BDE 47

inhibits iodide uptake in rat thyroid follicular FRTL-5 cells via non-competitive inhibition of the sodium/iodide symporter (NIS). Additionally, mRNA expression levels of thyroid peroxidase (TPO) was decreased by BDE 47. Together, NIS and TPO are considered critical molecules in thyroid hormone synthesis, and are targets of many thyroid disruptors (e.g., perchlorate and thiocyanate) (Wu et al. 2016). No additional data regarding the potential for PBDEs to interfere with thyroid hormone synthesis were located.

PBDEs are hepatic microsomal enzyme inducers, but there is little evidence that increased enzyme activity leads to greater clearance of thyroid hormones. The induction of hepatic UDPGT by PBDEs has been demonstrated in several studies (Fowles et al. 1994; Hallgren and Darnerud 2002; Hallgren et al. 2001; Skarman et al. 2005; Stoker et al. 2004; Szabo et al. 2009; Zhou et al. 2001, 2002) and this could increase the UDPGT-catalyzed deactivation and excretion of T_4 (i.e., the conjugation of T_4 with glucuronic acid). An indication that increased UDPGT activity may not be the main mechanism for the reduced T_4 levels is provided by Hallgren et al. (2001), who found that exposure to ≥18 mg/kg/day pentaBDE for 14 days caused serum T_4 reductions in both mice and rats with no effect on UDPGT activity in the mice, and increased UDPGT in the rats only at higher dose levels. In contrast, the decreases in serum T_4 correlated with the induction of microsomal phase I enzymes (EROD and MROD). Increased microsomal enzyme activity (discussed above) could also increase the formation of hydroxylated PBDE metabolites that can bind to T_4 plasma transport proteins. This would serve to increase the number of occupied sites on T_4-binding proteins and subsequently result in decreased serum levels of T_4; however, this mechanism is not fully elucidated.

Several studies have demonstrated that PBDE metabolites compete with T_4 for binding thyroid hormone transport proteins (TTR, thyroxine-binding globulin [TBG]). Meerts et al. (1998, 2000) tested 17 PBDE congeners and 3 hydroxylated PBDEs for possible interaction with T_4 binding to human TTR, a plasma transport protein of thyroid hormones, in an *in vitro* competitive binding assay. None of the pure congeners competed with T_4 for binding to human TTR without metabolic activation. Incubation of the congeners with rat liver microsomes induced by PB (CYP2B enriched), β-napthoflavone (CYPIA enriched), or clofibrate (CYP4A3 enriched) indicated that 9 of the 17 pure congeners generated metabolites (not identified) that were able to displace T_4 from TTR (>60% competition): BDE 15, BDE 28, BDE 30, BDE 47, BDE 51, BDE 75, BDE 77, BDE 100, and BDE 119. Testing of the three known hydroxylated PBDEs, used for their structural resemblance with the thyroid hormones 3,5-diiodothyronine (3,5-T_2), 3,3',5-triiodothyronine (T_3), and 3,3',5,5'-tetraiodothyronine (T_4) showed that the T_4-like (2,6-dibromo-4-[2,4,6-tribromophenoxy]phenol) and T_3-like (2-bromo-4-[2,4,6-tri-

bromophenoxy]phenol) hydroxylated PBDEs were 1.42- and 1.22-fold more potent, respectively, than T_4; the T_2-like hydroxylated PBDE (4-[2,4,6-tribromophenoxy]phenol) showed low affinity for TTR (0.41-fold less potent than T_4). Consistent with these findings, Hamers et al. (2006) reported that 6OH BDE-47, but none of the 19 PBDE congeners, competed with the natural ligand T_4 for TTR binding (4-fold less potent than T_4). Additionally, Ren and Guo (2012) reported that 5 of the 11 OH-PBDEs tested bound to TTR with 1.2–2-fold greater potency than T_4 and 1 of the 11 OH-PBDEs tested bound to TBG with 1.5-fold greater potency than T_4. In another study, all OH-PBDEs tested were considered strong binders of TTR (relative potency compared with T_4 between 0.1 and 1) and moderate-to-strong binders of TBR (relative potency compared with T_4 between 0.01 and 1), including 3-OH-BDE 47, 5-OH-BDE 47, 6-OH-BDE 47, 4-OH-BDE 49, and 6-OH-BDE 99 (Marchesini et al. 2008). Parent compounds (BDE 47, BDE 49, BDE 68, and BDE 99) and MeO-PBDEs (6-MeO BDE 57, 2'-MeO-BDE 68) showed no-to-weak binding (<0.01 relative potency compared with T_4). Marsh et al. (1998) tested the affinity of 4'-hydroxyl derivatives of 1,3,5-triBDE, 1,3,3',5'-tetraBDE, and 1,3,3',5,5'-pentaBDE were tested for human thyroid hormone receptor subunits THR-α and THR-β *in vitro*. These congeners were tested because they theoretically show the highest structural similarity to T_4 and T_3. None of the hydroxylated derivatives effectively competed with the thyroid hormones for binding to either receptor (affinities were 41–>1,000 times less than for T_4 and T_3).

Studies also suggest that PBDEs and/or their metabolites can alter thyroid hormone binding to thyroid receptors. In a reporter gene assay in Chinese hamster ovary (CHO) cells, 4OH-BDE-90 was antagonistic to both THR-α and THR-β receptors, with a potency 2-fold less potent in the THR-α assay and ~30% more potent in the THR-β assay than the reference compound tetrabrominated bisphenol A (TBBPA) (Kojima et al. 2009). However, receptor antagonism was not observed for the other three OH-PBDEs tested (4OH-BDE-17, 4OH-BDE-42, 4OH-BDE-49) or any of the eight PBDEs or four MeO-PBDEs tested (Kojima et al. 2009). In another reporter gene assay in fibroblast-derived CV-1 cells, T_3-dependent THR-α- and THR-β-responsive gene expression was decreased by BDE 100, BDE 153, BDE 154, BDE 290, and DE-71 in fibroblast-derived CV-1 cells by 35–45% (Ibhazehiebo et al. 2011). Thyroid responsive element (TRE) dissociation from TRs was also significantly increased by BDE 100, BDE 154, and BDE 290 by 30–45%; however, no changes in THR-α and THR-β cofactor recruitment were observed for 11 PBDEs, 2 OH-PBDEs, or DE-71 (Ibhazehiebo et al. 2011). In contrast, in a THR-α and THR-β cofactor recruitment assay, 4 of the 10 OH-PBDEs tested were TR agonists (2OH-BDE-28, 3OH-BDE-28, 5OH-BDE-47, 6OH-BDE-47), showing 70–90% of the maximal response induced by T_3 (Ren et al. 2013).

In general, lower-brominated PBDEs, and their hydroxylated (OH-PBDEs) and methoyxylated (MeO-PBDEs) metabolites, show estrogenic activities 5–7 orders of magnitude lower than the natural ligand 17β-estradiol (E2) in reporter gene assays, and higher-brominated PBDEs and their metabolites show anti-estrogenic activities that are 1–6 orders of magnitude lower than reference antiestrogenic compounds (Hamers et al. 2006; Kojima et al. 2009; Li et al. 2013b; Meerts et al. 2001; Mercado-Feliciano and Bigsby 2008b). A good correlation has been shown between estrogenic activity and ER binding affinity of low-brominated PBDEs (Li et al. 2013b; Mercado-Feliciano and Bigsby 2008b). One study reported no estrogenic activity in an ER-dependent gene transcriptional activation assay for "PBDEs" in human HeLa 9903 cells stably transfected with the human ERα receptor; however, the specific congener(s) were not identified (Kim et al. 2011b).

For two OH-PBDEs that have bromine substitution patterns similar to the thyroid hormones T_2 [3,5-diiodothyronine] and T_3 [3,3',5-triiodothyronine] (i.e., 4-(2,4,6-tribromophenoxy)phenol and 2-bromo-4-(2,4,6-tribromophenoxy) phenol, respectively), estrogenic activities were 2–10 times more potent than E2 (Meerts et al. 2001). The T_2-like hydoxylated PBDE 4-(2,4,6-tribromophenoxy)phenol also showed estrogenic activity in ERα- and ERβ-like human embryonic kidney cells, with maximum inductions of 50–95% of the maximum induction by E2 (Meerts et al. 2001).

Estrogenic effects were also demonstrated using cell proliferation assays in breast cancer cells exposed to the commercial pentaBDE mixture DE-71 (Mercado-Feliciano and Bigsby 2008b). Basal cell proliferation was significantly increased by up to 10-fold with DE-71 exposure (compared with increases up to 15-fold with exposure to the natural ligand E2). Co-exposure of cells to DE-71 and E2 significantly decreased proliferation relative to E2-only exposure in a concentration-dependent manner, suggesting an antagonistic effect of DE-71 on E2-induced cell proliferation (Mercado-Feliciano and Bigsby 2008b). However, neither basal nor E2-induced cell proliferation were altered in breast cancer cells exposed to BDE 47, BDE 99, BDE 100, or BDE 209 (Kwiecińska et al. 2011). Caspase-9 activity (apoptotic marker) was significantly decreased by ~40–60% in tests with all congeners compared with decreases of ~25% with exposure to E2 (Kwiecińska et al. 2011).

Estrogenic effects have also been reported in other *in vitro* and *in vivo* assays, including increased uterine mRNA expression of ERα and ERβ in adult female offspring of rats given subcutaneous injections of BDE 99 at 1 mg/kg/day (but not 10 mg/kg/day) from GD 10 to 18 (Ceccatelli et al. 2006); increased uterine mRNA and protein levels of calbindin-D9k, a biomarker for estrogenic compounds, in immature female rats exposed to BDE 47 at 50–200 mg/kg/day from PND 16 to 18 (Dang et al. 2007); increased

gene and protein expression of ERα and ERβ in porcine ovarian follicles by 5-OH-BDE-47 and 6-OH-BDE-47 (Karpeta et al. 2014); inhibition of E2 metabolism in rat liver microsomes by 11 OH-PBDEs and 1 MeO-BDE (Lai and Cai et al. 2012); inhibition of E2 sulfation (E2SULT) in V79 cells by 6-OH-BDE-47, BDE 19, BDE 47, and BDE 49 (Hamers et al. 2006); and increased production of vitellogenin in trout hepatocytes exposed to BDE 47, BDE 99, or BDE 205 (Nakari and Pessala 2005). However, estrogenic effects were not observed with exposure to BDE 47, BDE 99, or BDE 205 in recombinant yeast assays with human estrogen receptor (hER) (Nakari and Pessala 2005). In a human cohort study, total serum PBDE in adult females were positively associated with ERα and ERβ mRNA expression levels in the blood; however, BDE 47 serum levels were negatively associated with ERα and ERβ mRNA expression levels (Karmaus et al. 2011). Similarly, ERβ gene and protein expression were decreased in porcine ovarian follicles exposed go BDE 47; however, no change was observed in ERα gene or protein expression levels (Karpeta et al. 2014).

Anti-androgenic and anti-prostagenic activity was observed in reporter gene assays in human osteoblast cells following exposure to 16 different PBDE congeners, 6OH-BDE-47, and 2 commercial PBDE mixtures (DE-71, Octa LM) (Hamers et al. 2006). The most potent antiandrogens, BDE 19 and BDE 100, were 21 and 13 times less potent than the reference antiandrogenic drug flutamide. BDE 19 was also the most potent antiprostagen, and was 3 orders of magnitude lower in potency than the reference compound RU-486 (Hamers et al. 2006). Neither antiandrogenic nor antiprogestagenic activity were observed for BDE 169, BDE 206, or BDE 209 (Hamers et al. 2006). Antiandrogenic activity was also observed in two of five PBDEs tested (BDE 47, BDE 100) and the commercial pentaBDE mixture DE-71 tested in human breast cells (Stoker et al. 2005), and in five of eight PBDEs tested, three of four OH-PBDEs tested, and four of four MeO PBDEs (all low-brominated) tested in CHO cells (Kojima et al. 2009). In contrast, Christen et al. (2010) reported that BDE 100 and BDE 155 enhanced DHT-dependent activation of androgen receptor (AR)-responsive gene expression in human breast cells (no other congeners tested). However, findings were not concentration-dependent, with the greatest enhancement (~50%) at 10 nM (highest concentration used was 10 μM) (Christen et al. 2010). This suggests that very low concentrations of PBDEs may be androgenic, while higher concentrations appear to be antiandrogenic. No changes in AR gene or protein expression were observed in porcine ovarian follicular cells exposed to BDE 47, 5-OH-BDE-47 or 6-OH-BDE-47 (Karpeta et al. 2014). Anti-progestagenic activity was also observed in an *in vivo* study, where adult female offspring of rats given subcutaneous injections of PBDE 99 at 1 or 10 mg/kg/day from GD 10 to 18 had significantly decreased uterine mRNA expression levels of progesterone receptor (Ceccatelli et al. 2006).

The ability of the commercial pentaBDE mixture DE-71 and the pure congeners, BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 to compete with 1.0 nM [^{3}H]R1881 for binding to the rat AR was evaluated using a cytosolic extract prepared from rat ventral prostate tissue (Stoker et al. 2005). Relative binding curves suggested that all of the compounds competed with [^{3}H]R1881 for binding to the AR, with inhibition up to 80 and 98% for DE-71 and BDE 100, respectively. In order to determine if this inhibition was competitive, additional *in vitro* binding tests for BDE 100 were conducted to calculate the inhibition constant (K_i). These experiments showed that BDE 100 was a competitive inhibitor with a K_i value of 1 μM (Stoker et al. 2005).

Anti-glucocortogenic activity was observed in 3/8 PBDEs (PBDE 85, PBDE 99, PBDE 100), 2/4 OH-PBDEs (4OH-BDE-17, 4OH-BDE-49), and 1/4 MeO-PBDEs (4MeO-BDE-49) in a glucocorticoid receptor-mediated reporter gene assay with CHO cells (Kojima et al. 2009). Anti-glucocortogenic potencies were 3 orders of magnitude lower than for the reference compound RU-486.

In summary, the mechanistic studies show that PBDEs and/or their metabolites are capable of acting as thyroid hormone transporters or receptors and are weakly estrogenic, anti-androgenic, anti-prostagenic, and anti-glucocortogenic. However, these findings were not always consistent between different congeners, metabolites, and studies. Therefore, mechanisms of endocrine disruption by PBDEs have not been fully elucidated.

Mechanisms of Neurotoxicity. As detailed in Section 3.2.2.4 Neurological Effects, developmental exposure to PBDEs has been associated with altered neurodevelopment and behavior later in life in both humans and animals. The mechanisms for these behavioral and cognitive effects have not been elucidated; however, proposed mechanisms include neuroendocrine disruption (including altered thyroid hormone homeostasis), alterations in neurotransmitter systems (cholinergic, dopaminergic, glutamatergic, and/or gabaergic), altered calcium homeostatic mechanisms, altered intracellular communication, oxidative stress, and cell death. Additionally, monohydroxylated metabolites are more potent than the parent BDE in several of the mechanistic assays, suggesting that bioactivation by oxidative metabolism contributes to the neurotoxic potential of PBDEs.

Since altered thyroid hormone levels have been reported in both animals and humans (see Section 3.2.2.2 Systemic Effects, Endocrine subsection), one possible mechanism of neurotoxicity involves the well-documented key role of thyroid hormones in brain development. In support of this mechanism, BDE 99 down-regulates the transcription of the thyroid receptors α1 and α2 (TRα, TRα2) in cultured rat cerebellar

granular cells, leading to disruption in the expression of T_3-mediated genes, including decreased brain-derived neurotrophic factor (BDNF) (Blanco et al. 2011). BDE 99 and hydroxylated PBDE metabolites (3-OH-BDE-47, 6-OH-BDE-47, and 5'-OH-BDE-99) have also been shown to significantly decrease the activity of the selenodeiodinase type 2 iodothyronine deiodinase (DIO2), which converts T_4 to T_3 in the brain, in primary human astrocytes and H4 glioma cells; BDE 47 did not affect DIO2 activity (Roberts et al. 2015). Decreased DIO2 activity associated with exposure to BDE 99 and OH-PBDEs was attributed to multiple mechanisms, including observed downregulation of *DIO2* mRNA, competitive inhibition of DIO2, and enhance post-translational degradation of DIO2. Ibhazehiebo et al. (2011) showed that the TR-antagonist, BDE 209 (see *Mechanisms of Endocrine Disruption* section above), inhibits T_4-induced dendritic arborization in cultured rat cerebellar Purkinje cells. However, BDE 47, which was not found to be a TR-antagonist (see *Mechanisms of Endocrine Disruption* section above), did not alter dendritic arborization (Ibhazehiebo et al. 2011). Study authors indicate that other PBDEs and OH-PBDEs were evaluated for dendritic developmental effects; however, results were not reported (Ibhazehiebo et al. 2011). Additionally, Schreiber et al. (2010) showed that reduced migration and differentiation observed in cultured fetal human neural progenitor cells (hNPCs) following exposure to BDE 47 and BDE 99 was prevented with co-exposure to T_3. These findings indicate that *in vitro* neurodevelopmental changes were due to disruption of cellular thyroid hormone signaling. However, BDE 209 did not significantly interfere with the T_3-mediated response in either a human embryonic kidney reporter cell line expressing mouse TRα (HEK293-Gal4TRα) or a mouse cerebellar neural reporter cell line expressing TRα (C17.2α-HRLuc), with or without metabolic activation (Guyot et al. 2014). Preliminary studies also did not show altered T_3-mediated responses in C17.2α-HRLuc cells incubated with a commercial PBDE mixture (BDE-CM, AccuStandard, Inc.; according to manufacturer datasheet, the mixture contains equal parts BDE 28, 47, 99, 100, 153, 154, 183, and 209) (Guyot et al. 2014). Additionally, only slight, but statistically significant, changes were observed in the expression of T_3-responsive genes in C17.2α cells following exposure to BDE 209 and T_3, compared with T_3 exposure alone (Guyot et al. 2014).

Some studies suggest that the neurological effects of PBDEs might be related to alterations in cholinergic functions. For example, neonatal exposure to a single oral dose of BDE 99 (8 mg/kg) on PND 10 or a single oral dose of BDE 209 (≥5.76 mg/kg) on PND 3 altered the behavioral response to cholinergic agents (nicotine or paraoxen) in adult mice (Buratovic et al. 2014; Johansson et al. 2008; Viberg et al. 2002, 2007). Neonatal exposure to nicotine and adult exposure to BDE 99 (single 8 mg/kg oral dose at age 5 months) also affected behavior in mice, although the change was not seen in mice only exposed to BDE 99 as adults or mice only exposed to nicotine as neonates (Ankarberg et al. 2001). Additionally, the densities of cholinergic nicotinic receptors in the brain hippocampus and/or cortex were decreased by 7–

31% in adult mice exposed once to BDE 99 or BDE 153 at ≥0.8 mg/kg on PND 10 (Fischer et al. 2008; Viberg and Eriksson 2011;Viberg et al. 2003a, 2004b, 2005) and increased transcription of cholinergic receptors nAchR-β2, AChR5, and nAChR-α4 were observed in the cortex of 2-month-old mice exposed to BDE 99 at 12 mg/kg on PND 10 (Hallgren et al. 2015). However, no exposure-related effects were observed in any cholinergic parameters in 6- or 27-week-old mink from mink sows exposed to dietary pentaBDE at 0, 0.01, 0.05, or 0.25 mg/kg/day from pre-mating day 28 to PNW 6 (Bull et al. 2007). In rat neuroendocrine pheochromocytoma (PC12) cells and rat neuroblastoma (B35) cells, BDE 209 significantly decreased the Ach-evoked response *in vitro* (Hendriks et al. 2014). Additionally, *in vitro* exposure to BDE 99 led to altered neurotransmitter phenotype differentiation in rat PC12 cells, resulting in a decreased number of cholinergic cells and a greater number of dopaminergic cells; this was not observed with exposure to BDE 47 (Dishaw et al. 2011; Slotkin et al. 2013). BDE 47 also did not modulate human $\alpha_4\beta_2$ nicotinic acetylcholine (nACh) receptor function (expressed in *Xenopus* oocytes); however, its hydroxylated metabolite, 6-OH-PBDE-47, was a nACh antagonist (Hendriks et al. 2010).

Other studies have reported alterations in the dopaminergic system. Alterations have been observed in the striatum of mice exposure to 30 mg/kg/day of the pentaBDE mixture DE-71 for 30 days via gavage, including reductions in dopamine levels, altered dopamine handling (i.e., altered dopamine breakdown into DOPAC and HVA), and reductions in the striatal dopamine transporter (DAT) and vesicularmonoamine transporter 2 (VMAT2) (Bradner et al. 2013). DE-71 also inhibited the *in vitro* uptake of the neurotransmitter dopamine into rat brain synaptic vesicles; however, inhibition was not observed with commercial mixtures of octaBDE (DE-79) or decaBDE (DE-83R) (Mariussen and Fonnum 2002, 2003; Mariussen et al. 2003). Similarly, DE-71 reduced synaptosomal dopamine concentrations and increased medium dopamine concentrations in striatal synaptosomes derived from PND 7–21 rats (Dreiem et al. 2010). However, in contrast to the cholinergic system, acute neonatal exposure to BDE 99 (12 mg/kg) on PND 10 did not significantly affect dopaminergic gene transcription in the cortex or hippocampus on PND 11 or at 2 months of age; genes evaluated included tyrosine hydroxylase (*TH*), *DAT*, and dopamine receptors D1, D2, and D5 (*DRD*1, *DRD*2, and *DRD*5) (Hallgren and Viberg 2016).

Additional evidence suggests that alterations in the glutamatergic system may also contribute to observed neurological effects following PBDE exposure. Neonatal exposure to BDE 209 via gavage doses of 20 mg/kg/day from PND 3 to 10 resulted in significant upregulation of NR1 mRNA in the frontal cortex and hippocampus of PND 11 and PND 60 mice, as well as decreased binding of the regulatory complex REST/NRST (Repressor Element Silencing Transcription Factor/Neuron-Restrictive Silencer Factor) to the NR1 promotor (Verma et al. 2015). Additionally, extracellular glutamate levels (along with oxidative

stress and cell death) were significantly elevated in cultured mouse cerebellar neurons following *in vitro* exposure to BDE 47 (Costa et al. 2016). Antagonists of ionotropic glutamate receptors, but not metabotropic, prevented BDE 47-induced oxidative stress and cell death, providing additional evidence for a role of glutamatergic signaling in PBDE neurotoxicity (Costa et al. 2016). In rats, exposure to BDE 47 at doses ≥0.1 mg/kg/day for 30 days via gavage resulted in altered mRNA expression of the glutamate receptor subunits NR(1), NR(2)B, and NR(2)C (Yan et al. 2012).

Limited evidence suggests that alterations in the gabaergic system may also contribute to observed neurological effects following PBDE exposure. A commercial pentaBDE mixture (DE-71) caused a slight inhibition of *in vitro* uptake of the neurotransmitter GABA into rat brain synaptic vesicles, but commercial mixtures of octaBDE (DE-79) or decaBDE (DE-83R) did not alter GABA uptake (Mariussen and Fonnum 2003). Additionally, the metabolite, 6-OH-PBDE-47, was a partial agonist for the human $GABA_A$ receptor expressed in *Xenopus* oocytes; however, its parent compound (BDE 47) did not modulate $GABA_A$ receptor activity (Hendriks et al. 2010).

Effects of PBDEs on the function and development of the nervous system could also involve disruption of calcium homeostatic mechanisms and intracellular signaling events. In human neural progenitor cells (hNPCs), *in vitro* exposure to BDE 47 or 6-OH-BDE-47 led to transient increases in intracellular Ca^{+2} levels due to increased influx of extracellular Ca^{+2} as well as intracellular release from the endoplasmic reticulum (Gassmann et al. 2014). Based on additional studies using multiple inhibitors/stimulators of presumably involved signaling pathways, the increase in extracellular influx appears to be due to interference with the cell membrane, rather than alterations of Ca^{+} ion channel dynamics, and the increased ER release was associated with activation of protein lipase C and inositol 1,4,5-trisphophate receptor, independent of the ryanodine receptors (Gassmann et al. 2014). A series of studies evaluated the effects of *in vitro* exposure to PBDEs and their metabolites on calcium homeostasis in rat PC12 cells (Dingemans et al. 2008, 2010a, 2010b). Collectively, these studies show that hydroxylated metabolites of PBDEs lead to increased basal Ca^{+2} levels due to Ca^{+2} release from the endoplasmic reticulum and mitochondria as well as decreased depolarization-evoked Ca^{+2} levels. BDE 47 was shown to have similar, but less potent effects, while no effects on calcium homeostasis were observed with BDE 49, BDE 99, BDE 100, BDE 153, or methylated metabolites (Dingemans et al. 2008, 2010a, 2010b). In a similar study, BDE 209 did not alter calcium homeostasis in rat PC12 or B35 cells (Hendriks et al. 2014). BDE 49, OH-BDE-47, and 4'OH-BDE-49 have also been shown to be potent modulators of ryanodine receptors type 1 and 2, which regulate essential aspects of Ca^{+2} signaling; BDE 47 was without activity in this assay (Kim et al. 2011c; Pessah et al. 2010). In culture systems, BDE 47 and BDE 209 were shown

to increased intracellular Ca^{+2} content in mouse cerebellar granule cells and rat neonatal hippocampal neurons, respectively (Chen et al. 2010; Costa et al. 2016). *In vitro* exposure to DE-71 or BDE 47 also stimulated arachidonic acid release in rat cerebellar granule neurons; this effect was not seen with DE-79 (Kodavanti 2003; Kodavanti and Derr-Yellin 2002). The release of arachidonic acid appeared to be mediated by the activation of both Ca^{+2}-dependent and Ca^{+2}-independent cytosolic phospholipase A_2. *In vitro* exposure to DE-71and BDE 47 also caused translocation of protein kinase C, as indicated by increased phorbol ester binding; DE-79 did not induce this effect (Kodavanti and Derr-Yellin 2002; Rao et al. 2003). Other effects of penta mixture DE-71 and tetra congener BDE 47 included decreases in intracellular calcium buffering by microsomes and mitochondria (Kodavanti and Derr-Yellin 2002). The tetra- congener BDE 47 was generally more potent than the DE-71 mixture (mainly comprised of tetra- and penta- congeners) in these tests. All commercial mixtures and congeners tested (DE-71, DE-79, BDE 47, BDE 77, BDE 99, BDE 153) elevated phosphorylated extracellular signal-regulated kinase (pERK) ½, with congeners having a greater effect than mixtures (Fan et al. 2010). pERK ½ is a widely studied MAPK cascade known to be involved in learning and memory.

Neurotoxicity may be mediated by cell death, perhaps in response to oxidative stress, as increased apoptosis and upregulation of apoptotic proteins and markers of oxidative have been observed in the hippocampus, cortex, and cerebellum of rats following developmental exposure to PBDEs (He et al. 2009; Chen et al. 2014; Cheng et al. 2009; Costa et al. 2015; see Section 3.2.2.6, Developmental Effects for more details). In support, ROS were increased in rat cerebellar granular cells exposed to 25 µM BDE 99, and this increase was correlated with a decrease in the gene expression of the anti-apoptotic protein Bcl-2 (Blanco et al. 2011). Another study found that DE-71 was more toxic than octa- and deca-congeners in inducing cell death and free radical formation in cerebellar granule cells (Reistad et al. 2002). In cultured rat cortical cells, a high concentration of BDE 99 (30 µM) induced cell death without any apparent increase in caspase-3 activity (Alm et al. 2008). BDE 47 also induced apoptosis in primary cultured rat hippocampal neurons; changes in oxidative stress parameters included increased ROS levels, malondialdehyde content, glutathione peroxidase levels and decreased glutathione and superoxide dismutase levels (He et al. 2008c). BDE 47-induced apoptosis in human SH-SY5Y was shown to be mediated via the mitochondrial p53 pathway, as evidenced by up-regulation of p53 and Bax, down-regulation of Bcl-2 and Bcl-2/Bax ratio, enhancement of Cyt c release from mitochondria into the cytosol, and activation of caspase-3, as well as by ultrastructural abnormalities of mitochondria (Zhang et al. 2013c). In mouse cerebral granule cells, PBDE exposure caused decreased cell viability, induced apoptotic cell death, and increased ROS and lipid peroxidation following exposure to BDE 47, BDE 99, BDE 100, BDE 153, and BDE 209 (Costas et al. 2015, 2016; Huang et al. 2010). Huang et al. (2010)

reported a congener potency ranking of BDE 100 > BDE 47 > BDE 99 > BDE 153 >> BDE 209. Similarly, in cultured rat neonatal hippocampal neurons, BDE 209 decreased cell viability and increased the rate of apoptosis, ROS levels, malondialdehyde (MDA) content, and NO content (MAPKs) (Chen et al. 2010). In rat B35 cells, increased ROS generation in the absence of decreased cell viability was observed following exposure to BDE 209; no changes in ROS generation or cell viability were observed in rat PC12 cells (Hendriks et al. 2014).

Proteomic and genomic studies have identified multiple systems/pathways in the brain that can be altered following PBDE exposure; however, strong conclusions regarding mechanisms of neurotoxicity from these studies cannot be made at this point. In laboratory animals, *in vivo* exposure to ≥12 mg/kg/day of DE-71, BDE 99, BDE 203, BDE 206, or BDE 209 for 1–30 days has been shown to alter expression of proteins involved in mediating GABA and glutamate neurotransmission in the frontal cortex; neuronal survival, growth, and synaptogenesis in the cortex, hippocampus, cerebellum, and striatum; cytoskeletal proteins in the cortex and hippocampus; oxidative stress and apoptosis in the cerebellum and hippocampus; and metabolism and energy production in the hippocampus and cerebellum (Alm et al. 2008, 2006; Buratovic et al. 2014; Bradner et al. 2013; Kodavanti et al. 2015; Verma et al. 2015; Viberg 2009a, 2009b; Viberg and Eriksson 2011; Viberg et al. 2008). In mice exposed to 0.45 mg/kg/day for 28 days, combined analysis of proteomic and genomic data using biological network analysis indicated disturbances in the following functional categories: nervous system development and function, neurological disease, and behavior (Rasinger et al. 2014). Gene ontogeny analysis showed significant changes in mitochondrion morphogenesis, Wnt receptor signaling pathway, L-glutamate transport, and calcium ion transport into cytosol, while proteomics identified differential expression of dynamin 1, calcium/calmodulin-dependent protein kinase II delta, and alpha 4a tubulin (Rasinger et al. 2014). In culture systems, proteomic analysis of neonatal hippocampal neural stem/progenitor cells following exposure to BDE 47 and/or BDE 209 showed differential expression of 19 proteins, including proteins involved in metabolism, signal transduction, transcription, transport, and cell structures (Song et al. 2014). Key proteins showing downregulation were cofilin-1, which is associated with cell cycle and neuronal migration, and vimentin, which is implicated in nervous system repair mechanisms.

Epigenetic changes may also contribute to neurotoxicity following exposure to PBDEs. Byun et al. (2015) examined this hypothesis in mice exposed perinatally to BDE 47 by evaluating DNA methylation patterns in mitochondrial genes involved in respiration (cytochrome c oxidase I, II, and III), nuclear genome methylation markers (5hmc, L1Rn), and nuclear candidate genes related to behavioral and brain functions (BDNF, corticotropin releasing hormone receptor 1, melanocortin 2 receptor, nuclear receptor

subfamily 3 group C member 1, and alpha-synuclein). Significant changes in methylation were not observe in DNA methylation patterns for the majority of genes examined, although slight (<2-fold), but statistically significant, methylation decreases were observed in cytochrome c oxidase II, L1Rn, BDNF, and nuclear receptor subfamily 3 group C member 1 (NR3CL) in mice exposed to BDE 47, compared with control (Byun et al. 2015). However, global DNA methylation was significantly decreased in female, but not male, offspring of mouse dams exposed to tetraBDE from premating day 28 to PND 21 (Woods et al. 2012).

Mechanisms of Reproductive Toxicity. As discussed above (see *Mechanisms of Endocrine Disruption*), PBDEs have been shown to be weakly estrogenic and anti-androgenic. Additionally, altered steroidogenesis has been observed *in vitro.* Limited data are available regarding other potential mechanisms of reproductive toxicity, such as altered placental function due to increased prostaglandin synthesis and impaired mitochondrial function in sperm cells.

Testosterone secretion was increased by up to 3-fold in cultured rat Leydig cells exposed to a mixture of tetra- and pentaBDEs (PBDE-710) (Wang et al. 2011c) or BDE 47 alone (Zhao et al. 2011). These studies suggest that PBDEs may stimulate testosterone secretion by acting directly on Leydig cells to activate the cAMP pathway and increased expression of steroidogenic acute regulatory protein (StAR), as evidence by increased gene and protein expression of StAR (Wang et al. 2011c, Zhao et al. 2011) as well as increased intracellular levels of cAMP, increased PKAα nuclear translocation, and increased activity of CYP 11A1 (Wang et al. 2011c). In support, the observed increase in testosterone secretion was blocked in the presence of the adenylyl cyclase inhibitor SQ22536 (Wang et al. 2011c). However, gene expression of StAR was not upregulated in mouse Leydig cells exposed to BDE 47 (testosterone secretion was not evaluated) (Schang et al. 2016).

Testosterone production was also significantly increased by ~2–4.5-fold in porcine ovarian follicles exposed *in vitro* to BDE 47, BDE 99, or BDE 100 (Karpeta et al. 2011). Androstenedione (A4) and progesterone production was also significantly increased, but responses were not concentration-dependent. No exposure-related changes were observed in E2 production. Potential mechanisms underlying increased testosterone production were judged to be congener-specific. For BDE 47, observed increases in 17β-HSD protein expression and activity and decreases in CYP19 (aromatase) activity suggest that increased testosterone production is due to increased conversion of A4 to testosterone by 17β-HSD and decreased conversion of testosterone to E2 by CYP 19. For BDE 100, observed increases in CYP17 protein expression and activity and decreases in CYP19 activity suggest increased testosterone

production is due to increased conversion of progesterone to A4 by 17β-HSD (which is later converted into testosterone) and decreased conversion of testosterone to E2 by CYP 19. BDE 99 did not alter protein expression or activity of 17β-HSD, CYP 17, or CYP 19. The study authors suggest that the mechanism of action for BDE 99 is prior to the secretion of progesterone (i.e., StAR or 3β-HSD). In contrast, OH-PBDEs (5OH-BDE-47, 6OH-BDE-47) did not alter testosterone or A4 production in porcine ovarian follicles; however, E2 production was significantly increased for both metabolites by 2.4–2.9-fold (Karpeta et al. 2013). Additionally, the OH-PBDEs increased protein expression and activity of CYP 19, suggesting that the increase in E2 may be due to increased aromatase-mediated conversion of testosterone to E2. Similarly, changes in E2 secretion in mid-phase porcine luteal cells (increased) and late-phase porcine luteal cells (decreased) following *in vitro* exposure to BDE 47 was significantly correlated with CYP 19 activity, although neither 5-OH-BDE-47 nor 6-OH-BDE-47 altered E2 secretion (Gregoraszczuk et al. 2015). In an *in vivo* study, CYP 19 activity in the ovaries of female rats was not altered with exposure to BDE 209 doses up to 60 mg/kg/day for 28 days via gavage; however, CYP 17 activity in the adrenal glands was significantly decreased by up to 97% in females, but not males (Van der Ven et al. 2008a).

Progesterone production was significantly increased by 1.3–2.1-fold in mid-phase porcine luteal cells exposed to BDE 47 (≥250 ng/mL) or BDE 99 (≥50 ng/mL) for 24 hours, but not 48 hours (Gregorasczuk et al. 2012). Exposure to BDE 100 did not alter progesterone levels at concentrations up to 500 ng/mL at either time point. Following exposure for 24 hours, cells exposed to BDE 99 also showed a significant increase in the activity and protein level of 3β-HSD (which converts pregnenolone into progesterone); no changes in protein levels or activity of CYP11A1 (which converts 25-hydroxycholesterol into progesterone) were observed for any congener. Increased gene expression of 3β-HSD was also observed in mouse Leydig cells exposed to BDE 47; however, no exposure-related changes were observed in progesterone secretion (Schang et al. 2016). Another study did not observe increased progesterone production in early-, mid-, or late-phase porcine luteal cells exposed to BDE 47 for 24 hours at doses up to 50 ng/mL (lower than the lowest effective dose in the previous study) (Gregorasczuk et al. 2015). However, metabolites of BDE 47 (5-OH-BDE-47 and 6-OH-BDE-47) significantly decreased progesterone secretion in mid- and late-phase cells, respectively; 6-OH-BDE-47 also significantly inhibited 3β-HSD activity in late-phase cells (Gregorasczuk et al. 2015). Gregorasczuk et al. (2012) also measured activity of caspases 3, 8, and 9 in porcine luteal cells collected during the middle luteal phase following exposure to BDE 47, 99, or 100. Increased activation of both intrinsic (caspase 9) and extrinsic (caspase 8) apoptotic pathways was observed at 24 hours, with additional activation of caspase 3 at 48 hours, was observed with all congeners, indicating premature apoptosis of middle luteal cells

(apoptosis should occur during late luteal phase). The study authors proposed that the combined effects of altered steroidogenesis and premature apoptosis observed following *in vitro* exposure to PBDEs could negatively impact the estrous cycle by shortening the luteal phase, and potentially fecundability.

Several studies have also evaluated steroidogenesis in human adrenocortical carcinoma cells following exposure to PBDEs or their metabolites. The parent compound, BDE 47, did not alter testosterone, androstenedione, E2, pregnenolone, 17α-OH-pregnenolone, progesterone, or 17α-OH- progesterone levels in human adrenocortical carcinoma cells (van den Dungen et al. 2015). As observed in porcine follicular cells, increased E2 production accompanied by increased CYP 19 gene expression and activity was observed in human adrenocortical carcinoma cells following exposure to the methyoxylated metabolites 6Cl-2MeO-BDE-68 and 6MeO-BDE852/10 (He et al. 2008c). However, other tested metabolites (6Cl-2OH-BDE-7, 5Cl-6OH-BDE-47, 2MeO-BDE-28) showed decreased E2 production (He et al. 2008c). Testosterone production was increased by 2/10 tested MeO-PBDEs (6MeO-BDE85, 6MeO-BDE137), but 0/10 tested OH-PBDEs (He et al. 2008c). The activity of the steroidogenic enzyme CYP 19 was also evaluated in cultured H295R human adrenocortical carcinoma cells exposed to 19 PBDEs, 5 OH-PBDEs, and one methoxylated (MeO-)PBDE (Canton et al. 2005). Two low-brominated PBDEs (BDE 19, BDE 28) induced CYP 19 by 200%, while two higher-brominated PBDEs (BDE 206, BDE 209) inhibited CYP 19 by 61–64%. 6OH-BDE-99 and 6MeO-BDE-47 also inhibited CYP 19 by 46–67%. The 6OH-BDE-47 metabolite showed minimal inhibition accompanied by cytotoxicity. In another study evaluating 11 OH-PBDEs and 11 MeO-PBDEs, all OH-PBDEs inhibited CYP 19 (Canton et al. 2008). The most potent aromatase inhibitors were 6OH-BDE-49 and 3OH-BDE-47, which decreased CYP 19 activity by 54 and 27%, respectively. No CYP 19 inhibition was observed with the MeO-PBDEs.

Park and Loch-Caruso (2015) evaluated the effects of BDE 47 exposure on prostaglandin E2 synthesis in first trimester human extravillous trophoblast cells (HTR-8/SVneo), as prostaglandin E2 is a pro-inflammatory regulator of trophoblast cellular functions critical for successful placentation. Significantly increased prostaglandin E2 release was following *in vitro* exposure to BDE 47. mRNA expression of enzymes involved in prostaglandin synthesis and catabolism were also significantly altered, including increases in prostaglandin synthase 2 and COX-2 (rate-limiting enzyme of prostaglandin synthesis) and decreased 15-hydroxyprostaglandin dehydrogenase and prostaglandin E synthase. Prostaglandin changes were completely blocked following treatment with a COX-2 inhibitor, confirming that prostaglandin upregulation was COX-dependent. Additionally, significant ROS generation was observed following BDE 47 exposure. The peroxyl radical scavenger, α-tocopherol, blocked both ROS generation and

prostaglandin release; however, it had no effect on COX-2 mRNA levels. The study authors proposed that generation of ROS in the placenta following BDE 47 exposure stimulates prostaglandin E2 production via post-translational modifications of a COX-2-dependant pathway, and may lead to placental dysfunction (Park and Loch-Caruso 2015).

Following 8-week oral exposure to BDE 47, increased apoptosis was observed in early leptotene spermatocytes of adult male rats (Huang et al. 2015). Proteomic analysis of testicular tissue indicated differential expression of 64 proteins, including 20 proteins related to apoptosis. Of these 15/20 apoptotic proteins were located in the mitochondria. Protein expression data from cultured testicular mouse cells (GC1-spg cells) were consistent with *in vivo* results, showing significant decreases in Uqcrc1, Atp5b, Tufm, Sucla2, and Lap3, indicating mitochondrial dysfunction and apoptosis, and a significant decrease in the anti-apoptotic factor Bcl-2 (Huang et al. 2015).

Mechanisms of Immunotoxicity. As discussed in Section 3.2.2.3, Immunological and Lymphoreticular Effects, limited evidence from animal studies suggest that PBDEs may cause immunosuppression (Darnerud and Thuvander 1998; Feng et al. 2016b; Fowles et al. 1994; Watanabe et al. 2008, 2010b). Lundgren et al. (2009) suggested that decreased immune response to infection may be due to suppression of cytokines by PBDE exposure. In mice infected with human coxsackievirus B3 (CVB3), serum levels of IL-12, MIP-1β, RANTES, IFN-γ, and KC were markedly decreased (or completely lacking) in mice exposed to BDE 99 or Bromkal 70-5 DE (37% BDE 47, 35% BDE 99), compared with infected controls.

No information regarding potential mechanisms of immunotoxicity for PBDEs were located. Howie et al. (1990) examined the immunotoxic potencies of various polychlorinated diphenyl ether congeners on the inhibition of the plaque-forming splenic cell response to sheep red blood cell antigen in mice. The observed potency order (2,3,3',4,4',5-hexaCDE > 3,3',4,4',5-pentaCDE > 2,3',4,4',5-pentaCDE > 3,3',4,4'-tetraCDE > 2,2',4,4',5,5'-hexaCDE > 2,2',4,5,5'-pentaCDE > 2,2',4,4',5,6'-hexaCDE) generally paralleled the congener-specific potencies for induction of hepatic microsomal AHH and EROD. Worth noting is the fact that the resulting ranking order of potency did not follow the order that would have been expected for a response known to be AhR-mediated, such as the inhibition of the plaque-forming splenic cell response to challenge with sheep red blood cells antigen. For example, the laterally substituted congeners 3,3',4,4'-tetraCDE and 3,3',4,4',5-pentaCDE were less immunotoxic than their respective monoortho-substituted analogs; this was true also for their enzyme induction potencies. These findings showed that increasing *ortho*- substitution is less effective in reducing the “dioxin-like” activity of these compounds. Howie et al. (1990) suggested that the ether bridge in the polychlorinated diphenyl ether

molecules increases the bond length between the two phenyl rings, thus diminishing the effects of *ortho* substituents on the biochemical and toxic potencies of these compounds. However, these findings may or may not be relevant to immunotoxic activities of PBDEs because of the considerable difference in the molecular size of brominated and chlorinated analogues, which may influence receptor-mediated effects, as well as potential toxicokinetic differences.

Mechanisms of Hepatotoxicity. As discussed in Section 3.2.2.2 Systemic Effects (hepatic subsection), liver effects have been reported in adult, pregnant, and developing animals exposed to lower-brominated PBDEs. Evidence for hepatic effects in animals following exposure to decaBDE is less consistent.

Existing information suggests that PBDEs can be classified as mixed-type inducers of hepatic microsomal monooxygenases (see General Mechanisms of Toxicity Section). Observed effects of liver enlargement and hepatocellular hypertrophy are consistent with enzymatic induction. However, oxidative stress, inflammatory processes, and induction of apoptosis may also contribute to hepatotoxicity of PBDEs. In 12-week gavage studies in mice, administration of troxerutin, an antioxidant and anti-inflammatory agent, prevented tetraBDE-induced hepatotoxicity (increased liver weight, increased serum ALT, hepatocyte hypertrophy and vacuolization, and inflammatory cell infiltration) (Zhang et al. 2015a, 2015b). Moreover, tetraBDE-mediated induction of protein and genetic markers of oxidative stress, inflammation, proteasomal subunits, ER-stress pathways, and apopotisis are prevented by troxerutin. Zhang et al. (2015b) proposed that upregulation of NF-kB via the tetraBDE-induction of histone 3 acetylation at lysine 9 (H3K9) is due to tetraBDE-mediated decreases in SirT1 (which mediates deacetylation), and that this upregulation of NF-kB leads to the observed increases in mRNA levels of inflammation-related genes. Additionally, Zhang et al. (2015a) suggested that oxidative stress leads to apoptosis via proteasome dysfunction-mediated ER stress. Taken together, the therapeutic mechanism of actions for troxerutin could include antioxidant actions and restoration of proteasomal function, as well as the activation of SirT1. These are supported by similar decreases in markers of oxidative stress following vitamin E treatment as well as the blunting of troxerutin-mediate effects with concurrent EX527 injections (a SirT1-specific inhibitor) or epoxomicin injections (a selective proteasome inhibitor) (Zhang et al. 2015a, 2015b). *In vitro* studies also report elevated ROS levels, depleted GSH levels, mitochondrial damage and dysfunction, and apoptosis in HepG2 human hepatocellular carcinoma cells exposed to BDE 47 (Liu et al. 2015; Saquib et al. 2016; Yeh et al. 2015). As observed *in vivo*, known antioxidants (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) protect cultured HepG2 human hepatocellular carcinoma cells from BDE-47-induced oxidative stress and mitochondrial dysfunction (Yeh et al. 2015). However, Pereira et al. (2014) suggest that apoptosis may be mediated via direct

interaction of PBDEs with mitochondria, rather than secondary to PBDE-mediated oxidative stress. In isolated rat liver mitochondria, BDE 154 directly interacted with the mitochondrial membrane, permeabilizing the membrane and leading to ATP depletion. These events occurred in the absence of ROS accumulation in the mitochondria, suggesting that BDE 154 impairs mitochondrial bioenergetics and permeabilizes the mitochondria, potentially leading to cell death, in the absence of oxidative stress (Pereira et al. 2014). BDE 47 and BDE 99 have also been shown to directly interact with the mitochondrial membrane in isolated rat liver mitochondria, resulting in altered mitochondrial bioenergetics and ATP depletion (Pazin et al. 2015).

3.5.3 Animal-to-Human Extrapolations

Residues of PBDEs in humans reflect multiple exposure pathways and congener-specific elimination and thus, in general, represent steady-state body burdens that do not match the congener profiles in the original exposure sources. For example, profiles of PBDE congeners in human milk do not resemble the pattern of any of the previously used commercial mixtures, which were predominantly pentaBDE, octaBDE, and/or decaBDE, as illustrated by the finding that the major PBDE congener in milk from Swedish mothers was 2,2',4,4'-tetraBDE (BDE 47), which comprised approximately 55% of the total PBDEs (Darnerud et al. 1998). As discussed in Chapter 6, residue analyses indicate that tetra- to hexa-congeners predominate in humans, aquatic mammals, birds, fish, and other biota, indicating that the biological fate of PBDE congeners is qualitatively similar in various animal species. The wildlife residue data also indicate that different species have different tissue ratios of congeners, possibly reflective of interspecies differences in metabolic capabilities as well as potential differences in exposure. The likelihood of interspecies differences in the quantitative disposition of PBDEs is illustrated by the observation that metabolism and urinary excretion of a single oral dose of BDE 47 was significantly slower in rats than in mice (Orn and Klasson-Wehler 1998; Staskal et al. 2006b).

While alterations in thyroid hormone levels are consistently altered in in PBDE-exposed animals, human data are less consistent. Humans are possibly less sensitive than rats to effects of PBDEs on circulating levels of thyroid hormones. This difference is thought to derive from the rat thyroid having a smaller store of iodinated thyroglobulin that is more easily depleted when the availability of iodide is limited, and from a more rapid clearance of T_4 from the rat circulation; the latter resulting from rats not having a high affinity binding protein for T_4 in serum analogous to TBG in humans (Capen 1997). If the production of T_4 and T_3 is impaired sufficiently to deplete the thyroid of stored iodinated thyroglobulin, the thyroid cannot produce or secrete amounts of T_4 and T_3 needed to support physiological demands, circulating

levels of T_4 (free T_4) and T_3 decrease, and a state of thyroid hormone insufficiency ensues. TTR is the major thyroid hormone binding protein in rats, but not in man. In most mammals, including humans, TBG is the principal thyroid hormone binding protein; 74% of the total bound-T_4 is bound to TBG, and TTR and albumin bind only 11 and 15%, respectively, of the total (Schussler 2000). In contrast to most mammals, the rat utilizes TTR as the major T_4 plasma binding protein; approximately 75% of T_4 in rat serum is bound to TTR and only 25% to albumin. Both circulating T_3 and T_4 are highly protein bound with only a small fraction of their total present as free hormone, and this high degree of protein binding serves to maintain equilibrium between the extracellular and intracellular pools of these hormones (O'Connor et al. 1999).

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

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

(Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral 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 PBDEs, 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.

As discussed in Chapter 2 and Section 3.2.2.2. (Systemic Effects), the thyroid is a target of concern following exposure to PBDEs, with adverse effects including altered thyroid hormone expression (predominantly reduced serum T_4) and histological changes in the thyroid indicative of glandular stimulation (e.g., follicular cell hyperplasia similar to that induced by a hypothyroid state). Additionally, as discussed in Chapter 2 and Section 3.2.2.6 (Developmental Effects), the developing nervous system and the developing reproductive system are also targets of concern. Since these effects could be mediated by the neuroendocrine axis, several studies have tested PBDEs and their metabolites in *in vitro* endocrine disruption screens and *in vivo* gene expression assays. These studies, and their results, are summarized in Section 3.5.2 (Mechanisms of Toxicity) in the subsections on Mechanisms of Endocrine Disruption (thyroid hormone assays; anti-estrogenic, -androgenic, -progestagenic, and -glucocortogenic assays) and Mechanisms of Reproductive Toxicity (steroidogenesis assays). While results are not always consistent between studies, the data collectively indicate that there is a potential for some PBDEs to disrupt thyroid and other endocrine system functions in humans.

Additionally, a few studies specifically evaluated neuroendocrine disruption *in vitro*. BDE 47 and BDE 99 altered neurodevelopment of cultured fetal hNPCs (Schreiber et al. 2010). The migration distance of the hNPCs was reduced by up to 30% by BDE 47 and up to 35% by BDE 99. Differentiation of hNPCs into neurons was reduced up to 50% by BDE 47 and up to 68% by BDE 99, and differentiation of hNPCs into oligodendrocytes was reduced up to 51% by BDE 47 and up to 93% by BDE 99. Co-exposure with T_3 prevented the effects of PBDE exposure on migration and differentiation, indicating that neurodevelopmental changes were due to endocrine disruption of cellular thyroid hormone signaling. Similarly, Ibhazehiebo et al. (2011) showed that the TR-antagonist, BDE 209 (see discussion in Mechanisms of Endocrine Disruption), inhibits T_4-induced dendritic arborization in cultured rat cerebellar Purkinje cells. However, BDE 47, which was not found to be a TR-antagonist (see discussion in Mechanisms of Endocrine Disruption), did not alter dendritic arborization (Ibhazehiebo et al. 2011). Study authors indicate that other PBDEs and OH-PBDEs were evaluated for dendritic developmental effects, but results were not reported (Ibhazehiebo et al. 2011). In another study, hyperosmotic-stimulated somatodendritic vasopressin release in supraoptic tissue from the hypothalamus of rats was significantly reduced by 40–50% by BDE 46, BDE 77, and the commercial pentaBDE mixture DE-71 (no other PBDEs tested) (Coburn et al. 2007). The neuropeptide vasopressin, which is synthesized in magnocellular neuroendocrine cells, functions to maintain body fluid homeostasis, cardiovascular control, learning and memory, and nervous system development.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less

susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The fetus/infant has an immature (developing) blood-brain barrier that past literature has often described as being leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the blood-brain barrier, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or do they render it more vulnerable to toxic injury. Each case of chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

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).

Body burden data, as well as intake modeling, suggest that infants and toddlers have higher exposures to PBDEs as compared to older children or adults (EPA 2010; Lorber 2008; Trudel et al. 2011; Wong et al. 2013). Exposure during development may occur by transfer of PBDEs that have accumulated in women's bodies to the fetus across the placenta (Antignac et al. 2009, 2008; Chen et al. 2013; Kawashiro et al. 2008; Li et al. 2013a; Mazdai et al. 2003; Meijer et al. 2008; Qiu et al. 2009; Vizcaino et al. 2011; Wan et al. 2010). Placental transfer, although it may be limited in absolute amounts (Frederiksene et al. 2010), is a concern because of possible effects of PBDEs on sensitive immature tissues, organs, and systems, with potentially serious long-lasting consequences. Because PBDEs are lipophilic substances, they can additionally accumulate in breast milk and be transferred to nursing infants (Antignac et al. 2008, 2009; Malarvannan et al. 2013; Park et al. 2011; Schecter et al. 2010). Transfer of PBDEs via breast milk could be considerable and, like prenatal exposure, has the potential to contribute to altered development. Toddlers and older children are exposed to PBDEs in the same manner as the general population, primarily via ingestion of contaminated dust and consumption of contaminated foods (EPA 2010; Lorber 2008). However, exposure from these sources may be greater in young children due to: (1) greater hand-to-mouth behavior, increasing the risk of ingestion of contaminated dust and/or residues from PBDE-

treated materials; and (2) increased exposure relative to their body weight via diet due to increased caloric intake normalized to body weight and a higher general intake of animal fats. Additionally, children may be particularly vulnerable to PBDEs because, compared to adults, they are growing more rapidly and are generally expected to have lower and distinct profiles of biotransformation enzymes, as well as much smaller fat depots for sequestering these lipophilic chemicals.

In human studies, significant associations between umbilical cord and placental PBDE (BDE 28, BDE 47, BDE 99, BDE 153, BDE 183, and total) and adverse birth outcomes were reported in a comparison of 128 normal births and 25 cases of adverse birth outcomes (low birth weight, premature birth, still birth) (Wu et al. 2010; Xu et al. 2015a). Elevated maternal serum BDE 47 levels were also significantly associated with an increased risk of preterm birth in a case-control study of 197 full-term births and 82 pre-term births in Nashville, Tennessee (Peltier et al. 2015). A study of births from 20 healthy pregnant women in Taiwan found that elevated PBDE concentrations (BDE 47, BDE 99, BDE 100, and BDE 209) in breast milk was associated with significantly reduced infant birth weight, length, chest circumference, and Quetelet's index (i.e., BMI) (Chao et al. 2007). A significant negative association between breast milk PBDE concentrations (BDE 47, BDE 99, BDE 100, BDE 153, and their sum) and birth weight was also identified in a Swedish cohort of 254 women with median total PBDE levels of 2.4 ng/g lipid (Lignell et al. 2013). Several studies have also reported a negative association between one or more PBDE congeners in maternal serum and birth weight, length, and/or head circumference: a prospective reproduction study of 234 couples in Michigan and Texas (Robledo et al. 2015a), a birth cohort of 215 Chinese women with a median total PBDE level of 21.68 ng/g lipid (Chen et al. 2015), and a birth cohort of 686 Spanish women (Lopez-Espinosa et al. 2015). In other studies, no significant associations were observed between birth weight, length, or head circumference and maternal or cord serum PBDE concentrations (Foster et al. 2011; Harley et al. 2011; Mazdai et al. 2003; Miranda et al. 2015; Serme-Gbedo et al. 2016; Tan et al. 2009). In another study, a positive association between birth weight and length and colostrum PBDE (BDE 47, BDE 99, BDE 100, BDE 153, and their sum) was observed in a Tanzanian cohort of 95 women with a median total PBDE concentration of 19.8 ng/g lipid (Müller et al. 2016).

In general, available data from animal studies do not indicate that PBDEs are embryotoxic or fetotoxic at PBDE doses below doses that elicited maternal toxicity, although occasional observations of reduced pup weight were reported (Argus Research Laboratories 1985a, 1985b; Biesemeier et al. 2011; Bowers et al. 2015; Branchi et al. 2001, 2002, 2005; Breslin et al. 1989; Ellis-Hutchings et al. 2009; Fujimoto et al. 2011; Hardy et al. 2001, 2002; Kodavanti et al. 2010; Koenig et al. 2012; Life Science Research Israel

Ltd. 1987; Poon et al. 2011; Rice et al. 2007; Saegusa et al. 2012; Ta et al. 2011; Talsness et al. 2005, 2008; Tseng et al. 2008, 2013; Wang et al. 2011a; Watanabe et al. 2008, 2010b; WIL Research Laboratories 1986; Woods et al. 2012; Zhou et al. 2002). At PBDE doses that elicited maternal toxicity (15 mg/kg/day in rabbits, 50 mg/kg/day in rats), developmental effects observed included increased post-implantation loss due to late resorptions and skeletal variations commonly associated with maternal toxicity (Breslin et al. 1989; WIL Research Laboratories 1986). A few studies did report effects at doses below maternal toxicity, including delayed ossification and an increased incidence of internal variations in GD 20 rat fetuses exposed to pentaBDE at 2 mg/kg/day from GD 6 to 19 (Blanco et al. 2012), increased postimplantation loss and number of resorptions and decreased number of live fetuses/litter in mice exposed to decaBDE at ≥750 mg/kg/day from GD 7 to 9 (Chi et al. 2011), and subcutaneous edema and delayed ossification in rats exposed to a low purity (77%) decaBDE mixture at 1,000 mg/kg/day from GD 6 to 15 (Dow Chemical Co. 1985; Norris et al. 1975a).

A major target of concern in infants and children is the developing nervous system. Numerous studies have reported results suggestive of an effect of PBDE on neurodevelopment in children. PBDE levels in cord blood, maternal or infant serum, and/or breast milk have been correlated with cognitive score and adaptive behavior deficits in infants (Chao et al. 2011; Gascon et al. 2012; Shy et al. 2011); mental and physical development deficits in infants/toddlers at ages 12, 24, and 36 months (Herbstman et al. 2010); language and social developmental score deficits in toddlers at 24 months (Ding et al. 2015); increased impulsivity in toddlers at 24–36 months (Adgent et al. 2014; Hoffman et al. 2012); poor social competence and ADHD or increased attention problems in 4-year-old children (Cowell et al. 2015; Gascon et al. 2011); decreased IQ and increased hyperactivity in 5-year-old children (Chen et al. 2014); impaired fine motor coordination, verbal memory and comprehension, and sustained attention in 5–7-year-old children (Eskenazi et al. 2013; Roze et al. 2009); and poor attention and executive function deficits in 9–12-year-old children (Sagiv et al. 2015). In one birth cohort, no associations were observed between maternal serum PBDEs and neonatal behavior in 5-week-old infants (Donauer et al. 2015) or autistic behaviors at 4–5-year-old children (Braun et al. 2014); however, children from the same cohort showed associations between maternal serum PBDEs and decreased IQ and increased hyperactivity at 5 years of age (Chen et al. 2014) and executive function deficits at 5–8 years of age (Vuong et al. 2016a). Pre- and peri-natal studies in animals also consistently reported neurodevelopmental effects following exposure to lower-brominated PBDEs and decaBDE at doses ≥0.06 and ≥2.22 mg/kg/day, respectively, including neurobehavioral alterations, delayed ontogeny of reflexes, ultrastructural changes, altered nicotinic receptor density, altered electrophysiology, and altered gene and protein expression levels (Biesemeier et al. 2011; Blanco et al. 2013; Bowers et al. 2015; Branchi et al. 2001, 2002, 2005;

Buratovic et al. 2014; Chen et al. 2014; Cheng et al. 2009; Eriksson et al. 2001, 2002b, 2006; Fischer et al. 2008; Fujimoto et al. 2011; Gee and Moser 2008; He et al. 2009, 2011; Johansson et al. 2008; Koenig et al. 2012; Kuriyama et al. 2004, 2005; Rice et al. 2007; Sand et al. 2004; Ta et al. 2011; Viberg et al. 2002, 2003a, 2003b, 2004a, 2004b, 2005, 2006, 2007; Woods et al. 2012; Xing et al. 2009). Consistent reports of neurological effects have not been found in adult animal studies, and the only studies that did report neurological effects in adults observed altered neurobehavior at doses above those that cause neurodevelopmental effects in pre- and peri-natal studies (26.2 mg/kg/day of pentaBDE and ≥0.1 mg/kg/day of tetraBDE) (Driscoll et al. 2009; Yan et al. 2012).

Neurodevelopmental effects may be mediated through the neuroendocrine axis, as thyroid hormones regulate cell proliferation, migration, and differentiation during development, and maintenance of normal levels is essential to normal growth and development. In support, neuronal migration and differentiation of fetal human neural progenitor cells (hNPCs) were significantly impaired following *in vitro* exposure to tetraBDE (Schreiber et al. 2010), and decaBDE was shown to be a thyroid hormone receptor antagonist that significantly inhibited T_4-induced dendritic arborization in cultured rat cerebellar Purkinje cells (Ibhazehiebo et al. 2011). Additionally, PBDE-induced alterations in thyroid hormone binding to transport proteins and receptors have been demonstrated in several *in vitro* studies (Hamers et al. 2006; Ibhazehiebo et al. 2011; Marsh et al. 1998; Meerts et al. 1998, 2000; Ren and Guo 2012; Ren et al. 2013). In humans, evidence for thyroid hormone disruption in infants is inconclusive. Some studies reported negative associations between developmental exposure to PBDEs and infant serum or cord blood T_4 levels (Abdelouahab et al. 2013; Herbstman et al. 2010; Kim et al. 2011a); however, other studies reported no association (Kim et al. 2011d, 2012a, 2012b, 2015; Lignell et al. 2016; Lin et al. 2011; Mazdai et al. 2003; Shy et al. 2012). Associations between developmental PBDE exposure and infant serum or cord blood T_3 and TSH were similarly inconsistent (Abdelouahab et al. 2013; Eggesbo et al. 2011; Kim et al. 2011d, 2012a, 2012b, 2015; Lignell et al. 2016; Lin et al. 2011; Mazdai et al. 2003; Shy et al. 2012; Stapleton et al. 2011; Turyk et al. 2008). In contrast, reduced serum T_4 levels have been consistently reported in animals exposed to lower-brominated PBDEs during development (Bansal et al. 2014; Blanco et al. 2013; Bondy et al. 2011, 2013; Bowers et al. 2015; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Kuriyama et al. 2007; Miller et al. 2012; Poon et al. 2011; Shah et al. 2011; Skarman et al. 2005; Szabo et al. 2009; Wang et al. 2011a; Zhang et al. 2009; Zhou et al. 2002). Some studies also reported reduced serum T_3 levels, although findings are less consistent (Blanco et al. 2013; Bondy et al. 2013; Bowers et al. 2015; Shah et al. 2011; Zhang et al. 2009). Consistent changes in thyroid hormones were not found in animals exposed to decaBDE during development (Fujimoto et al. 2011; Rice et al. 2007; Tseng et al. 2008).

Disruption of circulating hormone levels can have markedly different effects, depending on the stage of development, and even transient disruptions can produce permanent effects, such as mental retardation, impaired motor skills, and hearing and speech impediments (Boyages 2000; Fisher and Brown 2000). Several factors might contribute to a high vulnerability of the fetus and neonate to PBDEs. Relatively brief periods of thyroid hormone insufficiency (e.g., 14 days) can produce measurable neurological deficits in newborn infants (van Vliet 1999). Furthermore, unlike the adult thyroid gland, which contains a relatively large store of T_4 that is sufficient to support circulating levels of hormone for several months, the neonatal thyroid contains only enough hormone to support circulating levels of hormone for ≥1 day (van den Hove et al. 1999; Vulsma et al. 1989). Thus, even acute exposures to a dose of lower-brominated PBDEs sufficient to suppress thyroid hormone production could potentially result in thyroid insufficiency in the neonate. The absorbed dose of lower-brominated PBDEs per unit of body mass is also likely to be higher in infants compared to adults exposed to similar levels of PBDEs because of higher intakes per unit of body mass and exposure from breast milk. It should be noted that screening of all newborn children for hypothyroidism is already a widely accepted and legislatively mandated practice (LaFranchi 1999; Landenson et al. 2000). Newborns are tested for thyroid hormone levels within the first few days of life in the United States and most other developed countries, and treatment is started immediately if indicated (LaFranchi 1999; Landenson et al. 2000).

The human relevance of the thyroid effects of lower-brominated BDEs in animals is unclear. Humans are generally regarded as being less sensitive than rats to effects of PBDEs on circulating thyroid hormones. This is thought to be related to a smaller and more rapid turnover of the hormone pool in the rat thyroid, and to a more rapid clearance of secreted hormone in the rat; the latter being, in part, related to the absence of TBG in rats (Capen 1997). TTR is the major thyroid hormone binding protein in rats, whereas TBG is the main binding protein in man and most other mammals. However, although TTR is a minor thyroid hormone binding protein in humans, it is the principal protein involved in T_4 transport to the brain in both rats and man (Blay et al. 1993; Sinjari et al. 1998). TTR does not transport T_4 from the bloodstream to the brain, but rather is the main T_4 binding protein in cerebral spinal fluid (CSF) in rats and humans. In the rat, T_4 is transported to the brain primarily through the blood-brain barrier, and not via the choroid plexus and CSF (Blay et al. 1993). Also, the mechanism by which lower-brominated BDEs cause decreased serum T_4 might involve hepatic microsomal enzyme induction and consequent increased metabolic formation of hydroxy signaling-metabolites, but humans are not particularly sensitive to this effect.

Based on limited findings from human and animal studies, another target of concern in infants and children exposed to PBDEs is the developing reproductive system. Main et al. (2007) found a significant positive relationship between levels of PBDE in breast milk and congenital cryptorchidism (undescended testes) in male offspring. The study compared levels of 14 PBDE congeners in breast milk of mothers of 62 Danish and Finnish boys with cryptorchidism to mothers of 68 controls from the same population. Significant elevation of concentrations in cases versus controls were seen for the sum of all 14 congeners, for the sum of the 7 most prevalent congeners found in all mothers (BDE 28, BDE 47, BDE 66, BDE 99, BDE 100, BDE 153, BDE 154), and for 5 of the 7 most prevalent congeners. No significant associations were observed between PBDE concentrations in children's adipose tissue and cryptorchidism (Koskenniemi et al. 2015). Other studies of reproductive development found no relationship between concentrations of individual PBDE congeners (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153) in mid-pregnancy serum samples from California mothers and hypospadias in their male offspring (Carmichael et al. 2010) and no relationship between current serum levels of PBDE and various measures of sexual maturation (e.g., age at thelarche, current breast development, age at menarche) in a small cohort of teen-aged Dutch children (Leijs et al. 2008). However, serum PBDE levels in 6–8-year-old females were significantly associated with delayed onset of puberty in a longitudinal cohort of U.S. girls (Windham et al. 2015a). A study of 55 Dutch boys found significant positive associations between maternal serum levels of BDE 154 collected on week 35 of pregnancy (but not other congeners measured, including BDE 47 and BDE 153, that occurred at higher levels) and serum levels of the sex hormones, E2, free E2, and inhibin B (but not testosterone, LH, FSH, or sex hormone binding globulin) in the baby boys at 3 months of age and testes volume in the boys at 18 months of age, but no effect on penile length at either age (Meijer et al. 2012). Additionally, Warembourg et al. (2016) reported an inverse association between cord serum BDE 209 and total testosterone (but not free testosterone, E2, aromatase index, sex hormone binding globulin, or Anti-Müllerian hormone) in 141 French boys.

In animal studies, reproductive effects were observed in adult F1 offspring exposed to a single dose of pentaBDE at 0.06 mg/kg on GD 6, including reductions in testicular weight, sperm/spermatid number, and daily sperm production in males and a decreased number of secondary follicles and ultrastructural changes in the ovaries in females (although F1 fertility when mated to an unexposed animal was not impaired) (Kuriyama et al. 2005; Talsness et al. 2005, 2008). In animals exposed pre- or perinatally to decaBDE, one study reported reproductive effects in adult male offspring exposed to decaBDE doses of 10–1,500 mg/kg/day from GD 0 to 17, including testicular lesions, decreased AGD, and altered sperm parameters (Tseng et al. 2013); however, no exposure-related changes in AGD, onset of puberty, or reproductive organ weight and histology were reported in offspring exposed to decaBDE at doses up to

1,000 mg/kg/day during gestation and lactation (Biesemeier et al. 2011; Fujimoto et al. 2011) or doses up to 20 mg/kg/day from PND 2 to 15 (Rice et al. 2007). In females, no exposure-related changes in reproductive development were reported in offspring exposed to decaBDE at doses up to 1,000 mg/kg/day during gestation and lactation (Biesemeier et al. 2011; Fujimoto et al. 2011) or doses up to 20 mg/kg/day from PND 2 to 15 (Rice et al. 2007). In *in vitro* assays, lower-brominated PBDEs have been shown to be mildly estrogenic, anti-androgenic, anti-progestagenic, and anti-glucocorticogenic and higher-brominated PBDEs have been shown to be mildly anti-estrogenic (Hamers et al. 2006; Kojima et al. 2009; Meerts et al. 2001; Mercado-Feliciano and Bigsby 2008a, 2008b; Stoker et al. 2005). PBDEs have also been shown to alter expression and activity of steroidogenic enzymes *in vitro* (Canton et al. 2005, 2008; He et al. 2008a; Karpeta et al. 2011, 2013; Wang et al. 2011c; Zhao et al. 2011).

The developing immune system may also be a target of concern in infants and children exposed to PBDEs. In a one-generation study in rats, F0 rats were exposed to pentaBDE at 0, 0.5, 5, or 25 mg/kg/day via gavage for 70 days prior to mating, through mating, gestation, and lactation (PND 21), and PND 43 F1 rats were assessed for serum immunoglobin levels, B and T lymphocyte quantification in the spleen, spleen cell proliferation *in vitro*, and immune organ weight and histology and PND 56 rats were assessed for immune function in the KLH antigen immune challenge (Bondy et al. 2013). Observed effects at PND 43 included reduced serum IgE and IgG1 levels in females; a significant, dose-related reduction in the proportion of B cells and a significant concomitant increase in the proportion of T cells in the spleen in males and females; increased proliferation of unstimulated spleen cells harvested from males and females; and histopathological changes in the thymic cortex in males. No exposure-related changes were observed in immune function in PND 56 rats (Bondy et al. 2013). Two studies examined immune function in PND 28 mice was assessed using the RSV intranasal infection test following exposure to decaBDE from GD 10 to PND 21 at doses ranging from 3.3 to 3,000 mg/kg/day (Watanabe et al. 2008, 2010b). At doses ≥260 mg/kg/day, RSV pulmonary viral titers were elevated at 1–5 days post-infection, and exposure to 3,100 mg/kg/day exacerbated the histopathological changes in the lung caused by RSV infection. In the only developmental immune study in humans, a reduced risk of atopic dermatitis was found in Japanese infants (diagnosed at 7 months of age by questionnaire) with higher PBDE concentrations in umbilical cord blood (Ochiai et al. 2014).

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).

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, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to PBDEs are discussed in Section 3.8.1.

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

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to PBDEs

PBDEs are persistent environmental contaminants that accumulate in adipose tissue, serum, and breast milk serum of the general population (see Section 3.4, Toxicokinetics). Therefore, PBDE concentrations in these tissues are indicators of general exposure for PBDEs, and PBDE concentrations in maternal adipose tissue, serum, breast milk, and cord serum are useful as markers of maternal body burdens as well as lactational and *in utero* exposures (Ahn et al. 2009; CDC 2015; Huwe et al. 2008; Kim et al. 2012a; Marchitti et al. 2013; Mazdai et al. 2003; Meironyté Guvenius et al. 2001). The National Report on Human Exposure to Environmental Chemicals (CDC 2015) has methods for many PBDE congeners to identify exposure and provides reference values representative of U.S. population for comparison with exposures to potentially more exposed populations; it is continually updated on-line (see http://www.cdc.gov/exposurereport/ to look for the most recent U.S. human PBDE exposure information). Studies have also proposed that PBDE concentrations in hair are also useful markers of exposure (Aleksa et al. 2012a, 2012b; Kucharska et al. 2015; Liu et al. 2016; Malarvannan et al. 2013; Poon et al. 2014), although Zheng et al. (2011) reported that PBDE concentrations in hair were not correlated with PBDE concentrations in indoor dust from urban, e-waste, and rural areas in South China. It is not clear if the lack of correlation between PBDE concentrations in indoor dust and hair reported by Zheng et al. (2011) indicates that hair is a poor monitor of exposure or if exposure via dust was not significant for the Chinese subjects involved in the study. Other potential exposure sources, including outdoor dust for individuals living near an e-waste area or ingestion of contaminated food, were not controlled for in this study. Urinary bromophenols have also been suggested as potential biomarkers of human exposure to PBDEs (Feng et al. 2016a; Ho et al. 2015).

Estimates of PBDE serum concentrations among electronics-dismantling workers before and after exposure-free vacation (median duration 28 days, range 21–35 days) indicate that the higher-brominated congeners have shorter half-lives than lower-brominated congeners (Sjödin et al. 1999b). The medians and ranges of percentage decreases in serum concentrations, based on 5–11 measurements per congener, were 14 (range 3.5–39), 14 (2.1–38), 14 (6.7–42), 30 (7.9–52), and 66 (47–100) for BDE 47, BDE 153, BDE 154, BDE 183, and BDE 209, respectively. Although actual half-lives were not calculated, the data suggest that the half-lives of the lower-brominated congeners were <1 year. Similar findings were found in another study of eight PBDE-exposed workers (four electronics dismantlers and four workers in a factory making flame-retarded rubber), where calculated apparent half-lives were: 15 days for BDE 209; 28, 39, and 18 days for nonabrominated congeners BDE 208, BDE 207, and BDE 206; 37, 72, 85, and

91 days for BDE 203 and three other octabrominated congeners of uncertain chemical structure; and 94 days for BDE 183 (Thuresson et al. 2006).

A study in Sweden examined the feasibility of using feces as a noninvasive matrix to determine serum concentrations of PBDEs in toddlers for biomonitoring purposes (Sahlström et al. 2015). The cohort consisted of 22 healthy toddlers 11–15 months of age. Twelve (tri- to decabrominated) BDEs were analyzed, but only nine could be quantified; not detected were BDE 28, BDE 99, and BDE 100. Median concentrations of BDEs in feces ranged from 18 ng/g lipid for BDE 209 to 0.055 ng/g lipid for BDE 196. Concentrations of tetra- to octaBDE in serum were significantly higher than in feces; the highest difference was for BDE 153. BDE 209 was significantly more concentrated in feces than in serum. Significant correlations in concentrations were found for all BDEs detected, except BDE 197 and BDE 203.

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

3.8.2 Biomarkers Used to Characterize Effects Caused by PBDEs

Biomarkers of effects for PBDEs are likely to be common to the general class of halogenated aromatic hydrocarbons, rather than specific for PBDEs, because PBBs, PCBs, and other structurally similar chemicals cause generally similar effects.

As discussed in Chapter 2, the thyroid, nervous system, and reproductive system are critical targets of exposure to lower-brominated PBDEs in animals, and evidence from human studies also suggests that these systems may be a target of human toxicity. Critical effects used for derivation of the MRLs for lower-brominated PBDEs include: endocrine effects in rats (reduced serum T_4) for the intermediate inhalation MRL (Great Lakes Chemical Corporation 2000); endocrine effects in F0 rat dams (reduced serum T_4) and reproductive and neurobehavioral effects in F1 adult offspring (impaired spermatogenesis, ultrastructural changes in ovaries, increased resorptions in F1 females mated to unexposed males, and increased spontaneous motor activity) for the acute oral MRL (Kuriyama et al. 2005, 2007; Talsness et al.

2005); and reproductive effects in male rats (decreased serum testosterone) for the intermediate oral MRL (Zhang et al. 2013b). There are several potential biomarkers for these effects, such as alterations in serum thyroid or reproductive hormone levels or changes in neurobehavioral screens; however, none of these effects are specific to PBDE exposure.

Similarly, the nervous system and pancreas are critical targets of exposure to decaBDE in animals. There are two human studies suggesting delayed cognitive development in children exposed to decaBDE (Chao et al. 2011; Gascon et al. 2012) and limited evidence for an association between BDE 153 and diabetes (BDE 209 was not assessed) in humans (Airaksinen et al. 2011; Lee et al. 2011; Lim et al. 2008; Smarr et al. 2016). Critical effects used for derivation of the MRLs for decaBDE include altered neurobehavior in juvenile mice following neonatal exposure for the acute oral MRL (Johansson et al. 2008; Viberg et al. 2003b) and altered insulin homeostasis (elevated serum glucose levels) in rats for the intermediate oral MRL (Zhang et al. 2013a). Again, there are potential biomarkers for these effects, such as alterations in serum glucose levels or changes in neurobehavioral screens; however, none of these effects are specific to decaBDE exposure.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Only one study was located that provided information regarding interactions between PBDE and other chemicals in humans. Fitzgerald et al. (2012) examined the association between exposure to PBDEs and neuropsychological function among 144 adult men and women residents of upper Hudson River communities and also studied the possible interactive effects of exposure to PCBs. A series of 34 tests to assess cognitive and motor function, affective state, and olfactory function were conducted. Serum samples were collected and analyzed for concentrations of nine of the most commonly detected PBDE congeners in human serum (ΣPBDE) and 30 PCB congeners that usually constitute 95% of the congeners found in human serum (ΣPCB). After adjustment for relevant confounders, the results of multiple linear regression analyses showed no significant associations between ΣPBDE and scores on the neuropsychological tests. However, in subjects with a ΣPCB concentration above the median of 467 ppb (on a lipid basis), an increase in ΣPBDE concentration from the 25^{th} to the 75^{th} percentile was significantly associated with decreases between 7 and 12% in scores of some tests of memory and learning. Tests also showed that the interaction was greater than additive. No specific mechanism was proposed for the interaction between PBDEs and PCBs.

A few animal studies have examined the effects of the interaction of PBDEs and other chemicals on thyroid-related parameters. For example, Hallgren and Darnerud (2002) reported that daily oral administration of 18 mg/kg/day BDE 47 and 4 mg/kg/day Aroclor 1254 to female rats for 14 days resulted in a significant decrease in plasma free T_4 that suggested additive effects compared to administration of either compound alone. The reduction in free T_4 coincided with a decrease in *ex vivo* binding of ^{125}I-T_4 to the hormone transporter TTR and induction of the microsomal enzymes EROD and MROD, and led the investigators to suggest that the reduced free T_4 could be explained by alterations in serum binding to TTR caused by metabolites of Aroclor 1254 or BDE 47. In the same study, co-administration of BDE 47 and a technical mixture of chlorinated paraffins resulted in a reduction in plasma free T_4 and induction of EROD that were greater than the effects of the single compounds, indicating synergistic effects. Consistent with the findings of Hallgren and Darnerud (2002), Miller et al. (2012) reported that oral co-administration of equimolar doses of the commercial PBDE mixture DE-71 and a mixture of various Aroclors to pregnant rats from GD 6 until PND 21 significantly reduced circulating levels of total T_4 in male and female offspring from PND 7 to 21 in a manner that indicated additive effects. The reduction in total T_4 was dose-dependent over a wide range of doses, 3–40 µmol/kg/day. The mixture of Aroclors resembled the PCB congener pattern found in contaminated fish consumed by residents near the Fox River in Wisconsin.

Wang et al. (2011a) found little evidence of interactions between perfluorooctane sulfonate (PFOS) and BDE 47 on postnatal levels of total T_3 and T_4 in serum from rats (dams and their offspring) administered the chemicals in the diet on GD 1 through PND 14. The investigators also examined the transcriptional and translational expression of several thyroid hormone-mediated genes in neonates' brains and found that PFOS and BDE 47 had interactive effects on only levels of brain-derived neurotrophic factor (*BDNF*); the chemicals showed a synergistic effect on PND 1 in the cortex and an antagonistic effect on PND 14 in the hippocampus. A possible mechanism for the interaction was not discussed. He et al. (2011) also found lack of interactive effects between BDE 47 and 2,2',4,4'-tetrachlorobiphenyl (PCB 153) on serum T_4 levels in rats. In this study, 10-day-old pups received a dose of up to 10 mg/kg BDE 47 and/or 5 mg/kg PCB 153. At 2 months of age, there was no evidence of any interaction between the chemicals on serum levels of T_4. However, performance on a Morris water maze was significantly impaired in the group dosed with 5 mg/kg BDE 47 and PCB 153 and in the group dosed with 10 mg/kg BDE 47 and PCB 153 relative to the groups dosed with either chemical alone. The effect of the combined action of BDE 47 and PCB 153 on performance on a Morris maze had been reported also in an earlier study (He et al. 2009).

Two studies by Eriksson and coworkers (Eriksson et al. 2006; Fischer et al. 2008), examined the interactive effects of BDE 99 and 2,2',5,5'-tetrachlorobiphenyl (PCB 52) or BDE 99 and methyl mercury on neurodevelopmental parameters in mice. In the first study, combined administration of equimolar amounts of BDE 99 and PCB 52 (1.4 µmol/kg each; 0.8 mg/kg BDE 99, 0.4 mg/kg PCB 52) to 10-day-old male mice resulted in reductions in spontaneous activity and habituation capability at 4 and 6 months of age that were significantly more pronounced than those obtained with a single much higher dose (14 µmol/kg) of PCB 52. This led the investigators to suggest that the interaction was greater than additive and that different mechanisms may be involved and/or different regions of the brain are differently affected. Using the same protocol, Fischer et al. (2008) reported that coexposure to BDE 99 and methyl mercury exacerbated neurobehavioral defects manifested as alterations in spontaneous behavior, lack of habituation, and impaired learning/memory in male mice tested during the first 6 months of life. BDE 99 and methyl mercury also interacted to promote a significant reduction in the density of cholinergic nicotinic receptors in the hippocampus, suggesting that the neurobehavioral alterations may involve the cholinergic system. The interactive properties of BDE 99 and methyl mercury were also assessed in a study in rats (Zhao et al. 2014). Combined administration of these chemicals to pregnant rats during gestation and up to PND 21 resulted in enhanced methylmercury-induced neurotoxicity in the pups compared to treatment with methylmercury alone. Specifically, tests showed delayed appearance of negative geotaxis reflexes, impaired motor coordination, and induction of oxidative stress in the cerebellum from pups. While retention of mercury was not affected by co-exposure to BDE 99, combined exposure to methylmercury and BDE 99 seemed to increase the concentrations of BDE 99 in selected brain regions from pups. The investigators concluded that combined exposure to methylmercury and BDE 99 produced oxidative stress due to inhibition of antioxidant enzymes and production of free radicals. In a study of the mechanism(s) of neurotoxicity of BDE 47, He et al. (2009) reported that the combined administration of BDE 47 and PCB 153 to 10-day-old rats induced ultrastructural alterations in neurons in the hippocampal CA1 region, assessed at the age of 2 months, in a manner that suggested a synergistic mode of action. These alterations were associated with changes in expression of mRNA and proteins involved in three apoptosis pathways. For the most part, the changes in expression levels of the various factors due to the combined action of BDE 47 and PCB 153 were consistent with an additive interaction between the two chemicals.

A study in rats reported that gestational and lactational exposure to 5.7 or 11.4 mg/kg/day of the commercial PBDE mixture DE-71 did not alter cochlear function in adult offspring and neither did exposure to 3 mg/kg/day of an environmental PCB mixture (equimolar to 5.7 mg/kg/day of the PBDE mixture) (Poon et al. 2011). Exposure to 6 mg/kg/day of the PCB mixture did impair cochlear function.

However, exposure of the rats to the combined two low doses of the chemicals, neither of which alone affected cochlear function, resulted in a deficit in cochlear function in the offspring similar to that in the high-dose PCB group, suggesting an additive effect of the mixture on the outcome measured. The mechanism of the interaction was not elucidated, but it did not appear to be directly related to reductions in serum T_4. The PCB mixture used in this study was the Fox River mixture (see above Miller et al. 2012).

It should be noted that the alterations in health outcomes in humans or animals summarized in Section 3.2, Discussion of Health Effects by Route of Exposure, that were caused by exposure to commercial or environmental PBDE mixtures, are in fact the result of interactions between the individual components of the particular PBDE mixture.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to PBDEs than will most persons exposed to the same level of PBDEs in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of PBDEs, or compromised function of organs affected by PBDEs. Populations who are at greater risk due to their unusually high exposure to PBDEs 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 PBDEs. As indicated in Section 3.4.4.2, the detection of PBDEs in human breast milk samples suggests that breast milk represents an elimination route of absorbed PBDEs in women. Both lower and higher-brominated congeners have been detected in breast milk (Antignac et al. 2008, 2009; Malarvannan et al. 2013; Park et al. 2011; Schecter et al. 2010). Therefore, women with high body burdens of PBDEs who breastfeed may be placing their infants at a higher risk of potential health effects, although it is unclear the degree to which PBDEs are cleared from the body during breast feeding (Hooper et al. 2007; Jakobsson et al. 2012; LaKind et al. 2009; Thomsen et al. 2010). In general, however, any risks from exposures in mother's milk are outweighed by the benefits of breastfeeding.

Pregnant women and developing infants and fetuses should be viewed as possibly sensitive populations for exposure to lower-brominated PBDEs, as they are for other thyroid hormone disrupting chemicals (Glinoer 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 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). As discussed in Section 3.2.2.2 (Endocrine Effects subsection), human studies have found inconsistent associations between PBDE levels in maternal/infant serum, cord blood, or breast milk and thyroid hormone levels in pregnant women and infants. However, decreased maternal, fetal, and neonatal serum T_4 levels have been consistently reported in animals exposed to lower-brominated PBDEs (but not decaBDE). Therefore, it is unclear whether or not exposure to lower brominate PBDEs will cause thyroid hormone disruption in humans, and mechanistic differences may account for the observed interspecies differences (as discussed in Section 3.5.3, Animal-to-Human Extrapolations).

Developing fetuses, infants, and children should also be regarded as a possibly sensitive population with regards to neurodevelopmental effects. As discussed in Section 3.7 (Children's Susceptibility), numerous studies have reported results suggestive of an effect of PBDE on neurodevelopment in children. PBDE levels in cord blood, maternal or infant serum, and/or breast milk have been correlated with cognitive deficits (including impaired verbal memory and comprehension), adaptive behavior deficits, increased impulsivity and impaired attention, poor social competence, and impaired fine motor coordination in infants and children. Additionally, pre- and peri-natal studies in animals consistently report neurodevelopmental effects following exposure to lower-brominated PBDEs and decaBDE (at higher doses). The susceptibility of the developing nervous system may be due to neuroendocrine effects, as discussed in Section 3.6 (Toxicities Mediated Through The Neuroendocrine Axis). For example, neuronal migration and differentiation of fetal hNPCs were significantly impaired following *in vitro* exposure to tetraBDE (Schreiber et al. 2010), and decaBDE was shown to be a thyroid hormone receptor antagonist that significantly inhibited T_4-induced dendritic arborization in cultured rat cerebellar Purkinje cells (Ibhazehiebo et al. 2011).

People with exposure to anti-thyroid drugs (e.g., lithium), thyroid disease, or otherwise compromised thyroid function might have a more pronounced response to PBDEs because of their underlying limitations in thyroid hormone production. Similarly, people with compromised function of other organs,

such as those with liver or kidney diseases (e.g., liver cirrhosis or hepatitis), could be considered more susceptible to health effects of PBDEs.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to PBDEs. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to PBDEs. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No texts were located that provide specific information about treatment following exposures to PBDEs; however, recommendations based on experiences with PCBs are relevant. The following texts provide specific information about treatment following exposures to PCBs:

Caravati EM, Mcguigan MA, Whyte IM, et al. 2004. Polyhalogenated biphenyls. In: Dart RC, ed. Medical toxicology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1342-1343.

Leikin JB, Pauloucek FP. 2008. Polychlorinated biphenyls. In: Leikin JB, Pauloucek FP, eds. Poisoning and toxicology handbook. 4th ed. Boca Raton, FL: CRC Press, Taylor & Francis Group, 840.

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 PBDEs. There is no indication of hazards associated with the treatments. The methods are particularly appropriate for trying under conditions of acute exposure, but PBDEs are not acutely toxic chemicals. Scenarios where life-threatening acute exposure would occur are unlikely, although accidental or intentional ingestion of the commercial products is a conceivable concern. The relevance of the methods to common background environmental exposures to these chemicals is unclear, and it is questionable whether current exposure and tissue levels in the general population are a health concern.

3.11.1 Reducing Peak Absorption Following Exposure

Ingested PBDEs 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 PBDEs, recommendations based on experiences with PCBs are relevant. Treatments for acute poisonings from PCBs and related substances include the induction of emesis or gastric lavage and stomach pumping to decrease gastrointestinal absorption of the chemicals (Lemesh 1992). These procedures would not be beneficial if performed too long after exposure occurred. Administration of activated charcoal as a slurry,

either aqueous or mixed with a saline cathartic or sorbitol, is frequently recommended to decrease the gastrointestinal absorption of PCBs, but the value of this treatment for reducing absorption of PCBs, PBBs, and PBDEs is unknown (HSDB 2012). 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 PBDEs in the serum and fat of people who were occupationally exposed to these chemicals indicates that PBDEs can be absorbed by the lungs, skin, and/or orally by hand-to-mouth contact. Although no specific methods to reduce absorption of dermally applied or inhaled PBDEs were located, multiple washings of contaminated skin with soap and water immediately following exposure have been suggested to reduce the dermal absorption of PCBs (HSDB 2012). 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

As discussed in Section 3.4, while decaBDE is absorbed to a lesser degree than lower-brominated PBDEs, all PBDE congeners can accumulate in lipid-rich tissues. However, lower-brominated PBDEs are more likely to accumulate as they are more slowly metabolized and eliminated from the body. No studies evaluating methods to reduce body burden of PBDEs were located.

Several methods to enhance the elimination of PBBs from the body have been examined in animals and may be applicable to PBDEs. 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 PBDE levels in serum and other body tissues, possibly posing a significant re-exposure problem. Although some of the studies observed no enhanced elimination (Kimbrough et al. 1980; McConnell et al. 1980), others identified treatments that were effective in enhancing the biliary and

intestinal elimination of PBB residues (Polin et al. 1991; Rozman et al. 1982). Polin et al. (1991) found that dietary intervention to reduce PBBs was dose dependent; treatment with 10% mineral oil and a 45% reduction in food intake resulted in a 69 and 23% reduction in body burden in rats fed PBBs at dietary concentrations of 0.1 and 100 ppm, respectively (Polin et al. 1991). A combination of mineral oil, colestipol, and dietary restriction was successful in reducing the PBB body burdens in chickens (Polin and Leavitt 1984; Polin et al. 1985), while each treatment alone had no effect in reducing PBB body burden. A 3-week treatment regimen that included dietary supplements of polyunsaturated oil, vitamins, and minerals, and heat stress has been applied in a pilot study to seven human subjects that were known to have been exposed to PBBs; following treatment, statistically significant reductions were measured in PBB concentrations in fat (Schnare et al. 1984). Although the lack of a separate control group complicates interpretation of the results of this study (each subject served as his/her own control), this treatment was developed for the purpose of reducing body burdens of fat-soluble psychoactive drugs (Schnare et al. 1984).

Additionally, a few human studies that have evaluated methods to reduce body burden of PCBs, another class of lipophilic compounds, may be applicable to PBDEs. A liquid diet was used for 16 individuals who developed symptoms following exposure to PCBs and polychlorinated dibenzofurans (Imamura and Tung 1984). Symptoms were reduced several months after the fasting period. This study is limited in that a control group was not used, and body burdens were not measured. Based on information for PCBs, mobilization of PBDEs from adipose tissue is not recommended in individuals with hepatic or renal disease (Lemesh 1992). More recently, 14 individuals administered 15 g/day of dietary olestra (a non-absorbable lipid in potato crisps) for 1 year showed a steady decline in serum lipid concentrations of PCBs (Jandacek et al. 2014). At the end of 1 year, PCB concentrations were significantly decreased by ~8% compared with pre-trial values. However, PCB concentrations were not significantly decreased compared with 14 concurrent controls administered 15 g/day of dietary olive oil (which showed a nonsignificant ~4% decrease in PCB concentration compared with pre-trial values). Further studies need to be conducted with larger study groups to determine the efficacy of olestra for reducing body burden of PCBs and/or other lipophilic compounds.

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 PBDEs. Although the mechanism of action of PBDEs is not completely understood, PBDEs share some toxicological properties with other structurally similar polyhalogenated aromatic compounds, particularly PBBs, PCBs, CDDs,

and CDFs (ATSDR 1994, 1998, 2000). 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 to enhancement of the CYP1A1 gene expression (see Section 3.5). The toxicity of specific congeners is related to their ability to assume a coplanar configuration for binding to AhR (Hardy 2002a). It may be inferred 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 the potent AhR activator TCDD (Bannister et al. 1989). In contrast to PBBs, PCBs, and related compounds, AhR binding affinity of PBDE congeners is not correlated with planarity (Chen et al. 2001). This may be due, in part, to increased distance between the phenyl rings relative to PBBs and PCBs. It has also been speculated that the large size of the bromine atoms of PBDEs relative to chlorine atoms of PCBs may distort the AhR binding site so that coplanar configuration is not required (Chen et al. 2001). Because AhR binding by PBDEs apparently differs in some respects from AhR binding by PBBs and other related compounds, AhR antagonists identified via experiments with PBBs, TCDD, and related compounds might not effectively antagonize AhR binding and effects of PBDEs.

PBDEs may also cause toxicity by other mechanisms of action. PBDE-induced decreases in thyroid T_4 hormone, which can affect neurobehavioral development, are likely to involve multiple mechanisms (see Section 3.5.3). These include induction of hepatic microsomal enzymes, particularly UDPGT, which can increase the rate of T_4 conjugation and excretion, and metabolic formation of hydroxy-metabolites of PBDEs. PBDEs and their hydroxy metabolites can bind with high affinity to thyroid transport proteins because they are structurally similar to T_4 hormone (i.e., are also hydroxy-halogenated diphenyl ethers) (see Section 3.5.2). Effects of PBDEs on thyroid status via induction of hepatic enzymes, however, are unlikely to occur in humans, and the impact of hydroxy-metabolites on serum T_4 needs further clarification. Effects of PBDEs on the function and development of the nervous system could also involve disruption of calcium homeostatic mechanisms and intracellular signalling events (Chen et al. 2010; Dingemans et al. 2008, 2010a, 2010b; Fan et al. 2010; Kodavanti 2003; Kodavanti and Derr-Yellin 2001, 2002; Smolnikar et al. 2001; Wiegand et al. 2001), altered cholinergic or dopaminergic functions (Ankarberg et al. 2001; Bradner et al. 2013; Dreiem et al. 2010; Fischer et al. 2008; Mariussen and Fonnum 2002, 2003; Mariussen et al. 2003; Slotkin et al. 2013; Viberg and Eriksson 2011; Viberg et al. 2002, 2003a, 2004b, 2005), and/or free radical-induced neuronal death (Chen et al. 2010; He et al. 2008b;

Huang et al. 2010; Reistad et al. 2002). Clinical interventions designed to interfere with the aforementioned mechanisms have yet to be developed.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PBDEs is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PBDEs.

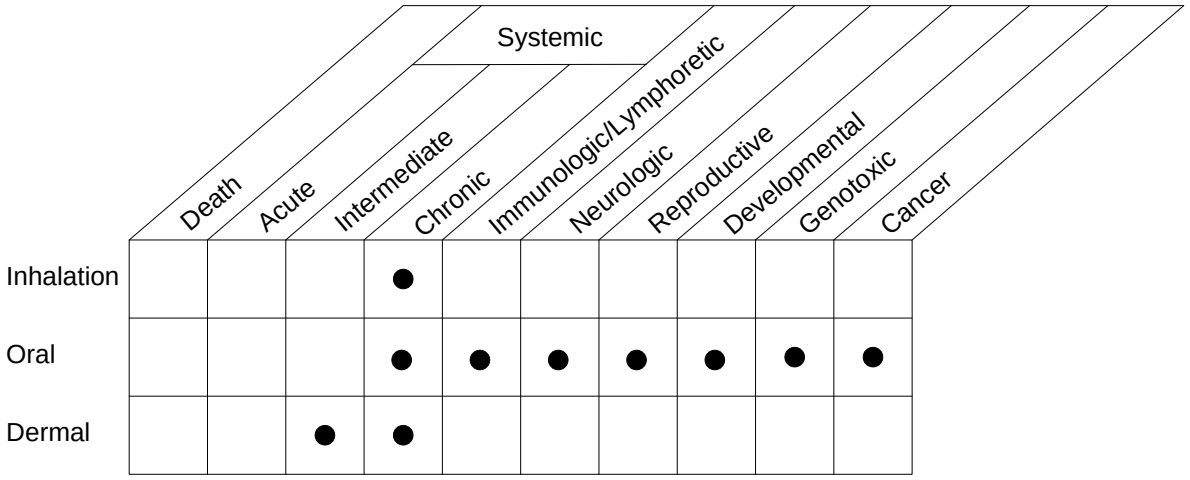
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

3.12.1 Existing Information on Health Effects of PBDEs

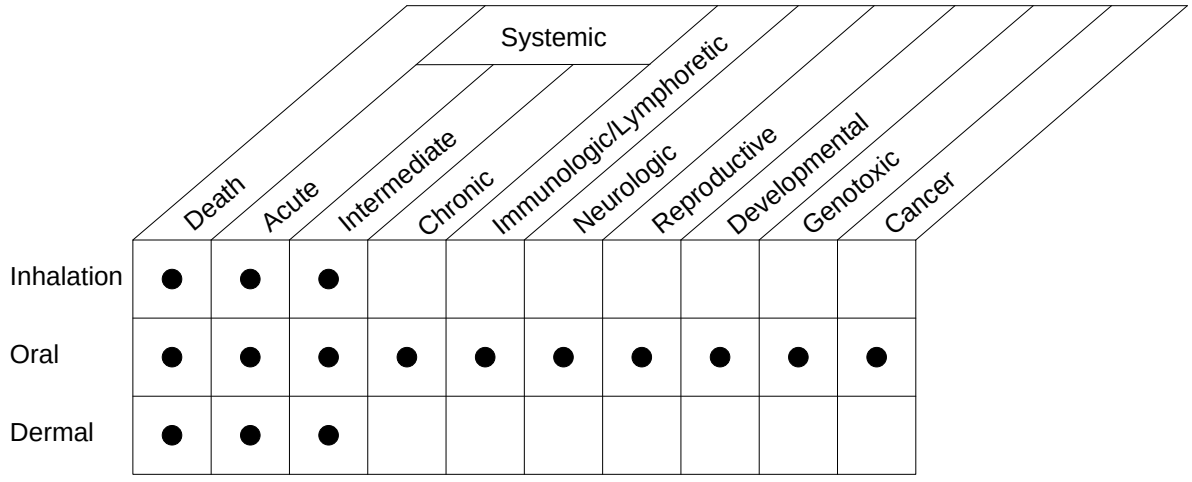
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PBDEs are summarized in Figure 3-8. The purpose of this figure is to illustrate the existing information concerning the health effects of PBDEs. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Studies on the systemic and carcinogenic effects of PBDEs in humans are based primarily on tissue PBDE levels without knowledge of route of exposure; in most cases exposure was attributed to the oral route (Figure 3-8). Information on health effects of PBDEs in animals is available for all effect categories, but is mainly limited to oral exposure studies in animals.

Figure 3-8. Existing Information on Health Effects of Polybrominated Diphenyl Ethers (PBDEs)



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Acute-duration studies of lower-brominated PBDEs have documented effects mainly on the developing nervous system, the developing reproductive system, the thyroid, and the liver of orally exposed rats and mice (Bruchajzer 2011; Bruchajzer et al. 2010, 2011; Darnerud and Sinjari 1996; Dingemans et al. 2007; Dufault et al. 2005; Eriksson et al. 2001, 2002b, 2006; Fischer et al. 2008; Fowles et al. 1994; Gee and Moser 2008; Hallgren and Darnerud 2002; Hallgren et al. 2001, 2015; He et al. 2009, 2011; Hoppe and Carey 2007; Kuriyama et al. 2005, 2007; Richardson et al. 2008; Sand et al. 2004; Stoker et al. 2004; Talsness et al. 2005, 2008; Viberg et al. 2002, 2003a, 2004a, 2004b, 2005, 2006; Zhou et al. 2001, 2002). The most sensitive effects were observed in F0 and F1 rats exposed to ≥0.06 mg/kg of pentaBDE on GD 6, including decreased maternal serum T_4 in dams, decreased number of spermatids and sperm and daily sperm production in F1 males, decreased relative epididymis weight in F1 males, altered neurobehavior in F1 males, ultrastructural changes in ovaries of F1 females, and increased resorptions in F1 females mated to unexposed males (Kuriyama et al. 2005, 2007; Talsness et al. 2005). Collectively, these end points were selected as a basis for an acute MRL for lower-brominated PBDEs. While hepatic effects were consistently observed, they occurred at much higher doses (≥8 mg/kg/day). Two studies in mice indicate that immunosuppression is a potentially critical health end point for acute exposure to lower-brominated PBDEs; additional studies may provide more support for this end point (Darnerud and Thuvander 1998; Fowles et al. 1994; see discussions of data needs for Immunotoxicity).

Several acute-duration studies of decaBDE have also documented effects on the developing nervous system in rats (Chen et al. 2014; Viberg et al. 2007) and mice (Buratovic et al. 2014; Johansson et al. 2008; Rice et al. 2007, 2009; Viberg et al. 2003b). The most sensitive neurobehavioral effects, decreased open field activity and impaired habituation, were observed in 2–6-month-old male mice that were exposed once to decaBDE at doses ≥2.22 mg/kg on PND 3 (Buratovic et al. 2014; Johansson et al. 2008; Viberg et al. 2003b). This effect was not observed at 1.34 mg/kg (Buratovic et al. 2014; Johansson et al. 2008). These neurobehavioral end points were selected as the basis for an acute MRL for decaBDE. The remaining acute database for decaBDE provides only limited data regarding hepatic, endocrine, body weight, and developmental effects in rats and mice (Bruchajzer et al. 2010; Carlson 1980b; Chi et al. 2011; IRDC 1974; NTP 1986; Sakamoto et al. 2013; Zhou et al. 2001). Additional studies, specifically neurodevelopmental studies in species other than mice and immunotoxicity screens, would help to clearly

establish the most sensitive target and species for acute exposure, as well as which animal toxicity data are the most relevant to humans and useful for assessing acute health risks of decaBDE.

The inhalation database for acute-duration exposure to lower-brominated PBDEs is essentially limited to a single 14-day unpublished industry-sponsored studies of octaBDE in rats (Great Lakes Chemical Corporation 1978). A liver effect level was identified in this study, but MRL estimation is precluded by small animal groups and incomplete assessment of other toxicological end points, particularly a lack of information on thyroid hormone levels. Additional dose-response studies may provide an adequate basis for derivation of an acute inhalation MRL for lower-brominated PBDEs. Acute-duration inhalation exposure toxicity studies of decaBDE were not located.

Intermediate-Duration Exposure. Available intermediate-duration oral studies in animals indicate that the male reproductive system, the developing nervous system, the thyroid, and the liver are the main systemic targets of repeated exposures to lower-brominated PBDEs. The most sensitive end points were reproductive effects in male rats exposed to tetraBDE for 8 weeks, which identified a minimal LOAEL of 0.001 mg/kg/day for a 34% decrease in serum testosterone levels (Zhang et al. 2013b). Histological changes in the testes were also observed at ≥0.03 mg/kg/day in the study by Zhang et al. (2013b) and a similar study in rats by Huang et al. (2015). The minimal LOAEL for decreased serum testosterone was selected as the basis for an intermediate-duration MRL for lower-brominated PBDEs. A study in mice supports that the male reproductive system is a target for tetraBDE toxicity, reporting histological changes in the testes at tetraBDE doses ≥0.045 mg/kg/day for 30 days (Wang et al. 2013). As observed with acute exposure, altered neurobehavior was consistently observed in animals exposed to lower-brominated PBDEs for intermediate durations during development, with effects occurring at or above the doses of observed male reproductive effects (≥2 and ≥0.03 mg/kg/day in rats and mice, respectively) (Blanco et al. 2013; Bowers et al. 2015; Branchi et al. 2005; Cheng et al. 2009; Koenig et al. 2012; Ta et al. 2011; Woods et al. 2012). Liver effects, including increased liver weight, hypertrophy, and histopathological changes, were observed following exposure to lower-brominated PBDEs at doses as low as 0.45 mg/kg/day (Becker et al. 2012; Bondy et al. 2011, 2013; Bruchajzer 2011; Bruchajzer et al. 2012; Dunnick et al. 2012; IRDC 1976, 1977; Maranghi et al. 2013; Oberg et al. 2010; WIL Research Laboratories 1984; Zhang et al. 2014, 2015a, 2015b).

The thyroid is also a critical target in both adult and developing animals, with consistent observations of reduced serum T_4 levels at doses as low as 2.85 mg/kg/day and enlargement and histological alterations to the thyroid at doses as low as 0.45 mg/kg/day (Bansal et al. 2014; Becker et al. 2012; Bondy et al. 2011,

2013; Bowers et al. 2015; Driscoll et al. 2009; Dunnick et al. 2012; Ellis-Hutchings et al. 2006; Ernest et al. 2012; Hoppe and Carey 2007; IRDC 1977; Kodavanti et al. 2010; Maranghi et al. 2013; Miller et al. 2012; Poon et al. 2011; Skarman et al. 2005; Stoker et al. 2004, 2005; Szabo et al. 2009; Wang et al. 2011a; WIL Research Laboratories 1984; Zhou et al. 2002). Essentially all of the available data on thyroid effects of lower-brominated PBDEs have been obtained from oral studies in rats. It is speculated that the extent that PBDEs affect circulating levels of thyroid T_4 or T_3 might vary with species, and rats are often regarded as more sensitive than humans. Studies designed to elucidate the mechanism(s) of action for thyroid and other effects of lower-brominated PBDEs would help to better understand how the animal toxicity data can best be used to identify target end points and assess health risks in humans.

Available intermediate-duration oral studies provide limited evidence for effects in the pancreas, nervous system, liver, immune system, reproductive system, and several organ systems in developing animals following repeated exposures to decaBDE. The most sensitive end points were pancreatic effects from a study in male rats exposed to decaBDE for 8 weeks, which identified a minimal LOAEL of 0.05 mg/kg/day based on a 12% increase in serum glucose levels (Zhang et al. 2013a). The increase in serum glucose is considered to be part of a spectrum of effects indicative of altered insulin homeostasis and toxicity to the pancreas, including decreased serum insulin and morphological changes in pancreatic islet cells, following decaBDE exposure to doses ≥1 mg/kg/day (Zhang et al. 2013a). This minimal LOAEL for elevated serum glucose levels was used as a basis for the intermediate-duration oral MRL for decaBDE. Other effects observed following intermediate-duration exposure to decaBDE were observed at higher doses. In animals exposed during development, adverse effects included histopathological changes in the liver, kidney, and testes of rats exposed to ≥2 mg/kg/day (Fujimoto et al. 2011; Tseng et al. 2008, 2013); altered hippocampal electrophysiology in rats exposed to 20.1 mg/kg/day (Xing et al. 2009); and impaired immunity in mice exposed to 2,900 mg/kg/day (Watanabe et al. 2010b). In adult animals, observed effects following intermediate-duration decaBDE exposure included decreased anxiety in mice at doses 20 mg/kg/day (Heredia et al. 2012); histopathological changes in the ovaries, liver, spleen, and thymus and altered immune end points (T-cell distribution, lymphocyte proliferation, serum immunoglobulins) in rats exposed to 300 mg/kg/day (Liu et al. 2012); altered CD4 T-cell function in mice exposed to 800 mg/kg/day (Feng et al. 2016b); reduced serum testosterone, reduced sperm count and viability, and degenerative changes in the seminiferous tubules in mice exposed to 950 mg/kg/day (Sarkar et al. 2015); and histopathological changes in the liver in mice exposed to 9,400 mg/kg/day (Lee et al. 2010; Liu et al. 2012; Sakamoto et al. 2013). Since the majority of the observed effects lack supporting evidence from other studies, and many were single-dose studies, additional intermediate-duration studies evaluating these end points following decaBDE exposure at multiple doses would help to better

understand how the animal toxicity data can best be used to identify target end points and assess health risks in humans. Of particular interest would be additional studies evaluating altered insulin homeostasis, the critical effect that serves as the basis for the current intermediate-duration oral MRL for decaBDE.

The inhalation database for intermediate-duration exposure to PBDEs consists of one well-conducted 13-week unpublished industry study of octaBDE in rats (Great Lakes Chemical Corporation 2000). Hepatic, nasal, lung, thyroid, and ovarian effects were observed, and a NOAEL for changes in thyroid hormone levels was used as the basis for estimation of an intermediate-duration inhalation MRL. Intermediate-duration inhalation exposure toxicity studies of decaBDE were not located.

Chronic-Duration Exposure and Cancer. One chronic study of high purity decaBDE has been conducted. In this study, a commercial decaBDE product (94–97% pure) was fed to rats and mice for 103 weeks (NTP 1986). Comprehensive gross and histological examinations were performed on all animals, but no hematology, clinical chemistry, or urine indices, or thyroid hormone levels, were evaluated. The lowest tested dose in the study, 1,120 mg/kg/day in male rats, was a LOAEL for a liver lesion (neoplastic nodules) that is precancerous and associated with thrombosis in the same tissue, precluding estimation of an MRL. Additional chronic dose-response information would provide information on the NOAEL/LOAEL threshold and an appropriate basis for derivation of a chronic MRL for decaBDE. Neoplastic effects in this study included increased incidences of neoplastic nodules in the liver in the male and female rats and hepatocellular adenoma or carcinoma (combined) in the male mice. Slightly elevated incidences of thyroid gland follicular cell tumors were additionally observed in exposed male mice, although the increases were equivocal.

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

particularly informative because acute and intermediate-duration oral studies indicate that the thyroid and developing central nervous system are particularly sensitive targets for lower-brominated PBDEs.

Genotoxicity. Limited information was located regarding the genotoxicity of PBDEs in humans. A study of Chinese workers exposed to PBDEs suggested an association between levels of total PBDEs in blood and frequency of micronuclei in peripheral lymphocytes, but no causality was demonstrated (Yuan et al. 2008). Moreover, other pollutants could have played a role. A study of the general population from Korea did not find an association between serum levels of 2,2',4,4'-tetraBDE and 2,2',4,4',5-pentaBDE and chromosome telomere length in peripheral lymphocytes (Shin et al. 2010). Cytogenetic examination of additional populations previously or currently exposed to PBDEs would provide valuable information. A study in mice reported that maternal exposure to decaBDE during gestation resulted in sperm DNA damage in male offspring examined at 71 days of age (Tseng et al. 2013). Additional studies trying to replicate these results would be helpful. Testing the offspring for fertility would also be informative. DecaBDE and 2,2',4,4',5-pentaBDE have been tested in prokaryotic organisms and both yielded negative results in gene mutation tests (Evandri et al. 2003; NTP 1986). Relatively few PBDE congeners have been examined for genetic effects in mammalian cells. DNA damage and increased recombination activity have been reported (He et al. 2008a, 2008b; Helladay et al. 1999; Ji et al. 2011; Pellacani et al. 2012). Further studies with the PBDE congeners that are most frequently found in the environment and in human blood and tissues would be valuable. Studies designed to explore possible mechanisms of genotoxicity of PBDEs and also of metabolites would also be valuable.

Reproductive Toxicity. Reports of five one-generation studies in rats and mice were located. No exposure-related changes were observed in reproductive end points (number of pregnancies, gestation length, number, size, or sex ratio of litters) at pentaBDE doses up to 25 mg/kg/day or tetraBDE doses up to 1 mg/kg/day (Bondy et al. 2011, 2013; Koenig et al. 2012; Poon et al. 2011; Ta et al. 2011; Woods et al. 2012). No fertility impairments were observed in F1 males or females that were exposed once to pentaBDE on GD 6 at doses up to 0.3 mg/kg/day, when mated to unexposed animals (Kuriyama et al. 2005; Talsness et al. 2005, 2008). However, in a one-generation study in mink, females exposed to pentaBDE at doses ≥0.25 mg/kg/day from pre-mating day 28 through PNW 6 did not whelp (Bull et al. 2007; Zhang et al. 2009). It is not clear in the study reported by Bull et al. (2007) whether mink exposed to 0.25 mg/kg/day never became pregnant or had complete litter loss. However, Zhang et al. (2009) reported that female mink exposed to 0.31 mg/kg/day had no exposure-related changes in mating success; rather, sows showed complete litter loss with 70% showing clear postimplantation loss. Despite a lack of effects from most one-generation studies, reduced serum testosterone and testicular damage (increased

multinucleated giant cells, germ cell loss, and apoptotic cells) was reported in adult male rats and mice exposed to tetraBDE doses as low as 0.001 and 0.045 mg/kg/day, respectively (Huang et al. 2015; Wang et al. 2013; Zhang et al. 2013b). Reduced serum testosterone in rats exposed to ≥0.001 mg/kg/day for 8 weeks was selected as the critical effect for the intermediate-duration MRL for lower-brominated PBDEs; therefore, additional studies with other congeners evaluating testicular damage may better characterize the reproductive toxic potential of PBDEs and assure the adequacy of the intermediate oral MRL. Also, studies in other species (e.g., rabbits) may be warranted to investigate species-specific reproductive effects and two-generation studies designed to assess effects on fertility in both sexes would better characterize the potential for reproductive toxicity as a result of exposure to lower-brominated PBDEs.

For decaBDE, information on the reproductive toxicity is limited to a single one-generation oral study in rats that found no exposure-related functional effects following exposure to an impure decaBDE mixture containing lower-brominated PBDEs (77% decaBDE, 22% nonaBDE, 0.8% octaBDE) at dietary doses up to 100 mg/kg/day for 60 days prior to mating through PND 21 (Dow Chemical Co. 1975; Norris et al. 1975a). Studies that evaluated reproductive organ histology following exposure to decaBDE generally did not report detectable effects. As suggested for lower-brominated PBDEs, studies in other species may be warranted to investigate species-specific reproductive effects and two-generation studies designed to assess effects on fertility in both sexes would better characterize the potential for reproductive toxicity as a result of exposure to decaBDE.

Developmental Toxicity. Numerous oral developmental toxicity studies have shown no evidence of teratogenicity in rats or rabbits exposed to lower-brominated PBDEs or decaBDE, although fetotoxic effects, including skeletal ossification variations at maternally toxic doses, have occurred with exposures to lower-brominated mixtures (Argus Research Laboratories 1985a, 1985b; Biesemeier et al. 2011; Blanco et al. 2012; Breslin et al. 1989; Chi et al. 2011; Dow Chemical Co. 1975, 1985; Ellis-Hutchings et al. 2009; Hardy et al. 2002; Life Science Research Israel Ltd. 1987; Norris et al. 1975a; WIL Research Laboratories 1986). The available evidence adequately shows that teratogenicity and fetal toxicity is not a critical effect of concern for either lower-brominated PBDEs or decaBDE. However, there is evidence that the developing nervous and endocrine systems, and potentially the developing reproductive and immune systems are sensitive targets of particular PBDE congeners. Numerous studies show that developmental exposure can lead to neurological changes at later life stages, as rats and mice exposed pre- or peri-natally to lower-brominated PBDEs or decaBDE show neurobehavioral alterations following exposure to lower-brominated PBDEs and decaBDE at doses ≥0.06 and ≥2.22 mg/kg/day, respectively, as

well as several other neurological effects at higher doses, including delayed ontogeny of reflexes, ultrastructural changes, altered nicotinic receptor density, altered electrophysiology, and altered gene and protein expression levels (Biesemeier et al. 2011; Blanco et al. 2013; Branchi et al. 2001, 2002, 2005; Cheng et al. 2009; Eriksson et al. 2001, 2002b, 2006; Fischer et al. 2008; Fujimoto et al. 2011; Gee and Moser 2008; He et al. 2009, 2011; Johansson et al. 2008; Koenig et al. 2012; Kuriyama et al. 2004, 2005; Rice et al. 2007; Sand et al. 2004; Ta et al. 2011; Viberg et al. 2002, 2003a, 2003b, 2004a, 2004b, 2005, 2006, 2007; Woods et al. 2012; Xing et al. 2009). Developing animals exposed to lower-brominated PBDEs, but not decaBDE, also consistently showed decreased serum T_4 levels, although these effects may be transient (Blanco et al. 2013; Bondy et al. 2011, 2013; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Kuriyama et al. 2007; Miller et al. 2012; Poon et al. 2011; Shah et al. 2011; Skarman et al. 2005; Szabo et al. 2009; Wang et al. 2011a; Zhang et al. 2009; Zhou et al. 2002). There is limited evidence that developmental exposure to lower-brominated PBDEs may effect reproductive system development (Kuriyama et al. 2005; Talsness et al. 2005, 2008) and that both lower-brominated PBDEs and decaBDE may effect immune system development (Bondy et al. 2013; Watanabe et al. 2008, 2010b). Additional studies evaluating reproductive and immune system development following exposure to PBDEs would better characterize the developmental toxic potential of PBDEs on these systems.

Immunotoxicity. Information regarding the immunosuppressive potential of PBDEs is limited. Immune function assays in adult animals are limited to lower-brominated PBDEs. Acute-duration oral studies in animals exposed to pentaBDE reported that plaque-forming splenic cell antibody response to injected sheep red blood cells was significantly reduced in mice exposed to 72 mg/kg/day pentaBDE for 14 days (Fowles et al. 1994) and *in vitro* production of IgG immunoglobulin from pokeweed mitogen-stimulated splenocytes was reduced in mice, but not in rats, exposed to 36 mg/kg/day pentaBDE for 14 days (Darnerud and Thuvander 1998). The only intermediate-duration immune function assay reported no exposure-related immune effects in the KLH antibody production assay or the PHA skin challenge in mink exposed to pentaBDE at doses up to 0.78 mg/kg/day for 9 weeks (Martin et al. 2007). The majority of studies report no histological changes in immune tissues with acute- or intermediate-duration exposure to PBDEs. However, as discussed in the Developmental section above, exposure to lower-brominated PBDEs or decaBDE during development may lead to impaired immune function (Bondy et al. 2013; Watanabe et al. 2008, 2010b). Additional oral studies using a battery of immunological tests and a lower range of doses for several congeners, including decaBDE, would serve to better characterize the immunotoxic potential of PBDEs.

Neurotoxicity. While a large body of evidence indicates that the developing nervous system is a target for PBDE toxicity, a limited amount of information is available on neurological effects of PBDEs in adult animals. In a comprehensive neurotoxicity screen, no adverse effects were observed in rats exposed once to pentaBDE at doses up to 1.2 mg/kg/day (Belles et al. 2010). In a neurobehavioral study, no exposure-related changes were observed in open-field behavior, anxiety-like behavior, or learning and memory in male rats exposed to low doses of pentaBDE at doses up to 0.015 mg/kg/day for 90 days (Daubie et al. 2011). In a higher dose study, impaired attention and inhibitory control were observed in male mice exposed to pentaBDE at 26.2 mg/kg/day for 125 days; no exposure-related changes were observed at 17.5 mg/kg/day (Driscoll et al. 2009). Impaired learning and memory were observed in male rats exposed to tetraBDE at doses ≥0.1 for 30 days (Yan et al. 2012).

For decaBDE, no studies evaluating neurological end points in adult rats or mice following acute exposure were identified. Decreased anxiety behavior was observed in male mice exposed to decaBDE for 15 days; however, no exposure-related changes were observed in a functional observation battery or learning and memory (Heredia et al. 2012). In another study, no changes were observed in open-field behavior of male rats exposed to decaBDE at doses up to 50 mg/kg/day 90 days (Wang et al. 2011b). No overt signs of neurotoxicity were observed in rats and mice exposed to decaBDE in estimated dietary doses as high as 16,000–19,000 mg/kg/day for 14 days, 8,000–9,000 mg/kg/day for 13 weeks, or 2,550–7,780 mg/kg/day for 103 weeks (NTP 1986). Although the high doses and extended exposure durations provided opportunities for the induction and/or development of clinical signs, the study is limited by lack of testing for subtle behavioral changes and neurodevelopmental effects. Additional comprehensive neurotoxicity batteries in adult animals exposed orally to repeat doses of PBDEs would better characterize the potential for PBDEs to cause neurotoxic effects in adults.

Epidemiological and Human Dosimetry Studies. There are numerous epidemiological studies evaluating potential associations between tissue PBDE concentrations and adverse health effects; however, none of the studies provided quantitative exposure information. Therefore, the available epidemiological studies are not useful for quantitative risk assessment. Available studies indicate that PBDE exposure may lead to neurodevelopmental effects (Adgent et al. 2014; Chao et al. 2011; Chen et al. 2014; Chevrier et al. 2016; Cowell et al. 2015; Ding et al. 2015; Eskenazi et al. 2013; Gascon et al. 2012; Herbstman et al. 2010; Hoffman et al. 2012; Roze et al. 2009; Sagiv et al. 2015; Shy et al. 2011; Vuong et al. 2016a). Evidence for associations between PBDE exposure and other effects in humans are inconsistent between studies, including observations of altered thyroid hormone levels (Abdelouahab et al. 2011, 2013; Bloom et al. 2008, 2014; Chevrier et al. 2010; Dallaire et al. 2009; Eggesbo et al. 2011;

Eguchi et al. 2015; Hagmar et al. 2001; Herbstman et al. 2008; Huang et al. 2014; Julander et al. 2005; Kicinski et al. 2012; Kim et al. 2011a, 2011d, 2012a, 2012b, 2013a; Leijs et al. 2012; Lignell et al. 2016; Makey et al. 2016; Mazdai et al. 2003; Shy et al. 2012; Stapleton et al. 2011; Turyk et al. 2008; Yuan et al. 2008; Wan et al. 2010; Wang et al. 2010; Xu et al. 2014a, 2014b, 2015a), male reproductive effects (Abdelouahab et al. 2011; Akutsu et al. 2008; Hagmar et al. 2001; Johnson et al. 2013; Meeker et al. 2009; Mumford et al. 2015; Turyk et al. 2008), female reproductive effects (Buck Louis et al. 2013; Chao et al. 2007, 2010; Chen et al.2011; Harley et al. 2010; Johnson et al. 2012; Karmaus et al. 2011; Wainman et al. 2016), non-neurological developmental effects (Agay-Shay et al. 2015; Carmichael et al. 2010; Chao et al. 2007; Chen et al. 2015; Erkin-Cakmak et al. 2015; Foster et al. 2011; Harley et al. 2011; Kim et al. 2011d, 2012a, 2012b, 2015; Koskenniemi et al. 2015; Leijs et al. 2008; Lopez-Espinosa et al. 2015; Ma et al. 2012a; Main et al. 2007; Mazdai et al. 2003; Meijer et al. 2012; Miranda et al. 2015; Müller et al. 2016; Ochiai et al. 2014; Peltier et al. 2015; Ren et al. 2011; Robledo et al. 2015a; Serme-Gbedo et al. 2016; Tan et al. 2009; Vuong et al. 2016b; Warembourg et al. 2016; Windham et al. 2015a; Wu et al. 2010; Xu et al. 2015b), and risk for diabetes (Airaksinen et al. 2011; Lee et al. 2011; Lim et al. 2008; Smarr et al. 2016; Turyk et al. 2015). In other epidemiological studies, serum PBDE levels were not significantly associated with carotid atherosclerosis, risk of stroke, bone mineral density, immune function, non-Hodgkin's lymphoma (Fernlof et al. 1997; Hardell et al. 1998; Kumar et al. 2014a, 2014b; Lee et al. 2012; Lind et al. 2012; Lindstrom et al. 1998;Weiss et al. 2006), breast cancer (Holmes et al. 2014; Hurley et al. 2011), thyroid cancer (Aschebrook-Kilfoy et al. 2015), prostate cancer (Pi et al. 2016), reproductive effects in men (Toft et al. 2014), Polycystic Ovary Syndrome (Vagi et al. 2014), or uterine fibroids (Trabert et al. 2015).

Epidemiological studies with quantitative estimates of exposure would be useful for quantitative risk assessment. Considering the possibility that PBDEs can be transferred to the fetus across the placenta and that greater amounts might be transferred to nursing infants via breast milk, as well as evidence that perinatal exposure to PCBs and other similar chemicals may induce subtle neurological damage and immunological and thyroid effects in children, transgenerational studies would be particularly informative. Additional studies evaluating the potential link between pre- and peri-natal PBDE exposure and childhood behavior disorders, such as Autism Spectrum Disorder (ASD) and ADHD, have been specifically requested by the scientific community based upon potential links between these disorders and endocrine disruption (de Cock et al. 2012; Messer 2010). However, limitations that are likely to constrain epidemiological investigations, such as unmeasured PBDE exposure concentrations and lack of controls for confounding co-exposures, may be difficult to address. Studies that assess PBDE concentrations in serum or breast milk along with concentrations of other persistent organic pollutants (POPs), such as

PCBs, PCDDs, and /or PCDFs, would be useful to evaluate responses that may be co-dependent on other persistent lipophilic agents.

Biomarkers of Exposure and Effect.

Exposure. PBDEs accumulate in adipose tissue, serum, and breast milk of the general population due to their lipophilic characteristics. Concentrations of PBDEs in breast milk are useful, non-invasive markers of maternal body burdens and of *in utero* and lactational exposures, but body burden assessments are limited by a lack of time-trend data for PBDEs in the milk of U.S. populations (Hooper and McDonald 2000). Breast milk monitoring programs would provide time-trend data that would verify whether regulatory action to limit the use of PBDEs is reversing the previous trend of an exponential increase in PBDE concentrations in breast milk (Norén and Meironyté 1998, 2000). Studies on the predictive value of concentrations of PBDEs in serum and adipose tissue could provide useful information for detection and monitoring of exposure. It should be noted, however, that solubilities in adipose and breast milk are likely to vary with the congener. For example, decaBDE is much less soluble in adipose than pentaBDE. These differences must be considered when designing studies evaluating PBDE exposure. Recent studies have indicated that PBDE concentrations in hair may also be useful to estimate exposure levels (Aleksa et al. 2012a, 2012b; Malarvannan et al. 2013), although Zheng et al. (2011) reported that PBDE concentrations in hair were not correlated with PBDE concentrations in indoor dust from urban, e-waste, and rural areas in South China. Additional studies would be useful to validate this approach.

A potential biomarker of exposure to PBDEs relates to their effect on the thyroid gland. Thyroid changes in rats and mice include reduced serum T_4 levels, with no changes in serum TSH (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998; WIL Research Laboratories 1984; Zhou et al. 2001, 2002). However, using thyroid changes as a biomarker may not be reliable, as thyroid changes are not specific to exposure to PBDEs and the effects associated with the thyroid in non-clinical studies are likely specific to the rodent and may or may not be directly relevant to the human. Additional studies could characterize thyroid effects of PBDEs in humans and develop specific correlations between levels and duration of exposure and alterations in serum levels of T_4.

Effect. Biomarkers that could be used to characterize health effects caused specifically by exposure to PBDEs have not been identified. Additional information on the mechanisms of toxicity may suggest a useful biomarker of effect; however, at this time, there is little to suggest that such biomarkers exist.

Absorption, Distribution, Metabolism, and Excretion. No information was located regarding the toxicokinetics of PBDEs in humans following controlled oral exposure, although information of toxicokinetics has been gathered based on levels of PBDEs and metabolites in tissues of environmentally exposed individuals and numerous animal studies and *in vitro* studies.

Absorption studies in animals indicate that decaBDE is absorbed to a lesser degree than lower-brominated PBDEs. The most recent and best available estimates of oral absorption efficiencies indicate a range of 70–85% for the tetraBDE (BDE 47), pentaDE (BDE 99, BDE 100), and hexaBDE (BDE 153, BDE 154), and 10–26% for decaBDE (BDE 209) (Chen et al. 2006; Hakk et al. 2002a, 2002b, 2009; Klasson Wehler et al. 2001; Morck and Klasson Wehler 2001; Morck et al. 2003; Örn and Klasson-Wehler 1998; Riu et al. 2008; Sandholm et al. 2003; Sanders et al. 2006a, 2006b; Staskal et al. 2005). Quantitative absorption studies in humans could corroborate the conclusions on oral uptake in animals that are based on elimination and excretion data.

Distribution studies in animals indicate that lower-brominated BDE congeners, following absorption and an initial wide distribution, are preferentially accumulated in adipose tissues (Chen et al. 2006; El Dareer et al. 1987; Hakk et al. 2002a, 2009; Morck and Klasson-Wehler 2001; Morck et al. 2003; Norris et al. 1975a; NTP 1986; Örn and Klasson-Wehler 1998; Riu et al. 2008; Sanders et al. 2006a, 2006b; Staskal et al. 2005, 2006a). In comparison, decaBDE is more readily distributed to highly perfused tissues and less readily distributed to adipose tissues. Evidence for the transfer of PBDEs from pregnant mothers to the developing fetus and for the transfer of PBDEs from maternal blood to breast milk and then to nursing infants comes from a number of studies of PBDE concentrations in maternal and cord serum samples and breast milk samples from groups of non-occupationally exposed women. In general, the tetra- and penta-brominated PBDEs have been the predominant congeners detected in maternal and cord serum samples and breast milk samples, but some recent studies assaying for a wider range of PBDE congeners have found evidence for distribution of hepta-, octa-, or decaBDEs into cord serum and breast milk (Antignac et al. 2009, 2008; Chen et al. 2013; Daniels et al. 2010; Hites 2004; Kawashiro et al. 2008; Li et al. 2013a; Malarvannan et al. 2013; Mazdai et al. 2003; Meijer et al. 2008; Park et al. 2011; Qiu et al. 2009; Schecter et al. 2010, 2006; Vizcaino et al. 2011; Wan et al. 2010). Maternal transfer of both lower-brominated PBDEs and decaBDE has also been shown in animal studies (Cai et al. 2011; Zhang et al. 2011). The available studies appear adequate to characterize distribution of PBDEs.

Current evidence indicates that CYP2B6-mediated metabolism of BDE 47 and BDE 99 produces multiple hydroxylated metabolites via hydroxylation and ether bond cleavage, based on *in vitro* studies with

human liver microsomes or hepatocytes and human recombinant CYPs (Erratico et al. 2012, 2013; Feo et al. 2013). The major metabolites of BDE 47 and BDE 99 formed by human liver microsomes were not the same as those identified using rat liver microsomes (Erratico et al. 2013, 2012, 2011). Different classes of CYP enzymes appear to be involved in *in vitro* rat liver metabolism of BDE 47 and BDE 99: CYP1A1, CYP2A2, and CYP3A1 for BDE 47 and CYP1A1, CYP2A2, CYP2B1, and CYP3A1 for BDE 99 (Erratico et al. 2011). Production of hydroxylated metabolites of BDE 153 (Lupton et al. 2009) and BDE 209 (Stapleton et al. 2009) has not been demonstrated with human liver microsomes or hepatocytes. It is uncertain if these latter findings are reflective of a limited *in vivo* capacity of humans to metabolize these BDE congeners or because the proper *in vitro* conditions for metabolizing these congeners were not provided. Currently, studies of metabolism of BDE 47 and BDE 99 using *in vitro* human and rat systems have found evidence of metabolic oxidative debromination only with BDE 47 in human liver microsomes. In contrast, a number of *in vivo* studies have found evidence for oxidative debromination by analysis of feces collected from rats exposed to BDE 47 (Marsh et al. 2006), BDE 99 (Hakk et al. 2002a), BDE 100 (Hakk et al. 2006), BDE 154 (Hakk et al. 2009), and BDE 209 (Morck et al. 2003; Sandholm et al. 2003). Additional metabolism studies would help to characterize the enzymes involved as well as the transformation of some congeners to biologically active hydroxylated BDEs. There are still data gaps in the toxicokinetics of decaBDE, including an incomplete understanding of the debromination of decaBDE to lower-brominated BDEs.

The detection of PBDEs in human breast milk samples suggest that breast milk represents an elimination route of absorbed PBDEs in women (see Jakobsson et al. 2012 and Frederiksen et al. 2009 for reviews of PBDE levels in breast milk); however, studies do not provide a clear account of the degree to which PBDEs are cleared from the body during breastfeeding (Hooper et al. 2007; Jakobsson et al. 2012; LaKind et al. 2009; Thomsen et al. 2010). Rat studies indicate that ingested PBDEs are principally excreted in the feces with <2% of administered radioactivity excreted in the urine within 3 days of dose administration (Chen et al. 2006; Hakk et al. 2002a, 2006; Morck et al. 2003; Norris et al. 1973, 1975b; Orn and Klasson-Wehler 1998; Sanders et al. 2006a; Riu et al. 2008). However, a different elimination pattern has been observed in mice, especially with BDE 47. In mice given single oral doses of ^{14}C-labeled PBDE congeners, fecal and urinary elimination were principal routes of elimination for BDE 47 (Orn and Klasson-Wehler 1998; Sanders et al. 2006a), whereas fecal elimination appeared to be more important than urinary elimination with BDE 99 (Chen et al. 2006) and BDE 153 (Sanders et al. 2006b). Complementary studies with female C57BL/6J given single intravenous 1-mg/kg doses of ^{14}C-labeled BDE 47, BDE 99, BDE 100, or BDE 153 also indicate that the importance of urinary excretion in mice is congener specific (Staskal et al. 2006b). Quantitative studies in humans could

determine which excretion route is more relevant for humans (feces or urine) for different congeners based on elimination and excretion data. Additionally, further studies regarding the degree of elimination in breast milk during breast feeding could better characterize exposure risks for breastfeeding infants.

Comparative Toxicokinetics. Insufficient data are available to determine whether there are qualitative differences in the toxicokinetic disposition of PBDEs between humans and animals and among animal species. However, elimination studies in rats and mice (discussed above) highlight that toxicokinetics may differ between species. Differences are likely to be dependent on the specific congener or mixture studied, and pharmacokinetic modeling studies could help to determine the validity of extrapolating data. Most of the available toxicokinetic studies of PBDEs have been performed in rats, and studies in other species could help to ascertain the most relevant animal model.

Methods for Reducing Toxic Effects. The mechanism by which PBDEs enter the blood stream is not known, there are no established methods for reducing body burden of PBDEs, and the mechanisms of toxic action of PBDEs are incompletely understood. A more complete characterization of the cytosolic AhR protein 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 PBDEs would also be valuable.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Body burden data, as well as intake modeling, suggest that infants and toddlers have higher exposures to PBDEs as compared to older children or adults (EPA 2010; Lorber 2008; Trudel et al. 2011; Wong et al. 2013). Several epidemiological studies have reported results suggestive of an effect of PBDE on neurodevelopment in children (Adgent et al. 2014; Chao et al. 2011; Chen et al. 2014; Chevrier et al. 2016; Cowell et al. 2015; Ding et al. 2015; Eskenazi et al. 2013; Gascon et al. 2012; Herbstman et al. 2010; Hoffman et al. 2012; Roze et al. 2009; Sagiv et al. 2015; Shy et al. 2011; Vuong et al. 2016a), and these findings are supported by developmental studies in animals (Biesemeier et al. 2011; Blanco et al. 2013; Branchi et al. 2001, 2002, 2005; Cheng et al. 2009; Eriksson et al. 2001, 2002, 2006; Fischer et al. 2008; Fujimoto et al. 2011; Gee and Moser 2008; He et al. 2009, 2011; Johansson et al. 2008; Koenig et al. 2012; Kuriyama et al. 2004, 2005; Rice et al. 2007; Sand et al. 2004; Ta et al. 2011; Viberg et al. 2002, 2003a, 2003b, 2004a, 2004b, 2005, 2006, 2007; Woods et al. 2012; Xing et al. 2009). Epidemiological

studies in infants are inconclusive regarding thyroid effects and exposure to PBDEs (Abdelouahab et al. 2013; Herbstman et al. 2010; Kim et al. 2011a, 2012a; Lin et al. 2011; Mazdai et al. 2003; Shy et al. 2012); however, numerous animal studies indicated that developmental exposure to lower-brominated PBDEs result in thyroid hormone alterations (Blanco et al. 2013; Bondy et al. 2011, 2013; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Kuriyama et al. 2007; Miller et al. 2012; Poon et al. 2011; Shah et al. 2011; Skarman et al. 2005; Szabo et al. 2009; Wang et al. 2011a; Zhang et al. 2009; Zhou et al. 2002). Additional studies would better characterize the potential susceptibility of children to the effects of PBDEs on the thyroid and neurodevelopment, particularly considering the possibility that these effects are related to the dependence of central nervous system development on thyroid hormones.

Data from two human epidemiological studies suggest that PBDE exposure may alter reproductive system development in boys (Main et al. 2007; Meijer et al. 2012). In contrast, other studies found no associations between serum or adipose tissue PBDE concentrations and reproductive development (Carmichael et al. 2010; Koskenniemi et al. 2015; Leijs et al. 2008). These findings, along with limited evidence of reproductive effects in animals exposed to lower-brominated PBDEs during development (Kuriyama et al. 2005; Talsness et al. 2005, 2008), indicate that additional studies of reproductive development in young animals would help to more fully assess children's susceptibility to PBDEs.

No information is available regarding the immunosuppressive potential of PBDEs in children, but serum levels of BDE 28 and 209 were found associated with an increased risk of asthma in a study of 3–6-year-old Chinese children (Meng et al. 2016). Limited evidence in young animals exposed to PBDEs (Bondy et al. 2013; Watanabe et al. 2008, 2010b) indicates that additional studies of immune competence in developing animals would also help to more fully assess children's susceptibility to PBDEs.

A recent small study of Swedish toddlers (n=22) found good correlations between concentrations of some PBDEs in serum and in feces, suggesting that fecal analysis, a noninvasive test, might be a good alternative for biomonitoring PBDEs in toddlers (Sahlström et al. 2015). Larger studies would be valuable to improve the predictive power of the statistical analyses performed in this study. In addition, it would be helpful to determine whether the method is applicable to infants and children of different ages.

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

Fifty-six ongoing research efforts have been identified that may provide data related to the toxic actions of PBDEs in humans (RePORTER 2014, 2016). These projects are summarized in Table 3-7.

Animal Studies. Dr. Charles Herbert of the Southern Research Institute is conducting chronic studies of the commercial pentaBDE mixture DE-71 in rats and mice under contract with NTP and Dr. Lu Taylor of the Battelle Memorial Institute is conducting a perinatal study BDE 47 in CB6F1-Tg(HRAS2) transgenic mice under contract with NTP.

Several animal studies are investigating neurobehavioral changes in animals exposed to PBDEs. Four ongoing studies are investigating behavioral and biochemical end points relevant to ADHD (Drs. Susan Schantz and Paula Eubig, University of Illinois Urbana-Champaign; Dr. Richard Seegal, Wadsworth Center). To assess the role of the immune system and its interaction with environmental contaminants in autism and other neurodevelopmental disorders, Dr. Isaac Pessah of the University of California at Davis is investigating the effects of perinatal PBDE exposure on brain development, complex social behaviors, and immune system function in mouse strains with low (C57BL/6J) or high (SJL mice) susceptibility to autoimmunity. Using an established mouse model, Dr. Margarita Behrens, from the Salk Institute for Biological Sciences, will examine the effects of exposure to PBDE on autism spectrum disorder. Dr. Helen Sable of the University of Memphis is examining if developmental PBDE exposure in rats alter dopamine receptor expression and enhance behavioral sensitization following psychostimulant exposure (as seen with PCBs).

Dr. Deena Small of the University of New England is examining bone growth and remodeling in mice exposed to pentaBDE from PND 1 to 60. In addition, Dr. Small will use cell culture-based assays that measure gene expression, enzyme activity and calcium deposition in cultured bone cell lines exposed to the pentaBDEs.

Toxicokinetic Studies. Dr. Tracey Woodruff of the University of California, San Francisco is measuring concentrations of PBDEs and OH-PBDEs in human maternal and fetal biological specimens from women undergoing voluntary, second trimester pregnancy terminations and generating original human data on whether fetal exposures to PBDEs alter gene expression of cytochrome P450 (CYP) enzymes in the second-trimester human fetal liver and placenta. Dr. James Olson of SUNY Buffalo is conducting a qualitative and quantitative characterization of the human CYP-specific *in vitro* metabolism of

Table 3-7. Ongoing Research for PBDEs in Humans

Investigator	Affiliation	Research description	Sponsor
Baccarelli, A	Harvard School of Public Health	Prenatal exposure to PBDEs and visual skills, attention, and fine motor skills in children	NIEHS
Barr, DB	Emory University	Prenatal exposure to PBDEs and birth outcomes	NIHES
Blumberg, B	University of California-Irvine	Endocrine disrupter modulation of the steroid and xenobiotic receptor, SXR, in development and lymphomagenesis	NIEHS
Caudle, WM	Emory University	Vesicular monoamine transporter 2 as a mediator of PBDE neurotoxicity	NIEHS
Chen, A	University of Cincinnati	Longitudinal study of exposure to PBDEs and child neurobehavior	NIEHS
Chen, S	Beckman Research Institute/City of Hope	Determine role and mechanism of PBDEs on development of breast cancer during the menopausal transition	NIEHS
Costa, LG	University of Washington	Low-level exposure to PBDEs: Testing the hermetic and epigenetic hypotheses	NIEHS
Croen, LA	Kaiser Foundation Research Institute	Prenatal and neonatal biologic markers for autism	NIEHS
Darrow, L	Emory University	PBDE body burdens, house dust concentrations, and associations with thyroid hormone	NIEHS
Di Giulio, R	Duke University	Thyroid metabolism disruption key in toxicant-induced development	NIEHS
Eskenazi, B	University of California Berkeley	Pesticides and PBDEs on neurobehavior	NIEHS
Eskenazi, B	University of California Berkeley	PBDEs, DDT, and neurodevelopment in school-aged Mexican-American children	NIEHS
Eskenazi, B	University of California Berkeley	DDT and PBDE exposure, puberty onset, and neurodevelopment in Mexican-American girls	NIEHS
Eubig, P	University of Illinois Urbana-Champaign	Effects of PCBs and PBDEs on three distinct components of response inhibition	NIEHS
Ferguson, PL	University of South Carolina at Columbia	Mechanisms of xenoestrogen stress: a proteomic and functional genomic approach	NIEHS
Fitzgerald, EF	State University of New York at Albany	Persistent organic pollutants and cognitive decline in the elderly	NIEHS
Getahun, D	Kaiser Foundation Research Institute	Flame retardant and adverse perinatal outcome	NIEHS
Giese, RW	Northeastern University	Discovery of xenobiotics associated with preterm birth	NIEHS
Hauser, RB	Harvard School of Public Health	Maternal and paternal flame retardant exposure, impact on fertility and pregnancy	NIEHS
Herbert, C	Southern Research Institute	Studies to evaluate the toxicologic and carcinogenic potential	NIEHS
Herbstman, JB	Columbia University	Pre- and postnatal PBDE exposure, thyroid hormones, and neurodevelopment	NIEHS

Table 3-7. Ongoing Research for PBDEs in Humans

Investigator	Affiliation	Research description	Sponsor
Hertz-Picciotto, I	University of California at Davis	Epidemiology and the environment in autism	NIEHS
Hertz-Picciotto, I	University of California at Davis	The CHARGE study: Childhood Autism Risk from Genetics and Environment	NIEHS
Hertz-Picciotto, I	University of California at Davis	Autism risk, prenatal environmental exposures, and pathophysiologic markers	NIEHS
Holland, NT	University of California Berkeley	Epigenetic effects of DDT/E and PBDEs on puberty	NIEHS
Kamen, DL	Medical University of South Carolina	Environmental determinants of autoimmunity among African Americans in coastal South Carolina	NIEHS
Klaassen, CD	University of Washington	Developmental exposure to PBDEs and long-lasting modifications of drug metabolism in children	NIEHS
Lasalle, JM	University of California at Davis	Epigenetic interaction of MECP2 and organic pollutants in neurodevelopment	NIEHS
Lasalle, JM	University of California at Davis	Methylomic and genomic impacts of organic pollutants in Dup15q syndrome	NIEHS
Loch-Caruso, RK	University of Michigan	Mechanisms of inflammation in gestational membranes	NIEHS
Louis, G	Eunice Kennedy Shriver National Institute of Child Health & Human Development	Longitudinal investigation of fertility and the environment	NICHD
Miller, PK	Alaska Community Action on Toxics (ACAT)	Protecting the health of future generations: assessing and preventing exposures	NIEHS
Morello-Frosch, RA	University of California, San Francisco	Effects of endocrine disrupting chemicals and chronic psychosocial stress on fetal growth	NIEHS
Olson, JR	State University of New York at Buffalo	Bioactivation of PBDEs by human cytochrome P-450	NIEHS
Pessah, IN	University of California at Davis	Calcium signaling defects in autism	NIEHS
Pessah, IN	University of California at Davis	Neurodevelopmental toxicology of autism	NIEHS
Peterson, M	University of Utah	Environment chemicals and gynecologic health	NICHD
Rappaport, SM	University of California Berkeley	Exposure Assessment for childhood leukemia	NIEHS
Robinson, JF	University of California, San Francisco	Polybrominated diphenyl ether effects on human neuronal development	NIEHS
Sable, HJ	University of Memphis	Assessment of psychostimulant addiction risk following developmental PCB exposure	NIEHS
Sabo-Attwood, TL	University of South Carolina at Columbia	Mechanisms of xenoestrogen stress: a proteomic and functional genomic approach	NIEHS

Table 3-7. Ongoing Research for PBDEs in Humans

Investigator	Affiliation	Research description	Sponsor
Schantz, SL	University of Illinois Urbana-Champaign	PCBs, PBDEs, hearing loss, and attention/impulsivity: mechanistic studies in animals	NIEHS
Schantz, SL	University of Illinois Urbana-Champaign	Health effects of PCB exposure from contaminated fish	ATSDR
Seegal, RF	Wadsworth Center	Developmental neuroendocrine effects of PCBs and PBDEs	NIEHS
Small, DJ	University of New England	Effect of polybrominated diphenyl ether flame retardant exposure on osteogenesis	NIEHS
Stapleton, HM	Duke University	Children's exposure to flame retardants: effects on thyroid hormone regulation	NIEHS
Stapleton, HM	Duke University	Deiodinase activity as a biomarker of response to brominated flame retardants	NIEHS
Taylor, LU	Battelle Memorial Institute	Studies to evaluate the toxicological potential of test articles	NIEHS
Turyk, ME	University of Illinois at Chicago	Diabetes and persistent organic pollutants	NIEHS
Van de Water, JA	University of California at Davis	Immune environment interaction and neurodevelopment	NIEHS
Wapner, R	Columbia University Health Sciences	Endocrine disruption in pregnant women: thyroid disruption and infant development	NIEHS
Webster, TF	Boston University Medical Campus	Measuring human exposure to PBDEs	NIEHS
Woodruff, TJ	University of California, San Francisco	Human maternal/fetal exposures to PBDEs and their metabolites during development	NIEHS
Woodruff, TJ	University of California, San Francisco	Mid-gestational exposure to endocrine disrupting chemicals and effects on placental development	NIEHS
Zhang, Y	Yale University	Polyhalogenated aromatic hydrocarbons and thyroid cancer risk in the Department of Defense Serum Repository (DoDSR) cohort	NIEHS
Zota, AR	George Washington University	Role of endocrine-disrupting chemicals and social stress on perinatal outcomes	NIEHS

Source: RePORTER 2014, 2016

NIEHS = National Institute of Environmental Health Sciences; PBDE = polybrominated diphenyl ether; PCB = polychlorinated biphenyl

2,2',4,4'-tetraBDE (BDE 47), 2,2',4,5'-tetraBDE (BDE 49), 2,2',4,4',5-pentaBDE (BDE 99), and 2,2',4,4',6- pentaBDE (BDE 100) as well as quantify OH-PBDEs in human milk and serum and assess the potential impact of CYP2B6 genotype on the body burden of PBDEs. Dr. Heather Stapleton of Duke University is identifying the products of hepatic metabolism of PBDEs (no further details available).

Mechanistic Studies. Several studies are investigating mechanisms of neurotoxicity. At the University of California at Davis, Dr. Janine Lasalle is investigating epigenetic changes in the genome of Mecp2 mutant mouse models of Rett syndrome and autism following *in vivo* exposure to BDE 47, Drs. Janine Lasalle and Isaac Pessah are investigating potential mechanisms of PBDE toxicity in susceptible neuronal cell models (chromosome 15q11-13 duplication syndrome [Dup15q] or fragile X syndrome [FMRI]), and Dr. Judy Van de Water is investigating mechanisms of PBDE toxicity in peripheral blood mononuclear cells from children with autism. Dr. Joshua Robinson of the University of California San Francisco is investigating the effects *in vitro* exposure to BDE 47 and BDE 99 on neuronal differentiation and gene expression in human embryonic stem cells. Dr. Lucio Costa of University of Washington is investigating genetic and epigenetic changes in cultured mouse neurons exposed to low, environmentally-relevant concentrations of BDE 47. Dr. William Caudle of Emory University is investigating the potential mechanisms by which the commercial pentaBDE mixture DE-71 disrupts VMAT2, which is a key mediator of cytosolic dopamine.

Additional studies are investigating mechanisms of thyroid hormone disruption. Dr. Heather Stapleton of Duke University is investigating the effects of PBDEs and their metabolites on intra- and extra-cellular thyroid hormone regulation *in vitro* to elucidate the mechanisms of action for thyroid toxicity. Dr. Deena Small of the University of New England is measuring thyroid hormone receptor- mediated transcription and thyroid hormone receptor binding of pentaBDEs *in vitro.* Dr. Richard Di Guilio of Duke University is investigating the potential role of inhibition of diodinases by PBDEs in altered thyroid hormone homeostasis, using zebrafish as a model.

Other mechanistic studies are investigating mechanisms of xenoestrogen stress (Drs. P. Lee Ferguson and Tara Sabo-Attwood of the University of South Carolina at Columbia), potential mechanisms behind the etiology of inflammation of extra-placental gestational membranes and associated release of cytokines and prostaglandins (which are associated with preterm birth) (Dr. Rita Loch-Caruso of the University of Michigan), the potential role of the steroid and xenobiotic receptor SXR in the development of lymphoma and leukemia in individuals exposed to PBDEs (Dr. Bruce Blumberg of the University of California-Irvine), and development of biomarkers of mitochondrial function in primary mouse hepatocytes exposed

to BDE 47 using metabolomic analysis (Dr. Hockenberry from the Fred Hutchison Cancer Research Center.

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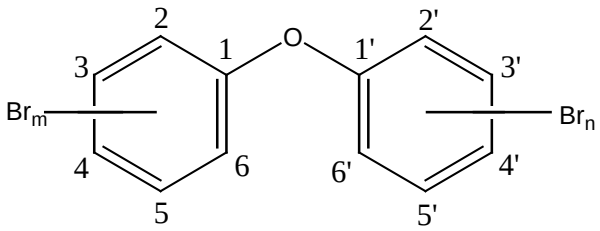
4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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



where m + n = 1 to 10

It can be seen from the structure that a large number of brominated compounds are possible. The 209 possible compounds for PBDEs are called “congeners”. However, the number of PBDE congeners that actually exist in commercial PBDE mixtures are much less compared to PCBs. Typically, only a subset of the 209 possible congeners is observed for PBDEs. PBDEs can also be categorized by degree of bromination. The term “homolog” is used to refer to all PBDEs with the same number of bromines (e.g., tribromodiphenyl ether or triBDE refers to PBDEs containing only three bromine atoms). Based on the number of bromine substituents, there are 10 homologous groups of PBDEs (monobrominated through decabrominated). Each homologous group contains one or more congeners. The mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decabromo-congeners can exist in 3, 12, 24, 42, 46, 42, 24, 12, 3, and 1 forms, respectively. Homologs with different substitution patterns are referred to as isomers. For example, the group of dibromodiphenyl ether or diBDE homologs contains 12 isomers. The numbering system for PBDEs is also shown above. The structures of representative PBDE molecules appear similar when drawn in one dimension. However, there are important three-dimensional differences in their structures due to the ether linkage and location/number of halogen atoms. The *ortho* positions of the aromatic rings must be nonhalogen-substituted for a diphenyl ether molecule to assume a planar or near planar configuration. Halogen substitution of the diphenyl ether molecule in the *ortho* position (2,2’,6,6’) will force the aromatic rings orthogonal to one another (e.g., the phenyl rings will be positioned in space with a dihedral angle >0°). This is particularly evident for decabromodiphenyl ether, which is predicted to have a dihedral angle of ~90° and a high barrier to rotation around the ether linkage preventing this

molecule from assuming a planar configuration. The benzene rings of non-*ortho* substituted PBDEs may assume a small dihedral angle (in which the dihedral angle is small, but >0°) or "near" planar configuration. These molecules are referred to as planar or coplanar congeners (Hardy 2002a).

Like PCBs, the 209 congeners for PBDEs are arranged in ascending numerical order using a numbering system developed by Ballschmiter and Zell (1980) that follow the IUPAC rules of substituent characterization in biphenyls. The resulting numbers assigned by Ballschmiter and Zell (which are also referred to as congener, IUPAC, or BZ numbers) are widely used for identifying individual congeners of PBDEs. For example, the PBDE congener, 2,2',4,4'-tetraBDE may be referred to as BDE 47 in this document. The identities of several PBDE congeners are shown in Table 4-1 (WHO 1994a, 1994b).

In the United States, Albemarle Corporation and Great Lakes Chemical Corporation previously marketed mixtures of PBDEs under trade names (e.g., DE-60F, DE-61, DE-62, DE-71, for pentaBDE mixtures; DE-79 for octaBDE mixtures; and DE 83R, Saytex 102E for decaBDE mixtures). The Great Lakes Corporation merged with Crompton Chemical Corporation and was renamed Chemtura, which produced decaBDE under the brand names AZUB DB-40, AZUB DB-65, AZUB 2DA-65, and AZUB 3DA-65 (EPA 2010). There were also several trade names used by producers from Europe and Japan for the BDE mixtures. The chemical identities of commercial mixtures of penta-, octa-, and decaBDEs are listed in Table 4-2 (WHO 1994a). La Guardia et al. (2006) published detailed congener composition profiles of penta-, octa-, and decaBDE flame retardant mixtures; 39 discrete PBDEs were found in the six commercial products evaluated by GC/MS electron ionization (EI) and electron-capture negative ionization (ECNI).

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

polybrominated biphenyl ethers	=	polybromobiphenyl ethers	=	PBBE
polybrominated biphenyl oxides	=	polybromobiphenyl oxides	=	PBBEs
polybrominated diphenyl ethers	=	polybromodiphenyl ethers	=	PBDEs or PBDPEs
polybrominated diphenyl oxides	=	polybromodiphenyl oxides	=	PBDOs or PBDPOs

Table 4-1. Chemical Identity of Polybrominated Diphenyl Ether (PBDE) Congeners[a]

IUPAC Number[b]	Compound/substituents	CAS number[c]
	Biphenyl	92-52-4
	MonoBDE	101-55-3
1	2	
2	3	
3	4	
	DiBDE	2050-47-7
4	2,2’	
5	2,3	
6	2,3’	
7	2,4	
8	2,4’	
9	2,5	
10	2,6	
11	3,3’	
12	3,4	
13	3,4’	
14	3,5	
15	4,4’	
	TriBDE	49690-94-0
16	2,2’,3	
17	2,2’,4	
18	2,2’,5	
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	
27	2,3’,6	
28	2,4,4’	
29	2,4,5	
30	2,4,6	
31	2,4’,5	
32	2,4’,6	
33	2’,3,4	
34	2’,3,5	
35	3,3’,4	
36	3,3’,5	
37	3,4,4’	
38	3,4,5	
39	3,4’,5	

Table 4-1. Chemical Identity of Polybrominated Diphenyl Ether (PBDE) Congeners[a]

IUPAC Number[b]	Compound/substituents	CAS number[c]
	TetraBDE	40088-47-9
40	2,2’,3,3’	
41	2,2’,3,4	
42	2,2’,3,4’	
43	2,2’,3,5	
44	2,2’,4,5’	
45	2,2’,3,6	
46	2,2’,3,6’	
47	2,2’,4,4'	
48	2,2’,4,5	
49	2,2’,4,5'	
50	2,2’,4,6	
51	2,2’,4,6'	
52	2,2’,5,5'	
53	2,2’,5,6'	
54	2,2’,6,6'	
55	2,3,3’,4	
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	
62	2,3,4,6	
63	2,3,4’,5	
64	2,3,4’,6	
65	2,3,5,6	
66	2,3’,4,4’	
67	2,3’,4,5	
68	2,3’,4,5’	
69	2,3’,4,6	
70	2,3’,4’,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	
76	2’,3,4,5	
77	3,3’,4,4’	
78	3,3’,4,5	
79	3,3’,4,5’	
80	3,3’,5,5’	
81	3,4,4’,5	

Table 4-1. Chemical Identity of Polybrominated Diphenyl Ether (PBDE) Congeners[a]

IUPAC Number[b]	Compound/substituents	CAS number[c]
	PentaBDE	32534-81-9
82	2,2’,3,3’,4	
83	2,2’,3,3’,5	
84	2,2’,3,3’,6	
85	2,2’,3,4,4’	
86	2,2’,3,4,5	
87	2,2’,3,4,5’	
88	2,2’,3,4,6	
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	
96	2,2’,3,6,6’	
97	2,2’,3’,4,5	
98	2,2’,3’,4,6	
99	2,2’,4,4’,5	
100	2,2’,4,4’,6	
101	2,2’,4,5,5’	
102	2,2’,4,5,6’	
103	2,2’,4,5’,6	
104	2,2’,4,6,6’	
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	
115	2,3,4,4’,6	
116	2,3,4,5,6	
117	2,3,4’,5,6	
118	2,3’,4,4’,5	
119	2,3’,4,4’,6	
120	2,3’,4,5,5’	
121	2,3’,4,5’,6	
122	2’,3,3’,4,5	
123	2’,3,4,4’,5	
124	2’,3,4,5,5’	
125	2’,3,4,5,6’	
126	3,3’,4,4’,5	
127	3,3’,4,5,5’	

Table 4-1. Chemical Identity of Polybrominated Diphenyl Ether (PBDE) Congeners[a]

IUPAC Number[b]	Compound/substituents	CAS number[c]
	HexaBDE	36483-60-0
128	2,2’,3,3’,4,4’	
129	2,2’3,3’,4,5	
130	2,2’,3,3’,4,5’	
131	2,2’,3,3’,4,6	
132	2,2’,3,3’,4,6’	
133	2,2’,3,3’,5,5’	
134	2,2’,3,3’,5,6	
135	2,2’,3,3’,5,6’	
136	2,2’,3,3’,6,6’	
137	2,2’,3,4,4’,5	
138	2,2’,3,4,4’,5’	
139	2,2’,3,4,4’,6	
140	2,2’,3,4,4’,6’	
141	2,2’,3,4,5,5’	
142	2,2’,3,4,5,6	
143	2,2’,3,4,5,6’	
144	2,2’,3,4,5’,6	
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	
150	2,2’,3,4’,5,6’	
151	2,2’,3,5,5’,6	
152	2,2’,3,5,6,6’	
153	2,2’,4,4’,5,5’	
154	2,2’,4,4’,5,6’	
155	2,2’,4,4’,6,6’	
156	2,3,3’,4,4’,5	
157	2,3,3’,4,4’,5’	
158	2,3,3’,4,4’,6	
159	2,3,3’,4,5,5’	
160	2,3,3’,4,5,6	
161	2,3,3’,4,5’,6	
162	2,3,3’,4’,5,5’	
163	2,3,3’,4’,5,6	
164	2,3,3’,4’,5’,6	
165	2,3,3’,5,5’,6	
166	2,3,4,4’,5,6	
167	2,3’,4,4’,5,5’	
168	2,3’,4,4’,5’,6	
169	3,3’,4,4’,5,5’	

Table 4-1. Chemical Identity of Polybrominated Diphenyl Ether (PBDE) Congeners[a]

IUPAC Number[b]	Compound/substituents	CAS number[c]
	HeptaBDE	68928-80-3
170	2,2',3,3',4,4',5	
171	2,2',3,3',4,4',6	
172	2,2',3,3',4,5,5'	
173	2,2',3,3',4,5,6	
174	2,2',3,3',4,5,6'	
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	
179	2,2',3,3',5,6,6'	
180	2,2',3,4,4',5,5'	
181	2,2',3,4,4',5,6	
182	2,2',3,4,4',5,6'	
183	2,2',3,4,4',5',6	
184	2,2',3,4,4',6,6'	
185	2,2',3,4,5,5',6	
186	2,2',3,4,5,6,6'	
187	2,2',3,4',5,5',6	
188	2,2',3,4',5,6,6'	
189	2,3,3',4,4',5,5'	
190	2,3,3',4,4',5,6	
191	2,3,3',4,4',5',6	
192	2,3,3',4,5,5',6	
193	2,3,3',4',5,5',6	
	OctaBDE	32536-52-0
194	2,2',3,3',4,4',5,5'	
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'	
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'	
201	2,2',3,3',4,5',6,6'	
202	2,2',3,3',5,5',6,6'	
203	2,2',3,4,4',5,5',6	
204	2,2',3,4,4',5,6,6'	
205	2,3,3',4,4',5,5',6	
	NonaBDE	63936-56-1
206	2,2',3,3',4,4',5,5',6	
207	2,2',3,3',4,4',5,6,6'	
208	2,2',3,3',4,5,5',6,6'	

Table 4-1. Chemical Identity of Polybrominated Diphenyl Ether (PBDE) Congeners[a]

IUPAC Number[b]	Compound/substituents	CAS number[c]
	DecaBDE	1163-19-5
209	2,2',3,3',4,4',5,5',6,6'	

[a]WHO 1994a
[b]Ballschmiter and Zell 1980
[c]No CAS numbers were identified for the individual PBDE congeners.

BDE = brominated diphenyl ether; CAS = Chemical Abstracts Service; IUPAC = International Union of Pure and Applied Chemistry

Table 4-2. Chemical Identity of Technical Polybrominated Diphenyl Ethers (PBDEs)

Characteristic	Pentabromodiphenyl ether	Octabromodiphenyl ether	Decabromodiphenyl ether
Synonym(s)	Pentabromodiphenyl ether; pentabromodiphenyl oxide; pentabromobiphenyl oxide; benzene, 1,1-oxybis, pentabromo derivative	Octabromodiphenyl ether; Octabromodiphenyl oxide; octabromobiphenyl oxide; benzene, octabromo derivative; phenyl ether, octabromo derivative	Decabromodiphenyl ether; decabromodiphenyl oxide; decabromobiphenyl oxide; benzene, 1,1'-oxybis-(2,3,5,6,-penta-bromo-) ether, bis-(pentabromophenyl);
Registered trade name	DE 71; Bromkal 70-5 DE; FR 1205/1215; Bromkal 70; Bromkal G1; Pentabromprop; Tardex 50; Tardex 50 L; Saytex 115	Bromkal 79-8DE; DE 79; FR 143; Tardex 80; FR 1208; Adine 404; Saytex 111	FR-300 BA; DE-83-RTM; Saytex 102; Saytex 102E; FR-1210; Adine 505; AFR 1021; Berkflam B10E; BR55N; Bromkal 81; Bromkal 82-0DE; Bromkal 83-10 DE; Caliban F/R-P 39P; Caliban F/R-P 44; Chemflam 011; DE 83; DP 10F; EB 10FP; EBR 700; Flame Cut BR 100; FR P-39; BR 100; FR 330BA; FR P-39; FRP 53; FR-PE; FR-PE(H); Planelon DB 100; Tardex 100; NC-1085; HFO-102; Hexcel PF1; Phoscon Br-250
Chemical formula	$C_{12}H_{10-y}Br_yO$ where y=4–6	$C_{12}H_{10-y}Br_yO$ where y=6–9	$C_{12}Br_{10}O$
Chemical structure			
Identification numbers:			
CAS registry	32534-81-9	32536-52-0	1163-19-5
NIOSH RTECS	No data	No data	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/IMCO shipping	No data	No data	No data
HSDB	7109	7110	2911
NCI	No data	No data	No data

Source: WHO 1994a

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

For consistency in this document, polybrominated diphenyl ethers or PBDEs will be used to identify this class of chemicals. The PBDE homologs are abbreviated as follows in this document:

dibromodiphenyl ether	=	DiBDE	=	diBDE
tribromodiphenyl ether	=	TrBDE	=	triBDE
tetrabromodiphenyl ether	=	TeBDE	=	tetraBDE
pentabromodiphenyl ether	=	PeBDE	=	pentaBDE
hexabromodiphenyl ether	=	HxBDE	=	hexaBDE
heptabromodiphenyl ether	=	HpBDE	=	heptaBDE
octabromodiphenyl ether	=	OcBDE	=	octaBDE
nonabromodiphenyl ether	=	NoBDE	=	nonaBDE
decabromodiphenyl ether	=	DeBDE	=	decaBDE

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information found in the literature regarding the physical and chemical properties of selected technical PBDE mixtures is presented in Table 4-3. Recent information regarding the vapor pressure, water solubility, Henry's Law constant, and log K_{ow} of some PBDE congeners is presented in Table 4-4.

Commercially available product mixtures of PBDEs (see Table 4-2) are not pure substances, but instead are mixtures of congeners. For example, the commercial mixture pentaBDE denotes the main component of the mixture contains the pentaBDE homolog. However, the commercial pentaBDE mixture actually contains tetraBDE (24–38%) and pentaBDE (50–62%) homologs with small amounts of hexaBDE (4–8%) and trace amounts of triBDE (0–1%) homologs. In this document, the commercial mixture of pentabromodiphenyl ether may be called "the commercial pentaBDE mixture," "technical pentaBDE," or "technical PeBDE" to distinguish this mixture of homologs from the pentaBDE homolog, which refers to PBDEs with only five bromine atoms (see Section 4.1). Commercial octaBDE is a mixture of hexa-, hepta-, octa-, and nonaBDE homologs with trace amounts of decaBDE (i.e., BDE 209). In this document, the commercial mixture of octabromodiphenyl ether may be called "the commercial octaBDE mixture," "technical octaBDE," or "technical OBDE" to distinguish this mixture of different homologs from the octaBDE homolog, which refers to PBDEs with only eight bromine atoms (see Section 4.1). The composition of commercial decabromodiphenyl ether is 97% of the decaBDE (i.e., BDE 209); the remainder is nonaBDE homologs and trace amounts of octaBDE homologs (WHO 1994a). In this document, commercial decabromodiphenyl ether may be called "the commercial decaBDE mixture,"

Table 4-3. Physical and Chemical Properties of Technical Polybrominated Diphenyl Ether (PBDE) Mixtures

Property	Pentabromodiphenyl ether	Octabromodiphenyl ether	Decabromodiphenyl ether
Molecular weight	Mixture	Mixture	959.22[a]
Color	Clear, amber to pale yellow[a]	Off-white[a]	Off-white[a]
Physical state	Highly viscous liquid	Powder	Powder[a]
Melting point	-7 to -3°C (commercial)[b]	85–89°C (commercial)[c]; 200°C (range, 167–257)[a]; 79–87°C[a]; 170–220°C[a]	290–306°C[a]
Boiling point	>300°C (decomposition starts above 200°C)[a,b]	Decomposes at >330°C (commercial)[c]	Decomposes at >320, >400, and 425°C[a]
Density (g/mL)	2.28 at 25°C[a]; 2.25–2.28[b]	2.76[a]; 2.8 (commercial)[c]	3.0[a]; 3.25[a]
Odor	No data	Faint[a]	Odorless[a]
Odor threshold:			
Water	No data	No data	Not applicable
Air	No data	No data	Not applicable
Solubility:			
Water	13.3 µg/L (commercial)[b,d]; 2.4 µg/L (pentabromodiphenyl ether component)[b]; 10.9 µg/L (tetrabromodiphenyl ether component)[b]	<1 ppb at 25°C (commercial)[c]; 1.98 µg/L (heptabromodiphenyl ether component)[c]	<0.1 µg/L[g]
Organic solvent(s)	10 g/kg methanol; miscible in toluene[d]	Acetone (20 g/L); benzene (200 g/L); methanol (2 g/L) all at 25°C[a]	No data
Partition coefficients:			
Log K_{ow}	6.64–6.97[d]; 6.57 (commercial)[b]	6.29 (commercial)[c]	6.265[e]
Log K_{oc}	4.89–5.10[e]	5.92–6.22[e]	6.80[e]
Vapor pressure	$2.2x10^{-7}$–$5.5x10^{-7}$ mm Hg at 25°C[d]; $3.5x10^{-7}$ mm Hg (commercial)[b]	$9.0x10^{-10}$–$1.7x10^{-9}$ mm Hg at 25°C[d]; $4.9x10^{-8}$ mm Hg at 21°C (commercial)[c]	$3.2x10^{-8}$ mm Hg[f]
Henry's Law constant (atm-m^3/mole)	$1.2x10^{-5}$[g]; $1.2x10^{-6}$[e]; $3.5x10^{-6}$[f]	$7.5x10^{-8}$[e]; $2.6x10^{-7}$[e]	$1.62x10^{-6}$[g]; $1.93x10^{-8}$[d]; $1.2x10^{-8}$[e]; $4.4x10^{-8}$[e]
Autoignition temperature	Decomposes above 200°C[b,d]	Decomposes above 330°C (commercial)[c]	Not applicable[a]
Flashpoint	No data	No data	None
Flammability limits	Not applicable (flame retardant)[b,d]	Not applicable (flame retardant)[c]	Non-flammable[a]

Table 4-3. Physical and Chemical Properties of Technical Polybrominated Diphenyl Ether (PBDE) Mixtures

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

[a]WHO 1994a
[b]ENVIRON 2003a
[c]ENVIRON 2003b
[d]EU 2001
[e]Estimated values were calculated using EPIWIN v4.10 (EPA 2014e).
[f]Hardy 2002a
[g]Estimated value was calculated using vapor pressure and water solubility values in table.

Table 4-4. Physical and Chemical Properties of Some Polybrominated Diphenyl Ether (PBDE) Congeners

Congener	Vapor pressure (mm Hg)[a,b]	Water solubility (µg/L)[a]	Henry's Law constant (atm m^3/mol)[a]	Log K_{ow}[c]	Log K_{OA}[d]
BDE 3	$1.94x10^{-3}$	–	–	–	–
BDE 15	$1.30x10^{-4}$	130	$2.07254x10^{-4}$	–	–
BDE 17	–	–	–	5.74	9.30
BDE 28	$1.64x10^{-5}$	70	$5.03331x10^{-5}$	5.94	9.50
BDE 47	$1.40x10^{-6}$	15	$1.48038x10^{-5}$	6.81	10.53
BDE 66	$9.15x10^{-7}$	18	$4.93461x10^{-6}$	–	10.82
BDE 77	$5.09x10^{-7}$	6	$1.18431x10^{-5}$	–	10.87
BDE 85	$7.40x10^{-8}$	6	$1.08562x10^{-6}$	–	11.66
BDE 99	$1.32x10^{-7}$	9	$2.26992x10^{-6}$	7.32	11.31
BDE 100	$2.15x10^{-7}$	40	$6.80977x10^{-7}$	7.24	11.13
BDE 138	$1.19x10^{-8}$	–	–	–	–
BDE 153	$1.57x10^{-8}$	1	$6.61238x10^{-7}$	7.90	11.82
BDE 154	$2.85x10^{-8}$	1	$2.36862x10^{-6}$	7.82	11.92
BDE 183	$3.51x10^{-9}$	2	$7.30323x10^{-8}$	8.27	11.96
BDE 190	$2.12x10^{-9}$	–	–	–	–

[a]Tittlemier et al. 2002.
[b]Liquid sub-cooled vapor pressures.
[c]Braekevelt et al. 2003.
[d]Harner 2001.

– = no data reported; BDE = brominated diphenyl ether

"technical decaBDE," or "technical DeBDE" which represents 97% BDE 209 congener with 3% nona- and octaBDE homolog impurities. The compositions of commercial product mixtures of PBDEs (e.g., technical penta-, octa-, and decaBDE) are given in Table 4-5.

Trace analysis of these commercial mixtures for 15 different 2,3,7,8-substituted brominate dibenzo-*p*-dioxins and dibenzofurans revealed no detectable amounts of these substances (Hardy 2002a). The commercial decaBDE product has been analyzed for trace quantities of 15 2,3,7,8-substituted PBDDs and PBDFs. None of the analytes were present at or above the quantization limits established under an EPA test rule (BFRIP 2002). While in today's commercial PBDE samples, there are no measurable quantities of PBDDs/PBDFs, there are some materials that have reported quantifiable concentrations of these contaminants. For example, hexabromodibenzofurans have been detected in commercial decaBDE mixtures at concentrations as high as 200 μg/kg. In other PBDE mixtures (e.g., tetra- to hexaBDEs), the sum of tetra-, penta-, and hexabromodibenzofurans were reported at a concentrations of 8,000 μg/kg. In addition, tetra- and pentabromo-*p*-dibenzodioxins have been measured in commercial decaBDE at concentrations of 0.05 and 0.35 μg/kg, respectively (WHO 1998).

When pyrolyzed up to 900°C, PBDEs may produce PBDFs and PBDDs (Buser 1986; EU 2001). The amount of PBDFs and PBDDs formed depends upon the conditions of pyrolysis. For example, 2,3,7,8-tetrabromodibenzofuran in ppm concentrations can be generated during pyrolysis of decaBDE in the temperature range of 400–700°C (Bieniek et al. 1989). PBDFs may also be produced during the pyrolysis of polymers containing PBDEs as flame retardants (Brenner and Knies 1993; Dumler et al. 1989, 1990; Lenoir et al. 1994). However, studies performed in the late 1980s may have suffered from analytical methods that could not differentiate between PBDDs/PBDFs formed (e.g., 2,3,7,8-substituted congeners) and decaBDE, which might have artificially elevated the concentrations of PBDEs detected (Hamm et al. 2001).

Table 4-5. Typical Congener Composition of Penta-, Octa-, and Deca-Brominated Diphenyl Ether (BDE)

Congener (weight percentage)	PentaBDE	OctaBDE	DecaBDE
BDE 47	25–37%		
BDE 99	35–50%		
BDE 100	6–10%		
BDE 153	3–5%	5–10%	
BDE 154	2–4%	1–5%	
BDE 183		40%	
BDE 196		8%	
BDE 197		21%	
BDE 203		5–35%	
BDE 206			2.2%
BDE 207		7%	0.24%
BDE 208		10%	0.06%
BDE 209			97%

Source: EPA 2010

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

5.1 PRODUCTION

The commercial production of PBDEs generally involves bromination of diphenyl oxide to varying degrees. The degree of bromination is controlled either through stoichiometry or through control of reaction kinetics (Pettigrew 1993).

The commercial production of PBDEs began in late 1970s (WHO 1994a). There are no current manufacturers of technical PBDEs in the United States. About 98% of the global demand for the technical pentaBDE mixture resided in North America (Hale et al. 2003). PentaBDE and octaBDE mixtures were voluntarily withdrawn from the U.S. marketplace by their manufacturers at the end of 2004, leaving only decaBDE being marketed for use in commercial products in the United States (EPA 2010). In December of 2009, the two remaining U.S. producers of decaBDE, Albemarle Corporation and Chemtura Corporation (formerly known as the Great Lakes Chemical Corporation), and the largest U.S. importer, ICL Industrial Products, Inc., announced commitments to phase out manufacture and importation of decaBDE for most uses in the United States by December 31, 2012, and to end manufacture and import for all uses by the end of 2013 (EPA 2013j). In 2003, the EU passed a Directive to ban the marketing and use of penta- and octaBDE that took effect in 2004. In 2008, the use of decaBDE was restricted by an EU Directive on the Restriction of the use of certain Hazardous Substances (RoHS) (EC 2014; EPA 2010).

Table 5-1 lists the facilities in each state that manufactured or processed technical decaBDE in 2014, the intended use, and the range of maximum amounts of technical decaBDE that are stored on-site (TRI14 2016). The data from the Toxics Release Inventory (TRI) listed in Table 5-1 should be used with caution, however, since only certain types of facilities were required to report. The TRI is not an exhaustive list. Facilities are only required to report to the TRI if they manufacture or process more than 25,000 pounds of a TRI listed chemical during the year, or otherwise use more than 10,000 pounds, and have the equivalent of more than 10 full-time employees. According to the EPA, TRI data have certain limitations. TRI data reflect releases and other waste management of chemicals, and not exposures of the public to those chemicals. TRI data alone are not sufficient to determine exposure or calculate potential adverse effects on human health and the environment.

Table 5-1. Facilities that Produce, Process, or Use Decabromodiphenyl Ether

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	2	1,000	99,999	7
CA	1	10,000	99,999	2, 3, 7, 8, 10
CT	1	10,000	99,999	8
GA	3	1,000	99,999	7, 8
IL	3	10,000	99,999	7
IN	1	50,000,000	99,999,999	2, 3, 4, 8
KS	1	1,000	9,999	8
MA	2	10,000	999,999	7
MS	1	10,000	99,999	7, 8
NH	1	Not reported	Not reported	Not reported
NJ	1	10,000	99,999	7
NV	1	10,000	99,999	7
NY	1	1,000	9,999	7
OH	4	1,000	99,999	2, 3, 7, 8
PA	3	100,000	999,999	1, 3, 7, 8
SC	5	10,000	99,999	7, 8
TX	2	1,000	9,999	7
VA	3	0	99,999	7

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

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

Source: TRI14 2016 (Data are from 2014)

5.2 IMPORT/EXPORT

Production and importation of the final commercial PBDE, decaBDE, ended on December 31, 2013.

5.3 USE

PBDEs were used as additive flame retardants in thermoplastics. Additive flame retardants are physically combined with the polymer material being treated rather than chemically combined (as in reactive flame retardants). This means that there is a possibility that the flame retardant may diffuse out of the treated material to some extent. PBDEs were used in different resins, polymers, and substrates at levels ranging from 5 to 30% by weight (EU 2001).

The commercial pentaBDE product was used predominantly (95–98%) for flame retardant purposes as an additive in consumer products manufactured by the furniture industry (ENVIRON 2003a). It was used almost exclusively to flame retard flexible polyurethane foam (FPUF), which is used in bed mattresses and cushioning in upholstered products. The commercial pentaBDE was typically used in FPUF as an additive mixture with aromatic phosphate esters (e.g., mixture of 75% pentaBDE and 25% aromatic phosphate esters). Mattress FPUF contains approximately 2–3% flame retardant mixture and cushion FPUF contains 3–5% flame retardant mixture (ENVIRON 2003a). Scrap materials from both industries have been used as padding beneath carpets, and as a result, carpet padding likely contained 3–5% flame retardant mixture. However, not all of the FPUF found in cushion, mattress, and carpet padding products were treated with commercial pentaBDE. Approximately 7.5% of the more than 2.1 billion pounds of FPUF produced annually in the United States used the commercial pentaBDE product as a flame retardant additive (ENVIRON 2003a). The majority of FPUF products treated with the commercial pentaBDE product were sold in California, the only state requiring by law that upholstered products achieve a prescribed level of ignition resistance (ENVIRON 2003a). A small percentage of pentaBDE was used in commercial adhesive products. Other former uses of commercial pentaBDE included coatings for specialty textiles, printed circuit board components, hydraulic and oilfield completion fluids, and rubber products. In the past, automotive and airplane seating cushions contained FPUF with commercial pentaBDE. However, this use was discontinued in the early 1990s. Prior to approximately 1990, the commercial pentaBDE product may have been used in small quantities as a flame retardant in specialty fire-resistant clothing using polyurethane treatment and in polyurethane coatings in carpets (ENVIRON 2003a). Commercial pentaBDE product was used in rigid polyurethane elastomers for instrument casings, and applied in printed circuit boards and microprocessor packaging previously (Betts 2006;

Hazrati and Harrad 2007). Electronic equipment containing pentaBDE produced in other countries (principally Asian) could also find its way into the United States (EU 2001).

The commercial octaBDE was used by the plastics industry as an additive flame retardant for manufactured products. It was used almost exclusively to flame retard ABS terpolymers used in computer casings and monitors (ENVIRON 2003b). In the EU, approximately 95% of the total commercial octaBDE product sold to the electronics and plastics industries was used in ABS before it was banned (EU 2003a). Although data are not available in the United States, similar volumes were likely (ENVIRON 2003b). The commercial octaBDE product formerly used in ABS products was 12–18% weight loadings of flame retardant. OctaBDE was always used as a flame retardant in conjunction with antimony trioxide. Other minor uses for octaBDE, were high impact polystyrene (HIPS), polybutylene terephthalate (PBT), and polyamide polymers (EU 2003a). Other former applications of octaBDE included use as additive flame retardant in polycarbonate, phenol-formaldehyde resins, and unsaturated polyesters (EU 2003a).

The commercial decaBDE product was an additive flame retardant used in a variety of polymer applications. Industry information indicates that decaBDE was used at loadings of 10–15% weight in polymers and always in conjunction with antimony trioxide (EU 2002). The major application for decaBDE was in HIPS, which is used in the television industry for cabinet backs. It was also used for a large number of other polymers with end-uses in electrical and electronic equipment (e.g., computers, connectors, electrical boxes, wire, cable, etc.). Examples include polypropylene (for electronics), acetate copolymers (ethylene-vinyl acetate [EVA] and other copolymers for wire and cable), ethylene-propylene-diene terpolymer (EPDM) and thermoplastic elastomers (for wire and cable), and polyester resins (for electronics). Other minor uses included styrenic rubbers, polycarbonates, polyamides, and terephthalates, and small amounts are reported to be used in hot-melt adhesives (EU 2002).

5.4 DISPOSAL

PBDEs were used as flame retardants in a wide range of consumer products (see Section 5.3). In the United States, waste disposal of PBDE-containing consumer products is described as transfers to disposal (landfill), recycling, energy recovery (incineration), or publicly owned treatment works (POTWs) (Darnerud et al. 2001). No other information was located on the past or present volumes of PBDE-containing consumer products disposed of by each method of waste transfer.

Landfill disposal of plastic consumables containing pentaBDE (e.g., polyurethane foams), octaBDE (e.g., computer monitors), and decaBDE (e.g., televisions) to landfills is likely to increase in the United States due to their limited useful lifespan. Given that all PBDEs have low water solubility (see Table 4-4), the potential for leaching of PBDE from landfills appears to be small (EU 2002). Well-designed landfills will include measures to minimize leaching and those measures would also be effective in minimizing the leaching of any PBDE particulates present (EU 2002). PBDEs have been detected in landfill leachate and landfill related aqueous samples worldwide (Daso et al. 2013; Kwan et al. 2013; Odusanya et al. 2009; Oliaei et al. 2010; Stubbings and Harrad 2014). The presence of hydrophobic compounds like PBDEs in leachate is expected to be a result of enhanced leachability due to the presence of other constituents present in the leachate (Stubbings and Harrad 2014). Mass transfer evaluation of PBDEs from e-waste solids found that lower pH conditions resulted in higher transfer of PBDEs to the aqueous phase, with the highest concentration of PBDEs detected at pH 5 and 25°C (Danon-Schaffer et al. 2013). The levels of PBDEs in the aqueous phase did show a trend with temperature at the temperature range evaluated, 10–25°C.

Incineration of waste materials containing PBDEs is thought to be a potential source of PBDFs and/or PBDDs. The formation of PBDFs/PBDDs as a result of uncontrolled landfill fires is also a possibility, although no data are available on the scale of this source. The results of pyrolysis experiments showed that PBDEs can form PBDFs and PBDDs (in much smaller quantities) under a wide range of heating conditions. If chlorine is present, mixed halogenated furans/dioxins can be formed (Oberg et al. 1987; Zier et al. 1991). Unless sufficiently high temperatures and long residence times are maintained, PBDFs/PBDDs can be generated during the incineration of products containing PBDEs. When heavy metals are present, the concentration of PBDDs and PBDFs are higher than when no metals are present. Sakai et al. (2001) measured residues of PBDFs/PBDDs in effluents from a municipal incineration plant burning domestic waste materials. Flue gases, fly ash, and bottom ash reportedly contained PBDFs/PBDDs at concentration ranges of 0.28–3.3 ng/N m^3, 0.082–13 ng/g, and 0.0058–27 ng/g, respectively. However, modern, properly operated municipal waste incineration should not emit significant quantities of PBDFs/PBDDs, regardless of the composition of municipal waste (WHO 1994a).

In the United States, waste disposal of industrial by-products containing PBDEs may also be described as transfers to disposal (landfill), recycling, energy recovery (incineration), industrial treatment works, or POTWs. The types of waste transfer may be different for manufacturing versus processing sectors, and also from within different types of processing. Waste disposal from manufacturing processes is predominantly to secure chemical landfills (e.g., those built with liners and leachate collection). Plastic

processors typically transfer most waste to disposal (landfill), recycling, energy recovery (incineration), and industrial treatment works, while minimal releases are to POTWs. In contrast, textile processors typically transfer most waste to POTWs. This difference in waste transfers between the plastic and textile sectors is because textile processors use water in their processing operation and other processors (e.g., processors of plastic) do not.

Recycling of plastic materials containing PBDEs is a common practice in industry. It has been demonstrated that decaBDE-containing resins can be successively recycled without generation of PBDDs/PBDFs (Brenner and Knies 1990; Donnelly et al. 1987; McAllister et al. 1990). For example, virgin HIPS resins (containing antimony trioxide [Sb_2O_3] and decaBDE) and repeatedly ground and injected molded (e.g., "recycled") HIPS/decaBDE/Sb_2O_3 resins both met the requirements of the German Chemicals Banning Ordinance with respect to 2,3,7,8-substituted PBDD/PCDF congeners. These resins were at least 1 order of magnitude below the regulated limit values for PBDDs/PCDFs (1 ppb for the sum of four congeners, 5 ppb for the sum of all eight regulated congeners).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

PBDEs have not been identified in any of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites evaluated for PBDEs is not known.

The widespread use of PBDEs since the late 1970s has resulted in their presence in the environment. PBDEs were released into the environment from their manufacture and use as additive flame retardants in thermoplastics in a wide range of products (WHO 1994a). Waste containing PBDEs may be incinerated as municipal waste, deposited in landfills, discharged to municipal sewage-treatment plants, or emitted directly to the atmosphere as particulates (Darnerud et al. 2001).

Adsorption of PBDEs generally increases as bromination of PBDEs and organic carbon content of soil and sediment increase. As a result, most PBDEs have little or no mobility in soil and are not expected to leach (e.g., into groundwater). PBDEs, particularly lower BDE homologs (e.g., tri- and tetraBDE), have the potential for long-range transport in the atmosphere (Dodder et al. 2000). The detection of PBDEs in remote regions of the world suggests that long-range transport of these congeners is occurring (Dickhut et al. 2012; Hung et al. 2010). Biodegradation is a slow environmental fate process for PBDEs, but under certain conditions, some PBDEs compounds (e.g., decaBDE) may degrade by direct photolysis to form lower-brominated congeners. However, determining the rate and extent of degradation processes (e.g., biodegradation and photolysis) for PBDEs, such as decaBDE and pentaBDE commercial mixtures, is still an active area of research.

Studies of the biota indicate that lower-brominated congeners (e.g., BDE 47) are being preferentially bioconcentrated. Lower-brominated diphenyl ether (e.g., tetra- and pentaBDE) concentrations increase with respect to trophic level; thus, organisms that reside higher on food chains tend to have higher concentrations of these brominated diphenyl ethers (Shaw et al. 2009). Body-burden data indicate that the general population is exposed to PBDEs through a variety of pathways (CDC 2015; Lorber 2008; Trudel et al. 2011). The primary exposure pathway to PBDEs for residents of North America is through indoor dust contact (ingestion and dermal exposure) (EPA 2010; Lorber 2008. Dust contact is also the primary exposure pathway for BDE 209 in the United Kingdom. For Europeans, food consumption appears to be the primary exposure pathway for most congeners (Abdallah and Harrad 2014; Law et al. 2008; Trudel et al. 2011). Body burden data, as well as intake modeling, suggest that infants and toddlers

have higher exposures to PBDEs as compared to older children or adults. PBDE levels increase from infant to toddler and then PBDE concentrations gradually decrease at older ages. Most studies indicate that concentrations of PBDEs in body fluids and tissues are a factor of 10–100-fold higher for individuals living in the United States compared to individuals living in other regions of the world (e.g., Europe).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

The widespread use of PBDEs from the 1970s until 2013 resulted in their presence in the environment. PBDEs were released into the environment from their manufacture and use in a wide range of consumer products (WHO 1994a). PBDEs were used as additive flame retardants in thermoplastics. Additive flame retardants are physically, rather than chemically, combined with polymers. Thus, there is a possibility that some PBDEs congeners may diffuse out of the treated materials to some extent (EU 2001). Although these substances are no longer manufactured in the United States and Europe, the disposal of consumer products that contain penta-, octa-, and decaBDE will result in their continued release to the environment. Waste from products containing PBDEs may be incinerated as municipal waste, deposited in landfills, or discharged to municipal sewage-treatment plants (Darnerud et al. 2001).

6.2.1 Air

Estimated releases of 2,180 pounds (~0.9 metric tons) of decaBDE to the atmosphere from 34 domestic manufacturing and processing facilities in 2014, accounted for about 1.5% of the estimated total

environmental releases from facilities required to report to the TRI (TRI14 2016). These releases are summarized in Table 6-1. There are no TRI data for penta- or octaBDE.

The estimated release of decaBDE from the 2014 TRI continues to reflect a decreasing trend as production slowed and was eventually discontinued in 2013. The total on-site and off-site releases of decaBDE since 1998 are illustrated in Figure 6-1 (TRI14 2016).

No quantitative information was located on the releases of the pentaBDE technical mixtures to the atmosphere from its former production and use. However, the release of pentaBDE technical mixtures to air had the potential to occur during the curing phase, since the polyurethane foam was at elevated temperatures (e.g., up to 160°C) for several hours during this phase. Since pentaBDE technical mixtures were additive flame retardants, they are subject to volatilization or leaching from the polymer matrix during the lifetime of the use of the foam article. Losses of foam particles containing the substance (e.g., due to abrasion) may also occur. However, most congeners in pentaBDE technical mixtures have very low vapor pressures (see Table 4-3) and therefore, losses from polyurethane foam due to volatilization would be expected to be low. Migration of pentaBDE technical mixtures from consumer products may be a significant diffuse source of lower-brominated congeners of pentaBDE technical mixtures to the atmosphere. Although no studies were found that determined the migration rate of pentaBDE technical mixtures from polymers into the air, estimates have been made. The estimated migration rate for pentaBDE technical mixtures is 0.39% per year (Danish EPA 1999).

Similarly, no quantitative information is available on emissions of octaBDE technical mixtures to the atmosphere from production operations. The major sources of air emissions of octaBDE technical mixtures were thought to be a result of grinding and bagging operations.

The EPA National Center for Environmental Assessment (NCEA), Office of Research and Development completed a comprehensive exposure assessment of PBDEs (EPA 2010). A series of studies were summarized that estimated the release of PBDEs from various products under laboratory conditions. Two computer workstations manufactured after 2000 consisting of a monitor, computer, keyboard, mouse, and printer were used for 93 and 150 days and PBDE concentrations were monitored during their operation. BDE 47, BDE 100, BDE 99, and BDE 85 concentrations in surrounding air were <0.3 ng/m^3 for one of the workstations; however, concentrations of BDE 47, BDE 100, and BDE 99 were 150, 28, and 61 ng/m^3, respectively, in air monitored for the second workstation. An emission test was summarized that used the back panel of a television set treated with octaBDE manufactured before 1979. Maximum

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Decabromodiphenyl Ether[a]

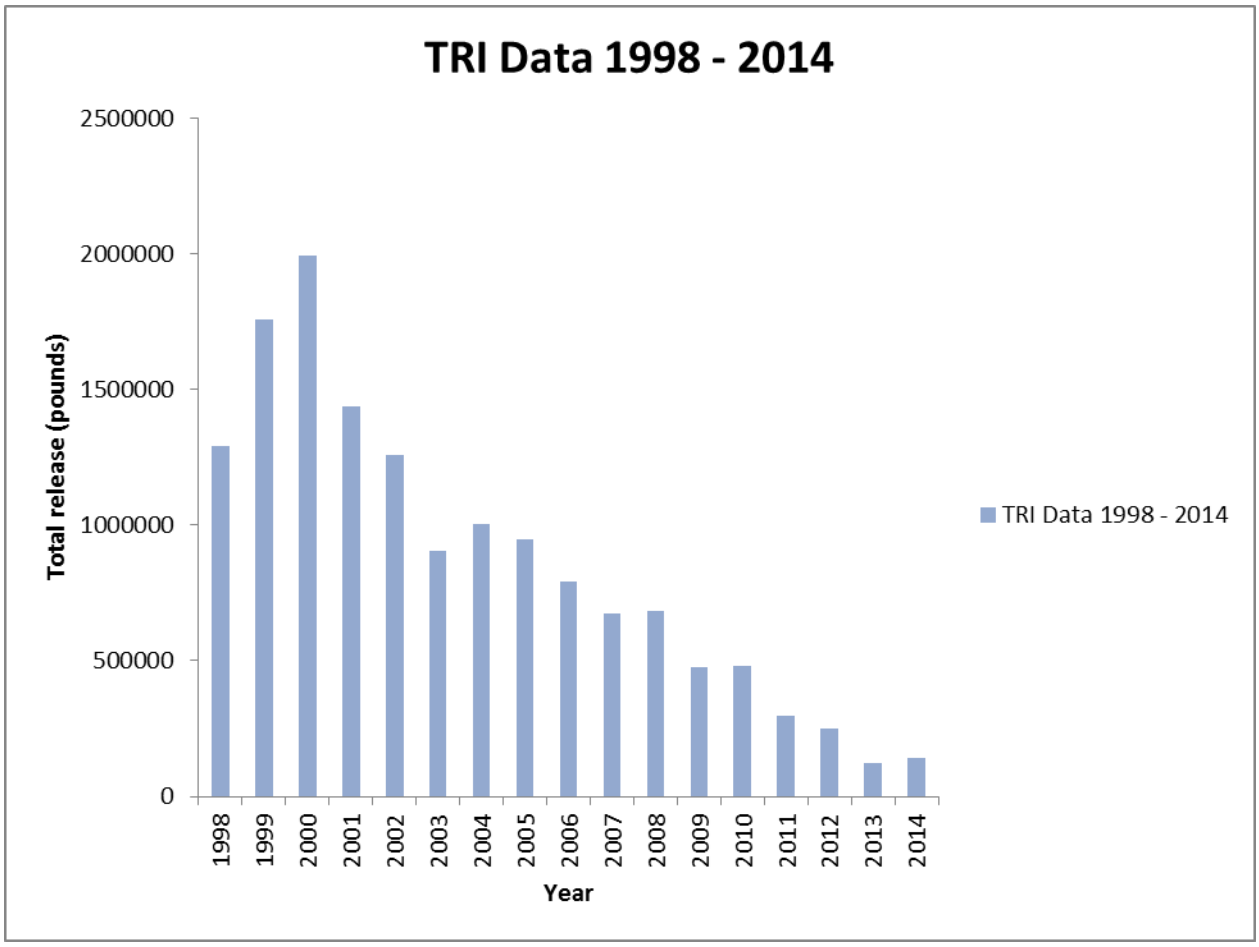
		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	2	120	0	0	5,374	0	120	5,374	5,494
CA	1	1	0	0	139	0	1	139	140
CT	1	0	0	0	0	1,747	0	1,747	1,747
GA	3	347	0	0	2,917	0	347	2,917	3,264
IL	3	0	0	0	5	0	0	5	5
IN	1	5	0	0	0	0	5	0	5
KS	1	NR	NR	NR	NR	NR	NR	NR	NR
MA	2	18	5	0	84	1	23	85	108
MS	1	28	0	0	0	0	28	0	28
NH	1	NR	NR	NR	NR	NR	NR	NR	NR
NJ	1	0	0	0	0	150	0	150	150
NV	1	NR	NR	NR	NR	NR	NR	NR	NR
NY	1	0	0	0	137	0	0	137	137
OH	4	505	0	0	75	112,501	505	112,576	113,081
PA	3	1,152	0	0	6,919	0	1,152	6,919	8,070
SC	5	0	0	0	67	0	0	67	67
TX	2	5	0	0	6,182	0	5	6,182	6,187
VA	1	0	0	0	2,504	0	0	2,504	2,504
Total	34	2,180	5	0	24,403	114,399	2,185	138,802	140,987

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

NR = not reported; RF = reporting facilities; UI = underground injection

Source: TRI14 2016 (Data are from 2014)

Figure 6-1. Total On- and Off-Site Releases of Decabromodiphenyl Ether, 1998–2014



Source: TRI14 (2016)

concentrations of BDE 28, BDE 47, BDE 66, BDE 100, and BDE 99 were reported as 0.5, 8, 0.24, 0.27, and 0.84 ng/m^3, respectively (EPA 2010). These data suggest that older treated consumer products may continue to release PBDEs long after they were originally treated.

More generalized approaches were summarized that could be used to estimate the possible total volatilization of PBDEs from treated plastic products (EPA 2010). The EU utilized a regression derived equation to estimate the percentage loss of PBDE that volatilizes from plastic components treated with PBDEs:

$$PercentVolatilized = 1.1 \times 10^6 \times VP \times SL$$

where VP is the vapor pressure in units of mm Hg and SL is the service life of the product, assumed to be 10 years

For instance, using a vapor pressure of 3.47x10^{-8} mm Hg for decaBDE, the volatilization loss after 10 years would be approximately 0.38% (EPA 2010). Since approximately 6,710 metric tons of decaBDE were used in plastics the EU before it was banned, the total loss to air over the assumed 10-year lifetime would be approximately 25.5 metric tons (EPA 2010).

Breivik et al. (2002) developed a regression-derived equation using the octanol-air partition coefficient (K_{OA}) to estimate emission factors of PCBs from commercial sealants, which was also applied to estimate the emission factors of PBDEs

$$\log EF = -0.839 \times \log K_{OA} + 4.83$$

The emission factor (EF) is the ratio of the mass of PBDE emitted divided by the mass PBDE used per year. Both equations above were used to estimate total emissions of penta-, octa-, and decaBDE from products used in the United States (EPA 2010).

6.2.2 Water

Estimated releases of 5 pounds (~0.002 metric tons) of decaBDE to surface water from 34 domestic manufacturing and processing facilities in 2014, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2016). These releases are summarized in Table 6-1.

Industrial and urban effluents are sources of PBDEs to surface waters and sediments. Limited data on industrial and urban effluents were located for the United States. Hale et al. (2002) measured the concentration of PBDEs in soil and stream sediments collected near a polyurethane manufacturing plant (near the Dan River, Virginia). Summed concentrations of BDE 47, BDE 99, and BDE 100, the dominant congeners in these samples, ranged from <1 to 132 μg/kg (ng/g) dry weight. In 1995, sediment samples were collected up- and downstream near an area where the Swedish plastics industry used brominated flame retardants (Sellström and Jansson 1995; Sellström et al. 1998a). Samples were analyzed for tetraBDEs (50 ng/g dry weight) and pentaBDEs (sum of three congeners, 2,300 ng/g dry weight). These PBDEs were found in higher concentrations downstream of the plant than upstream, which indicates that the plastics industry was the most likely source of these compounds. Surficial sediment samples were collected at eight locations along River Viskan near several textile manufacturing facilities that used various brominated flame retardants in the production of textiles. The concentrations of BDE 47, BDE 99, BDE 100, and BDE 209 in sediments increased as samples were collected further downstream where additional industries were located (Sellström et al. 1998a). The lowest concentrations of PBDEs were found upstream of the textile industries. The combined concentration of BDE 47, BDE 99, and BDE 100 ranged from not detected to 120 ng/g (μg/kg) dry weight; the concentration of BDE 209 ranged from not detected to 16,000 ng/g (μg/kg) dry weight. Allchin et al. (1999) surveyed the concentrations of PBDEs in sediments from several rivers and estuaries in Great Britain. Sediments were collected upstream and downstream of suspected sources of pentaBDE and octaBDE, including a manufacturer, several industries, landfills, and a reference site. The highest concentrations of BDE 47, BDE 99, pentaBDE (as BDE 71), and octaBDE (as BDE 79) were in sediments near or downstream from a manufacturing site at Newton Aycliffe in River Skerne. The highest concentrations of decaBDE (as BDE 83) were found downstream of a sewage-treatment plant on River Calder. High concentrations were also detected on River Skerne downstream of a manufacturing site. BDE 99 concentrations were identical or slightly higher than BDE 47 in most sediments (Allchin et al. 1999). The sum of five pentaBDE congeners (BDE 47, BDE 99, BDE 100, BDE 153, and BDE 209) ranged from 0.07 to 10.6 ng/g (μg/kg) dry weight in freshwater sediments from Denmark (Christensen and Platz 2001). The highest concentrations were found in sediment close to populated areas.

A study conducted by the U.S. Geological Survey (USGS) analyzed waste water treatment plant (WWTP) effluent from nine cities located in Oregon and Washington for anthropogenic compounds, including PBDEs (USGS 2012). Detectable levels in the low ng/L range were observed at every WWTP, and the highest concentrations measured were for congeners BDE 47, BDE 99, and BDE 100. The greatest

PBDE concentrations were observed in Richland and Portland, Oregon. The Portland PBDE values showed varying concentrations as a function of the time of the day that samples were obtained. The lowest PBDE levels were observed in the morning hours and afternoon and then increased 2–4 times by evening hours. Shreder and LaGuardia (2014) measured PBDEs in the effluent of laundry waste water from 20 residences located near the Columbia River in Washington state. BDE 47 and BDE 209 were detected in the laundry waste water effluent of all 20 homes at median levels of 1,230 and 140 ng/L, respectively. The median concentration of total PBDE (sum of BDE 28, 47, 66, 85, 99, 100, 153, 154, 183, 206, and 209) in the laundry waste water was reported as 2,550 ng/L. BDE 47, BDE 49, and BDE 209 were also detected in the influents of two WWTPs near the Columbia River, Washington that primarily serve residential households. The sum total levels of BDE 47, BDE 49, and BDE 209 in the influents of the WWTPs ranged from 35 to 206 ng/L. Effluent PBDE levels were below the detection limit at one WWTP and 28.2 ng/L at the other facility (Shreder and LaGuardia 2014).

Although the available information indicates that leaching of PBDEs from landfills is minimal, movement of polymer particles containing pentaBDE, octaBDE, and decaBDE commercial mixtures within the landfill could lead to entry into leachate water of groundwater. PBDEs have been detected in landfill leachate and landfill related aqueous samples (Daso et al. 2013; Kwan et al. 2013; Odusanya et al. 2009; Oliaei et al. 2010; Stubbings and Harrad 2014). The presence of hydrophobic compounds like PBDEs in leachate is expected to be a result of enhanced leachability due to the presence of other constituents present in the leachate (Stubbings and Harrad 2014). Mass transfer evaluation of PBDEs from e-waste found that lower pH conditions resulted in higher transfer of PBDEs to the aqueous phase, with the highest concentration of PBDEs detected at pH 5 (Danon-Schaffer et al. 2013). It is not currently possible to assess the significance of this type of process. Well-designed landfills already include measures to minimize leaching in general, and these measures would also be effective in minimizing leaching of any PBDEs present (EU 2002, 2003a).

6.2.3 Soil

Estimated releases of 24,403 pounds (~11.1 metric tons) of decaBDE to soils from 34 domestic manufacturing and processing facilities in 2014, accounted for about 17% of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2016). These releases are summarized in Table 6-1.

PBDEs are released to land (i.e., landfills) as waste from their manufacture (both raw material and polymer) and as municipal wastes with the disposal of consumer products. The disposal of consumer products containing PBDEs is likely to increase worldwide due to rapid obsolescence of plastic products.

PBDEs may be present in biosolids and may therefore be inadvertently released to soils from the use of biosolids as a nutrient amendment to agricultural soils. Biosolids are sewage sludge that has been treated to meet regulatory requirements for land application and must adhere to concentration limits and loading rates for chemical pollutants, treatment and use requirements for controlling and reducing pathogens and the attraction of vectors, and management practices (NRC 2002). PBDEs were detected in biosolids destined for land applications in four different regions of the United States (Hale et al. 2001c). The total concentrations of pentaBDE in biosolids ranged from 1,100 to 2,290 μg/kg dry weight. The concentration of decaBDE (BDE 209) varied widely among biosolids from different regions; the concentration of BDE 209 ranged from 84.8 to 4,890 μg/kg dry weight in the biosolid samples. Kim et al. (2013b) analyzed 288 samples of sludge and biosolids from 15 WWTPs in Canada. Total PBDE levels were 230–82,000, 530–8,800, and 420–6,000 μg/kg, in primary sludge, waste biological sludge and treated biosolids respectively. BDE 209, BDE 99, and BDE 47 were reported as the predominant congeners. In the biosolids, these three congeners accounted for approximately 80% of the total. The median percentages of BDE 209, BDE 99, and BDE 47 were 47, 16, and 16%, respectively, of the total amount of all PBDE congeners in the biosolids.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

PBDEs exist in both the vapor phase and the particulate phase in the atmosphere. Particulate-phase PBDEs will be removed from the atmosphere by wet and dry deposition. A vapor phase–particulate phase analysis of indoor air samples obtained from Birmingham, United Kingdom found that 66–86% of BDE 47, 54–65% of BDE 99, 63–74% of BDE 100, <20–48% of BDE 153, and 37–48% of BDE 154 existed in the vapor phase (Harrad et al. 2004). Strandberg et al. (2001) performed a vapor phase–particulate phase analysis of outdoor air samples obtained from the Great Lakes region and found that about 80% of BDE 47, 55–65% of BDE 100 and BDE 99, and 30% of BDE 154 and BDE 153 existed in the gas phase. Several PBDE congeners have been detected in Arctic regions, suggesting that these substances undergo aerosol-mediated, long-range atmospheric transport. BDE 47, BDE 99, BDE 100, and BDE 209 were measured in air, snow, and sea ice samples throughout western Antarctica between 2001 and 2007 (Dickhut et al. 2012). Fourteen PBDE congeners are monitored for, and have been

detected at, Alert and Nuuk monitoring stations as part of the Arctic Monitoring and Assessment Programme (Hung et al. 2010), indicating the importance of long-range transport as an environmental fate process for these substances.

In water, PBDEs are expected to adsorb strongly to suspended solids and sediment, and bioconcentrate in aquatic organisms. The volatilization of PBDEs from water to air is expected to be attenuated by adsorption in the water column. In soil, PBDEs are adsorbed strongly and will be immobile. They are not likely to leach into groundwater. Volatilization of PBDEs from soil to air is limited by the low volatility of PBDEs and strong adsorption of PBDEs to soil. There is potential for PBDEs to volatilize from soil to air, particularly if the organic carbon content of the soil is low, as demonstrated by PBDEs being monitored in air as described in Section 6.4.1.

PBDEs adsorb strongly onto suspended solids and sediments in the water column. Volatilization of PBDEs from water surfaces will be attenuated by adsorption, and is thus not an important fate process. Sediment-water partition coefficients (K_p) have been measured for several components of commercial pentaBDEs (Watanabe 1988). K_p values for tetra-, penta-, and hexaBDEs are 28,300, 49,200, and 62,700 L/kg, respectively, which suggest strong partitioning to sediment. Log organic carbon-water partition coefficients (K_{oc}) were estimated for PBDEs: di- (4.11); tri- (4.35–4.41); tetra- (4.57–4.73); penta- (4.89–5.17); hexa- (5.11–5.69); octa- (5.92–6.22); and deca- (6.80) (Lyman et al. 1990).

DecaBDE and octaBDE commercial products do not bioconcentrate in fish to the same extent as congeners from the penta mixture. Monitoring data show that higher-brominated congeners such as BDE 209 are taken up in marine organisms. The reported bioconcentration factors (BCFs) for commercial decaBDE mixtures are typically <50 (Hardy 2002b). A single study on a mixed range of PBDEs, between hexaBDE and decaBDE, indicated little bioconcentration in carp (e.g., *Cyprinus carpio*) with a BCF of <4 after 8 weeks of exposure (WHO 1994a). A bioconcentration study was carried out with rainbow trout under static conditions. The concentration of ^{14}C-decaBDE/L in water was 20 µg. Fish were exposed to decaBDE for 0, 0.5, 1, 2, 4, 6, 12, 24, or 48 hours. For each of the exposure periods, there was no measurable accumulation of decaBDE in flesh, skin, or viscera (WHO 1994a). The bioconcentration of BDE 209 was studied by exposing zebrafish embryos to BDE 209 at concentrations of 0, 0.08, 0.38, and 1.92 mg/L until 14 days post-fertilization (Chen et al. 2012). BCFs of 29, 9, and 20 were calculated for exposure of 0.08, 0.38, and 1.92 mg/L, respectively. Several lower-brominated congeners were also detected in the larvae, with the main metabolite being nonaBDE. These results are

consistent with other finding that indicate that BDE 209 was bioavailable and taken up by zebrafish larvae from spiked sediments (Garcia-Reyero et al. 2014).

An abundance of monitoring data illustrates the uptake of lower-brominated diphenyl ethers by aquatic organisms, which results in bioconcentration (see Section 6.4.4). The commercial pentaBDE product undergoes bioconcentration with a BCF of approximately 14,000 (Hardy 2002b). Congener components of pentaBDE commercial product bioconcentrate to different extents. For example, approximately 50–70% of PBDEs detected in fish is a single isomer (BDE 47). The next most prominent isomer is typically BDE 99 followed by BDE 100. In a laboratory study of Baltic blue mussels (*Mytilus edulis* L), BCFs from water absorption were found to be 1,300,000 for BDE 47, 1,400,000 for BDE 99, and 1,300,000 for BDE 153 (Gustafsson et al. 1999). At several sites along the coast and in the Schelde Estuary (the Netherlands), BCFs for blue mussels were determined (Booij et al. 2000). The maximum BCFs were $1x10^9$ for BDE 99 and BDE 100, $\approx 2.5x10^7$ for BDE 28, $\approx 2.5x10^8$ for BDE 47 and $\approx 1.6x10^8$ for BDE 153. Biomagnification of PBDE congeners BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 155 in the marine food chain was demonstrated by comparing concentrations in the blubber of harbor seals with their prey fish (Shaw et al. 2009). Biomagnification factors (BMFs) from fish to seals were 21.4–109, 17.9–213, 6.9–29.8, 148–700, 11.3–447, and 12.4–236 for BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 155, respectively (Shaw et al. 2009). BDE 209 was detected at measurable concentrations in fish and seal tissue, although it did not appear to biomagnify like the other congeners. A laboratory study was conducted using juvenile carp fed BDE 209 amended food over a 60-day period (Stapleton et al. 2004). BDE 209 was not highly accumulated in the carp; however, seven debrominated lower congeners not initially present (penta- to octaBDEs) were detected in whole fish samples and liver tissue, suggesting that while BDE 209 did not accumulate in the fish, it may be a source of lower-brominated metabolites in aquatic organisms.

Other studies have demonstrated the biomagnification of lower-brominated PBDE congeners. Haglund et al. (1997) examined the concentrations of tetra- to hexaBDEs in herring, salmon muscle, and gray and ringed seals collected along the Swedish coast of the Baltic Sea between 1981 and 1988. The concentrations of tetraBDEs (e.g., BDE 47) were found to increase with trophic level. Concentrations of PBDEs in herring and their predators, grey seal and guillemot, all collected at the same location of the Baltic Sea, have been compared to estimate potential biomagnification (de Wit 2002). The herring were caught in the autumn of the same year as guillemot egg collection (1987). BMFs for guillemot egg versus herring were 19, 17, and 7.1 for BDE 47, BDE 99, and BDE 100, respectively. Burreau et al. (2000) analyzed small herring and salmon from the Atlantic Ocean (near Iceland) for several PBDEs. The

calculated biomagnification factors for Atlantic salmon versus small herring were 3.5, 3.8, and 6.0 for BDE 47, BDE 99, and BDE 100, respectively. These authors concluded that biomagnification was occurring for the lower-brominated congeners.

Biosolids from the Metropolitan Water Reclamation District of Greater Chicago, Stickney WWTP, collected between 2004 and 2007, were applied at two sites at a depth of 15−20 cm (Hale et al. 2012). Maximum total soil PBDE concentrations were 565 and 1,810 μg/kg for high clay soil and sandy soil, respectively. Corn grown at the two sites after the third year of annual biosolid application was evaluated for PBDEs using GC/MS with ENCI. PBDEs were not detected in the 46 grain, stover, or root samples examined, suggesting little uptake by corn from soils amended using biosolids. However, earthworms exposed to PBDE containing biosolids were shown to accumulate these substances (Gaylor et al. 2013). Earthworms were exposed to a Class B anaerobically digested biosolid (ADB) containing 5,560±440 μg/kg dry weight total penta congeners (BDE 47, 99, 100, 153, 154, and 183) and a composted biosolid (CB) containing 1,130±79 μg/kg dry weight total penta congeners over the course of a 28-day incubation period. Total penta PBDE body burdens in worms exposed to ADB amended soils were about 5 times greater than those in the substrate, and worms exposed to CB amended soils had body burdens about 4 times greater than in the substrate.

6.3.2 Transformation and Degradation

Photolysis appears to be the dominant transformation process for PBDEs. However, the importance of photochemical transformation reactions in the environment cannot be determined due to lack of information. Based on a very limited number of studies, biodegradation does not appear to be significant for PBDEs.

6.3.2.1 Air

In air, PBDEs may undergo indirect photolysis with hydroxyl radicals or direct photolysis with sunlight. Vapor-phase PBDEs may be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. The half-lives for this reaction in air are estimated to be 29, 140, and 476 days, respectively, for penta-, octa-, and decaBDE homologs, calculated using a structure estimation method (Meylan and Howard 1993). This estimation is calculated using an atmospheric concentration of $5x10^5$ hydroxyl radicals per cm^3 and is based on a 24-hour day of sunlight. The half-lives of PBDEs that are expected to be present in the particulate phase in the air will be longer than the estimated half-lives

calculated for the gas-phase reaction. Thus, for the higher-brominated PBDEs (e.g., octa- and decaBDEs), indirect photolysis with hydroxyl radicals will be less important.

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

6.3.2.2 Water

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

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

environment. Organic solvents can act as hydrogen donors in photolysis reactions, which will potentially affect the distribution of products formed.

The photolysis of PBDEs was examined under environmentally relevant conditions. Hua et al. (2003) studied the degradation of decaBDE in several different experiments: (1) on humic acid-coated silica particles; (2) on glass surfaces in contact with aqueous humic acid solutions; and (3) on glass surfaces in contact with water. DecaBDE dissolved in toluene was deposited on the solid substrate under a stream of nitrogen (to evaporate the solvent) and then desiccated to remove any residual toluene. The adsorbed decaBDE on the solid substrate was then inundated with the aqueous test solution, followed by irradiation for the duration of the test period. In all experiments, natural sunlight (location, 40° 26' N, 86° 55' W) was used. The extent of degradation was determined using HPLC with UV detection or by GC/MS. In the first experiment, solar irradiation of decaBDE adsorbed onto humic acid-sand indicated that the photolysis of decaBDE was slow. After 96 hours of exposure to sunlight, 88% of initial decaBDE remained on the coated sand. There is some evidence that lower-brominated congeners (e.g., BDE 155) were formed in the experiment (EU 2002). In the second experiment, decaBDE was adsorbed on glass tubes containing a humic acid. In this study, the concentration of decaBDE decreased relatively quickly over the first 24 hours of exposure, after which, the concentration remained stable. Bromide ion accumulated at an almost linear rate from start to end of the 72-hour exposure period. Approximately 70% of the initial decaBDE remained after the 72-hour exposure. The difference in kinetics (for the disappearance of decaBDE vs. the appearance of bromide ion) suggests that after the initial degradation of decaBDE, bromide ion was generated by the degradation of lower-brominated diphenyl ether congener products (possibly octa- and nonaBDEs). Bromide ion mass balance for the system indicated that 70% of the total bromine present was accounted for by decaBDE or bromide, with the remaining 30% present as unidentified compounds. In the third experiment, Hua et al. (2003) investigated the photodegradation of decaBDE adsorbed on glass tubes, which were filled with aqueous solutions (without humic acid). The result of this test showed a much more rapid loss of decaBDE than found in the analogous test using humic acid solutions. Approximately 29% of the initial decaBDE present remained after 72 hours. The rate of decaBDE loss and bromide ion accumulation was relatively constant over the entire 72-hour test period. Mass balance indicated that approximately 50% of the total bromine was present as either decaBDE or bromide ion, while the remaining 50% was possibly unidentified nona- and octaBDE congeners. The difference between the tests using glass tubes with and without humic acid solution is possibly due to the absorption of light by humic acids, which may attenuate the degradation process. These studies indicate that adsorbed decaBDE may undergo photolysis forming octa- and nonaBDEs under somewhat environmentally relevant conditions. Lower-brominated diphenyl ether congeners are

also formed although only to a minor extent. These tests do not provide evidence that lower-brominated diphenyl ethers (e.g., tetra- and pentaBDEs) are a major degradation product of decaBDE (EU 2002). There is also insufficient information from these studies to estimate the rate of photolysis or if intermediate degradation products build up after long-term exposures (EU 2002).

Söderström et al. (2004) examined the time course of photolysis of decaBDE (BDE 209) in toluene, on silica gel, sand, sediment, and soil using artificial sunlight and on the natural matrices (e.g., sediment, soil, and sand) using natural sunlight. On natural samples, BDE 209 was first dissolved in toluene and then deposited on the natural matrix. The toluene was allowed to evaporate, and then the sample was reconstituted with water to resemble natural conditions. BDE 209 was photolytically labile and formed debromination products in all matrixes studied. Nona- to tetraBDEs were formed as well as some PBDFs. The half-lives in toluene and on silica gel were <15 minutes, and half-lives on other matrices ranged from 40 to 200 hours. No differences were observed in the debromination patterns under different matrices or light conditions. These experiments show that photolytic debromination of BDE 209 is a possible pathway for the formation of more bioavailable, lower-brominated PBDEs. However, the most commonly found BDEs in environmental samples (e.g., BDE 47, BDE 99, and BDE 100) were only formed to a minor degree (Söderström et al. 2004).

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

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

PBDEs are unlikely to biodegrade rapidly in the environment under aerobic conditions. PentaBDE did not undergo biodegradation (determined by CO_2 evolution) after 29 days in an Organisation for Economic

Co-operation and Development (OECD) 301B ready biodegradation test (EU 2001). The substance tested was a composite sample from two producers with the following composition: 33.7% tetraBDE, 54.6% pentaBDE, and 11.7% hexaBDE. The test was extended to 93 days to allow sufficient opportunity for adaptation to occur. At the end of 93 days, 2.4% of the theoretical amount of CO_2 had been evolved. Thus, pentaBDE was determined to be not readily biodegradable. No degradation (as oxygen uptake) was seen for octaBDE after 28 days in an OECD 301D ready biodegradation test (EU 2003a). Thus, octaBDE was determined to be not readily biodegradable. The biodegradability of decaBDE has been studied under aerobic conditions using an activated sludge inoculum (EU 2002). DecaBDE at 100 mg/L was incubated with activated sludge (at 30 mg/L) over a 2-week period using a method similar to an OCED 301C MITI test. No degradation (as measured by biochemical oxygen demand) was observed. Thus, decaBDE was determined to be not readily biodegradable.

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

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

6.3.2.3 Sediment and Soil

Information on the transformation and degradation of PBDEs in soil is limited. The extent to which PBDEs undergo direct photolysis in soils and sediment is unknown. However, sunlight would only penetrate the uppermost few millimeters of soil and will not impact sediment. Photolysis of PBDEs is possibly important for land-applied sewage sludge contaminated with PBDEs. However, no information was available on this possibility. Based on studies in water, most PBDEs biodegrade slowly in soils or sediment under aerobic or anaerobic conditions. The anaerobic biodegradation of BDE 47, BDE 99, and BDE 209 was studied using microcosms prepared from loam sediment (pH 6.3, 16.4% organic carbon) obtained from a pond located in West Lafayette, Indiana (Tokarz et al. 2008). After an 8-month incubation period, microcosms containing BDE 47 showed variable losses (up to 30% of the initially applied amount) of the parent congener without concurrent increases in expected debromination products, suggesting that other degradation mechanisms other than reductive debromination may have occurred. Only about 3% degradation of BDE 99 was observed after 8 months, with BDE 28 being the most important debromination product. After 10 months, only slight decreases in the initial BDE 209 concentration was observed in six microcosms, and the half-life of this congener was estimated to range from 6 to 50 years; however, some aged microcosms exhibited greater degradation after 3.5 years, yielding nine degradation products (Tokarz et al. 2008).

6.3.2.4 Other Media

The bacteria, *Pseudomonas aeruginosa*, that was isolated from an electronic waste dismantling area was capable of degrading BDE 209 under aerobic conditions, especially in the presence of co-metabolic substrates such as glucose (Shi et al. 2013). Nonabromodiphenyl ethers (BDE 208, BDE 207), four octabromodiphenyl ethers (BDE 203, BDE 202, BDE 197, BDE 196), and one heptabromodiphenyl ethers (BDE 183) were noted as degradation products.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to PBDEs depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of PBDEs in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on PBDEs levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily

equivalent to the amount that is bioavailable. The analytical methods available for monitoring PBDEs in a variety of environmental media are detailed in Chapter 7.

Monitoring studies indicate that PBDEs are transported globally. Atmospheric, water, and biota concentrations of PBDEs tend to be dominated by lower-brominated congeners (e.g., BDE 47). Sediments tend to be dominated by higher-brominated congeners (e.g., BDE 209). Biota monitoring studies indicate that PBDE concentrations have increased since the late 1970s, with lower-brominated congeners (e.g., BDE 47) being preferentially bioconcentrated. Studies indicate that PBDE concentrations increase with respect to trophic level; organisms that reside higher on the food chain tend to have higher concentrations of PBDEs.

6.4.1 Air

PBDEs will exist in both the vapor and particulate phase in both indoor and outdoor air (Harrad et al. 2004). The higher-brominated congeners (hepta-deca) have lower vapor pressures and partition more to the particulate phase, while the lower-brominated substances have a greater tendency to partition to the vapor phase. Concentrations of PBDEs in outdoor air in the United States are typically in the range of 20–200 pg/m^3, with BDE 47 and BDE 99 being the congeners most often detected (EPA 2010). Monitoring data from the 1990s showed infrequent detections of decaBDE; however, more recent monitoring data have shown an increase in the frequency of detection of this substance both in outdoor and indoor air samples (EPA 2010; Hoh and Hites 2005). Monitoring data from Europe and Asia suggest lower concentrations of PBDE in air samples as compared to data obtained in the United States.

Representative concentrations of PBDEs in outdoor air samples obtained at various locations are summarized in Table 6-2. Air samples obtained from urban (Chicago, Illinois), rural (Sleeping Bear Dunes, Michigan and Sturgeon Point, New York), and remote (Eagle Harbor, Michigan) shorelines of the U.S. Great Lakes all contained quantifiable concentrations of BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 (Dodder et al. 2000; Strandberg et al. 2001). The most significant congeners were BDE 47 and BDE 99. Air measurements were averaged over a 3-year period between 1997 and 1999. The concentration of total PBDEs ranged from 5.5 pg/m^3 in rural environments to 52 pg/m^3 in urban air from Chicago, Illinois. The concentration of BDE 47 was 48 pg/m^3 observed near Chicago, Illinois. The average concentration of decaBDE at the remote and rural locations was <0.10 pg/m^3 for each of the years investigated. The average concentration of decaBDE in the particulate phase at the urban location ranged from 0.20 to 0.35 pg/m^3 (Strandberg et al. 2001).

Table 6-2. Concentrations (pg/m^3) of Several Polybrominated Diphenyl Ethers (PBDEs) in Air Samples

Location	BDE 47	BDE 99	BDE 100	BDE 209	ΣPBDEs[a]	Reference
Urban, United States	48	25	3.0	No data	77*	Dodder et al. 2000
Rural, United States	6.2–9.2	4.3–5.0	0.6–0.9	No data	2–4.8*	Dodder et al. 2000
Remote, United States	3.7	2.6	0.33	No data	6.9*	Dodder et al. 2000
Alert, Northwest Territories Canada	No data	No data	No data	No data	1–28	Alaee et al. 1999
Eagle Harbor, Wisconsin	2.9	2.1	0.28	<0.10	5.5*	Strandberg et al. 2001
Chicago, Illinois	3.9–42	2.4–15	0.68–3.3	1.5–878	13–980	Hoh and Hites 2005
Sleeping Bear Dunes, Michigan	0.51–27	0.32–23	0.030–5.1	<0.29–21	1.4–61*	Hoh and Hites 2005
Bloomington, Indiana	1.9–21	1.2–11	0.26–2.75	<0.29–21	6.4–44*	Hoh and Hites 2005
Rohwer, Arkansas	1.2–42	0.87–35	0.17–3.7	<0.10–135	2.7–165*	Hoh and Hites 2005
Cocodrie, Louisiana	2.0–24	0.89–11	0.21–2.7	<0.10–14	5.1–42*	Hoh and Hites 2005
Sturgeon Point, New York	3.8	2.8	0.39	<0.10	7.2*	Strandberg et al. 2001
Sleeping Bear Dunes, Michigan	8.4	5.3	0.80	<0.10	15*	Strandberg et al. 2001
Chicago, Illinois	33	16	2.0	0.20–0.35	52*	Strandberg et al. 2001
Ammarnäs, Sweden	6.3	1.6	0.4	No data	8.3	de Wit 2000, 2002
Hoburgen, Sweden	0.7	0.35	0.07	No data	1.1	de Wit 2000, 2002
Stoke Ferry, United Kingdom	4.7–50	5.5–13	1.1–3.9	No data	6.7–58	Peters et al. 1999
Hazelrigg, United Kingdom	3.2–61	3.1–22	0.62–5.4	No data	4.1–69	Peters et al. 1999
Dunai Island, Russia	No data	No data	No data	No data	1–8*	Alaee et al. 1999
Arctic	2.2–2.8	2.0–2.3	0.40–0.47	1.0–1.8	6.7–8.6*	Hung et al. 2010

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

BDE = brominated diphenyl ether

PBDEs were monitored at five different locations (Chicago, Illinois; Sleeping Bear Dunes, Michigan; Bloomington, Indiana; Rohwer, Arkansas; and Cocodrie, Louisiana) across the United States from 2002 to 2003 (Hoh and Hites 2005). Total PBDE concentrations at the urban site (Chicago, Illinois) were 3–6 times greater than the other locations, with BDE 47, BDE 99, BDE 100, and BDE 209 being the most abundant congeners at all five locations. DecaBDE concentrations as high as 960 and 410 pg/m^3 were observed in Chicago on two dates in 2003.

Throughout the year of 1997, air samples were taken from a rural site in southwestern England called Stokes Ferry and a semirural site in northwestern England called Hazelrigg and analyzed for PBDEs (Peters et al. 1999). Tri- and heptaBDEs were detected; the combined concentrations of BDE 47, BDE 99, and BDE 100 ranged from 7 to 69 pg/m^3 at Hazelrigg and from 6 to 58 pg/m^3 at Stoke Ferry (de Wit 2002). PBDEs have also been measured in air samples taken from remote stations in the Arctic (e.g., Alert, Northwest Territories, Canada; Dunai Island, eastern Siberia, Russia) between January 1994 and January 1995 (de Wit 2002). The total concentration of several di- to hexaBDEs ranged from 1 to 4 pg/m^3 at Alert for the majority of the year; however, in July 1994, the concentration was 28 pg/m^3. At Dunai, the major congeners found were BDE 47 and BDE 99. In Sweden during 1990–1991, air samples collected from Ammarnäs in the northern mountains and Hoburgen on the southern tip of Gotland in the Baltic Sea, had measurable amounts of BDE 47, BDE 99, and BDE 100 (de Wit 2002). Total PBDE concentrations were approximately 1 and 8 pg/m^3, respectively. The concentration of BDE 47 was found to be highest in the gas phase, while BDE 99 and BDE 100 were highest in the particulate phase. No decaBDE was found, although the limit of detection limit for decaBDE is much higher than for the lower-brominated diphenyl ethers.

Indoor air concentrations of PBDEs vary depending upon potential sources such electronics or foams used in upholstery stuffing for furniture that were treated with PBDEs (EPA 2010; Harrad et al. 2006; Hazrati and Harrad 2006). Harrad et al. (2004) found a significant positive correlation between PBDE concentrations in indoor air and both the number of electrical appliances and the number of chairs containing FPUF. Concentrations of tetra- and pentabrominated congeners (BDE 47, BDE 99, and BDE 100) in indoor air were always higher than those detected in outdoor air. On average, indoor air concentrations were 150, 120, and 140 times higher than outdoor air for BDE 47, BDE 99 and BDE 100, respectively. Indoor air concentrations of PBDEs also tended to be higher in workplace environments as compared to domestic residences; however, these concentrations could vary substantially from one room to another (Harrad et al. 2004). Air samples collected from 31 homes, 33 offices, and 25 automobiles in the West Midlands, United Kingdom were analyzed for the presence of PBDEs (Harrad et al. 2006).

Total PBDE concentrations in samples obtained from homes ranged from 4 to 245 pg/m^3 (24 pg/m^3, median), while concentrations in offices and cars ranged from 10 to 1,416 (71 pg/m^3, median) and from 4 to 1,416 pg/m^3 (41 pg/m^3, median), respectively. PBDE congeners 47 and 99 were reported as the major contributors to the overall total (Harrad et al. 2006). Although the previous study reported a statistically significant positive correlation between the PBDE concentrations and the number of electrical devices and FPUF-containing chairs (Harrad et al. 2004), no clear statistical evidence of such correlations were reported in these indoor air environments (Harrad et al. 2006; Hazrati and Harrad 2006). PBDE concentrations in the air of one office did drop dramatically after an older computer was replaced by a relatively newer one and a statistically significant positive correlation was observed between automobile age and PBDE concentrations when two highly contaminated outliers were removed from the analysis. Further observations indicated a seasonal variation of the PBDE concentrations in indoor air, with higher concentrations being observed during the summer months (Hazrati and Harrad 2006). BDE 47, BDE 99, BDE 100, BDE 183, and BDE 209 were detected in 63, 22, 29, 32, and 42% of air samples taken aboard aircraft during routine flights (Allen et al. 2013). Concentrations ranged from below the detection limits to a maximum concentration of 2,100,000 pg/m^3 for BDE 209.

Concentrations of PBDEs were measured in floor dust, indoor air, ventilation filter dust and carpets in 10 buildings located in Michigan (Batterman et al. 2010). Median concentrations of total PBDEs were reported as 8,754 ng/g in settled dust, 1,250 pg/m^3 vapor-phase air, and 155 pg/m^3 particulate-phase air. The highest concentrations of PBDEs were generally noted in rooms that contained sources such as computer servers. Monitoring data from one building that was built in 2006 indicated a very low concentration of PBDEs in settled dust at the time it was constructed (145 ng/g); however, these concentrations increased exponentially to >10,000 ng/g 5–8 months after the building was opened. Despite the voluntary phase-out of pentaBDE and octaBDE in 2004, high concentrations of congeners associated with these mixtures (BDE 47, BDE 99, BDE 100, BDE 153, and BDE 203) were detected in dust and air samples, suggesting that there are significant sources of these PBDEs in products that remain in the market and that were used in this building even after the phase out in 2004.

6.4.2 Water

Due to the hydrophobic nature of PBDEs, this class of compounds is expected to be present in water at very low concentrations or at concentrations below the limit of detection of acceptable analytical methods. In 1999, the concentration of PBDEs in Lake Ontario surface waters ranged between 4 and 13 pg/L with ~90% in the dissolved phase (Luckey et al. 2001). BDE 47 and BDE 99 were the most

abundant congeners, together making up >70% of the total PBDEs. Streets et al. (2006) reported 18 and 3.1 pg/L average concentration of ΣPBDEs (BDE 47, BDE 66, BDE 100, BDE 99, BDE 85, BDE 154, and BDE 153 of pg/L) in Lake Michigan Water for the dissolved phase and particulate phase, respectively. In Japan, PBDEs were not detected in 75–200 water samples (ENVIRON 2003a). In nine English freshwater lakes grab samples were obtained from April 2008 to February 2012, average concentrations of the sum total of PBDEs, which included BDE 17, BDE 28, BDE 49, BDE 47, BDE 66, BDE 100, BDE 99, BDE 85, BDE 154, and BDE 153, ranged from 41.5 to 73.3 pg/L (Yang et al. 2014).

The EPA utilized data from the San Francisco Monitoring Program for Trace Substances in surface water to estimate possible concentrations of PBDEs that might be found in drinking water. Thirty-three water samples were obtained from the San Francisco Estuary, with total PBDEs concentrations ranging from 3 to 513 pg/L, and a mean concentration of 146.2 pg/L (Oros et al. 2005). It was reported that the most frequently detected congeners were BDE 47, BDE 99, and BDE 209. The source of these PBDEs was most likely effluent from municipal treatment plants. Concentrations of PBDEs monitored in the Spokane River in the state of Washington exhibited seasonal variation (Furl and Meredith 2010). Dissolved PBDE concentrations collected in the fall of 2005 were approximately 6 times greater (926 pg/L) as compared to concentrations observed in the spring of 2006 (146 pg/L). The variation in PBDE concentrations were likely a result of dilution of local sources in the spring from increased flow due to snowmelt in the upper watershed.

6.4.3 Sediment and Soil

Hale et al. (2002) reported the concentration of PBDEs in soil samples collected in the vicinity of a polyurethane foam-manufacturing facility. Concentrations in these soils are likely to be higher than those to be expected in rural and potentially urban areas of the United States. Total PBDE concentrations in these samples ranged from not detected to 76 μg/kg dry weight. BDE 99 was the predominant congener in soil followed by BDE 47 and BDE 100. Concentrations of total PBDEs in soil obtained from a large automotive shredding and metal recycling facility in Brisbane, Australia ranged from 29 to 726 ng/g dry weight as compared to background concentrations at an uncontaminated site (0.2–2 ng/g dry weight) (Hearn et al. 2013). BDE 209 was the predominant congener in dust, soil, and air at the facility.

In Eastern China, near dismantling areas for waste electrical and electronic equipment that are considered a potential exposure source of PBDEs, 45 farmland soil samples were collected from 12 locations (Dong et al. 2014). The farmland soil PBDE concentrations ranged from 2.96 to 200 ng/g and air concentrations

ranged from 884 to 2,791 pg/m^3. The PBDE concentrations in high-mountain pasture soil, grass, and milk from grazing cows in the Italian Alps were analyzed (Parolini et al. 2012). Thirteen BDE congeners were investigated, including BDE 17, BDE 28, BDE 71, BDE 47, BDE 66, BDE 100, BDE 99, BDE 85, BDE 154, BDE 153, BDE 138, BDE 183, and BDE 190. Average ΣPBDE concentrations in soil from 0 to 7 cm soil depth were 0.43–1.55 ng/g dry weight, 1.7–8.2 ng/g dry weight in grass vegetation, and 0.659–1.576 ng/g dry weight in milk. The average total PBDE concentration in soil samples collected from the Ny-Alesund region of the Arctic was reported as 0.042 ng/g dry weight (Wang et al. 2015). BDE 99 was the predominant congener, with an average value of 0.0097 ng/g dry weight.

The EPA used 33 surface soil measurements taken from 15 states in the United States to estimate ingestion rates and dermal exposure rates of PBDEs from soil. The concentration of 30 total BDEs in the soils was reported to average 103 ng/g dry weight, with a geometric mean (GM) concentration of 5.3 ng/g (EPA 2010). BDE 47 (1.9 ng/g), BDE 99 (3.6), BDE 100 (0.4), BDE 153 (5.7), BDE 154 (4.8), BDE 183 (37.4), and BDE 209 (15.3) were included in this evaluation.

Sediment concentrations of PBDEs tend to be dominated by higher-brominated congeners (e.g., BDE 209) (deWit 2002). Temporal trends suggest that concentrations of PBDEs in sediments are increasing. Burdens of PBDEs in sediment appear to be a function of distance from the source and their organic carbon content (Hale et al. 2003). Representative concentrations of PBDEs in sediment samples are summarized in Table 6-3.

A 20-year field study regarding the land application of Class B biosolids to a site located in Arizona was discussed by Quanrud et al. (2011). Risk assessments were made based on the intake of compounds via inhalation, dermal sorption, or ingestion. PBDE concentrations were detected, primarily in the surface 30-cm depth sample, and surface accumulation of PBDEs occured due to their hydrophobic nature, which resulted in sorption to colloids. The maximum amount of PBDE detected was 80 ng/g soil as congener BDE 209. A risk evaluation of PBDEs based on Hazard Indices indicated that the health risk to humans of PBDEs was negligible when all three routes of exposure were considered.

Li et al. (2006) collected 199 sediment samples from 16 locations of Lake Superior, Lake Michigan, Lake Huron, Lake Erie, and Lake Ontario and analyzed these samples for PBDE concentrations. The concentrations of PBDEs in surface sediment ranged from 0.5 to 6.7 ng/g dry weight tri- to heptaBDE congeners and from <4 to >240 ng/g dry weight for BDE 209. PBDEs were detected in 100% of sediment samples obtained from the San Francisco Bay with total PBDE concentrations ranging from

Table 6-3. Concentrations (ng/g) of Several Polybrominated Diphenyl Ethers (PBDEs) in Sediment and Suspended Particulate Samples

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs	BDE 209	Reference
Sediment	Lake Superior	No data	No data	No data	No data	12	Zhu and Hites 2005
Sediment	Lake Michigan	No data	No data	No data	2.6[a]	320	Zhu and Hites 2005
Sediment	Lake Michigan	No data	No data	No data	1.67–3.97[a]	43.9–95.6	Song et al. 2005
Sediment	Lake Huron	No data	No data	No data	1.02–1.87[a]	21.5–36.0	Song et al. 2005
Sediment	Lake Erie	No data	No data	No data	1.1[a]	40	Zhu and Hites 2005
Sediment	Lake Ontario	No data	No data	No data	2.8[a]	14	Qui et al. 2007
Sediment	Hadley Lake, Indiana	16±2 (dw)	37±8 (dw)	7.1±1.5 (dw)	584 (dw)[b]	480±170 (dw)	Dodder et al. 2002
Sediment	Baltic Sea	ND–3.4	ND–2.4	ND–1.3	ND–5.4	ND	Nylund et al. 1992
Sediment	Upstream plastics plant, Sweden	3.7	8.8	1.6	14.1	No data	Sellström and Jansson 1995
Sediment	Downstream plastics plant, Sweden	780	1,200	270	2,250	No data	Sellström and Jansson 1995
Sediment	River Viskan (Sweden), up-stream and downstream textile industries	<2–50	<1–53	<0.4–19	ND–120	ND–16,000	Sellström et al. 1998a
Sediment	22 European river mouths	<0.17–6.2 (dw)	<0.19–7.0 (dw)	No data	No data	<0.51–1,800	de Wit 2002
Sediment	Seven rivers, Great Britain	<0.3–368 (dw)	<0.6–898 (dw)	No data	No data	<0.6–3,190	Allchin et al. 1999
Sediment	Netherlands, several sites	0.3–7.1 (dw)	<0.2–9 (dw)	No data	No data	<4–510 (dw)	de Boer et al. 2000b
Suspended particulates	Netherlands, several sites	<2–9 (dw)	<0.1–23 (dw)	No data	No data	<9–4,600 (dw)	de Boer et al. 2000b

[a]Tri- to hepta-PBDE congeners.
[b]Includes sum of BDE 47, BDE 99, BDE 100, BDE 209, and other congeners (not specified).

BDE = brominated diphenyl ether; dw = dry weight; ND = not detected

2.1 to 8.0 ng/g dry weight and a median concentration of 4.3 ng/g dry weight (Klosterhaus et al. 2012). BDE 209 was the primary congener of each sample, accounting for approximately 38–68% of the total PBDE amount.

In the United States, Dodder et al. (2002) analyzed four surficial sediments from Hadley Lake (Indiana). This lake is in the vicinity of a production point source. DecaBDE (BDE 209) was the major congener detected at concentration ranging from 19 to 36 μg/kg (ng/g) dry weight. Other congeners detected (in decreasing order: BDE 99, BDE 153, BDE 154, BDE 47, and BDE 100) were <5 μg/kg (ng/g) dry weight. PBDEs were above the detection limit (i.e., 0.5 μg/kg [ng/g] dry weight) in 22% of surficial sediment samples (from 133 sites) in freshwater tributaries of Virginia (Hale et al. 2001b). BDE 47 was the predominant congener followed by BDE 99 and BDE 100. The maximum concentration detected in sediment was 52.3 μg/kg (ng/g) dry weight. Hale et al. (2002) reported that stream sediment adjacent to a former polyurethane foam production facility in North Carolina contained up to 132 μg/kg (ng/g) dry weight of pentaBDE. Since the phase out of PBDE-containing flame retardants, levels of these substances have begun declining in sediment and other environmental media. Sutton et al. (2015) reported that levels of BDE 47 have declined by over one-third in sediment samples obtained from the San Francisco Bay from 2000 to 2012; however, no decline of BDE 209 was evident, presumably since decaBDE was not phased out until 2013.

In Japan, tetra-, penta-, hexa-, and decaBDEs have been detected in river sediments (Watanabe et al. 1986, 1987, 1995). The combined concentrations of tetra- and pentaBDEs ranged from 21 to 59 ng/g (μg/kg) dry weight. The concentration of decaBDE (BDE 209) ranged from <25 to 11,600 ng/g (μg/kg) dry weight (deWit 2002). In 1999, sediment samples from several locations in the Netherlands contained BDE 47, BDE 99, and BDE 209 (de Boer et al. 2000b). Concentrations ranged from 0.3 to 7.1 ng/g (μg/kg) dry weight for BDE 47, not detected to 5.5 ng/g (μg/kg) dry weight for BDE 99, and not detected to 510 ng/g (μg/kg) dry weight for BDE 209. The concentration of PBDEs in suspended particulate matter ranged from not detected to 9 ng/g (μg/kg) dry weight for BDE 47, not detected to 23 ng/g (μg/kg) dry weight for BDE 99, and not detected to 4,600 ng/g (μg/kg) dry weight for BDE 209 (de Boer et al. 2000b). The concentration of several brominated flame retardants was measured in sediments collected from the mouths of major European rivers (de Wit 2002). Elevated concentrations of BDE 47 and BDE 99 were found in Humber and Mersey rivers (Great Britain). In two rivers of the Netherlands, the sum of BDE 47 and BDE 99 ranged from 1.61 to 13.1 ng/g (μg/kg) dry weight. The highest hexaBDE concentrations (as BDE 153) were found in the river Seine (France), three rivers in the Netherlands, and the rivers Schelde (Belgium), Forth (Great Britain) and Ems (Germany); the concentration of

BDE 153 ranged from 0.013 to 0.056 ng/g (μg/kg) dry weight in these sediments. The concentrations of decaBDE were highest in sediment from the Seine, ranging from 2.4 to 3.9 ng/g (μg/kg) dry weight. The concentrations of decaBDE in River Mersey (Great Britain), Schelde, and River Liffey (Ireland) ranged from 34 to 1,800 ng/g (μg/kg) dry weight. In the southern Baltic Sea (Bornholm Deep), the upper layer of sediment was analyzed for BDE 47, BDE 99, and BDE 100; the combined concentration of these three congeners was 0.52 ng/g (μg/kg) dry weight (Nylund et al. 1992).

A well-studied sediment core collected from the southern part of the Baltic Sea proper was analyzed for PBDEs and a number of organochlorine contaminants (Nylund et al. 1992). The retrospective temporal trend from 1939 to 1987 showed that the PBDE concentrations (i.e., sum of BDE 47, BDE 99, and BDE 100) have increased with a sharp increase after 1980. The PBDE concentration in the sample from 1989 was 2.9 ng/g (Nylund et al. 1992). Measurable amounts of BDE 28, BDE 47, BDE 66, BDE 99, and BDE 100 were found in sediment cores from a freshwater lake in Germany, the Wadden Sea (the Netherlands), and Drammenfjord (Oslo Fjord, Norway) (Zegers et al. 2000). Samples from the Drammenfjord and freshwater lake also contained BDE 153 and BDE 154, and the Wadden Sea and freshwater lake samples contained BDE 209. The lower-brominated PBDEs appear in the 1960s, and BDE 209 appears about 10 years later. The Drammenfjord sediment core shows increasing concentrations of BDE 47 starting in the 1940s (range, 0.02–0.18 ng/g dry weight) and increasing concentrations of BDE 99 (range, 0.5–0.28 ng/g dry weight), BDE 100 (range, not detected–0.07 ng/g dry weight), and BDE 154 (range, not detected–0.06 ng/g dry weight) beginning in the 1950s up to 1999. In the sediment core from Lake Woserin, lower-brominated PBDE congeners were detected in the sediment horizons beginning in the late 1950s, and the concentrations increased until the late 1970s, and then leveled off when residues of BDE 209 first appeared. A similar leveling-off trend is also observed in the Wadden Sea core (Zegers et al. 2000). It is important to note that this study identified the presence of PBDEs compounds in sediments from the late 1950s and early 1960s. This is nearly a decade prior to any significant commercial production of these substances. The existence of PBDEs at these early dates may be a result of vertical mixing of sediment cores or blurring of core horizons through burrowing activity of benthic organisms, or may lend some credibility to the likelihood that either the substances identified in the environment as PBDEs are not necessarily PBDEs.

6.4.4 Other Environmental Media

Dust. The predominant PBDE exposure pathway for the general population of the United States is from indoor dust (EPA 2010; Lorber 2008). Total PBDE (sum of BDE 28, 47, 66, 85, 99, 100, 153, 154, 183,

206, and 209) levels in dust samples obtained from 20 residences located near the Columbia River in Washington state ranged from 311 to 19,700 ng/g, with BDE 209 being the predominant congener (Shreder and LaGuardia 2014). Total PBDE concentrations in settled dust from 10 office buildings located in Michigan ranged from 1,340 to 38,900 ng/g (median, 15,800 ng/g) (Batterman et al. 2010). BDE 47, BDE 99, and BDE 209 had the highest concentrations for the individual congeners, with a maximum value of 29,000 ng/g measured for BDE 209 in one of the office buildings. A study of eight office buildings in Boston, Massachusetts had even greater PBDE concentrations in settled dust. BDE 209 was detected in 100% of the samples at concentrations ranging from 912 to 106,204 ng/g (Watkins et al. 2011). Total pentaBDE congeners ranged from 141 to 61,264 ng/g in these office buildings. Lower concentrations of the lesser brominated congeners, Σtri–hexaBDE, were detected in dust samples in Europe as compared to the United States and Canada (Harrad et al. 2008). Concentrations of BDE 209 in dust samples are similar in the United States and the United Kingdom. Congener pattern analysis of indoor dust suggests that North American dusts are contaminated with decaBDE and pentaBDE commercial formulations, whereas U.K. dusts are predominantly contaminated with decaBDE. For example, the average concentration of total PBDE congeners in eight homes located in West Midlands, United Kingdom was about 215 ng/g, with a range of 16.2–625.4 ng/g (Harrad et al. 2006). Dust samples obtained from Spain and Belgium had total PBDE ranges of 2.9–380.2 and 6.2–384.8 ng/g, respectively (Harrad et al. 2006). Concentrations in North America also seem to be greater than even source-dominated areas in other parts of the world. The mean total concentration of 10 PBDE congeners in dust samples obtained from an office building located near a large automotive shredding and metal recycling facility in Brisbane, Australia was 2,014 ng/g (Hearn et al. 2013).

Food. Food ingestion typically accounts for <20% of the total PBDE intake for adults in North America (EPA 2010; Lorber 2008); however, it accounts for the majority of intake for the European population, with the exception of BDE 209 where dust exposure is the primary source (Abdallah and Harrad 2014; Trudel et al. 2011). Schecter et al. (2006) measured concentrations of 13 PBDE congeners in 62 food samples in the United States. Concentrations of total PBDEs ranged from 7.9 pg/g in milk to 3,762 pg/g in canned sardines. Fish, meat, and dairy products tended to have the highest concentrations of PBDEs. The results of these measurements for meat and fish are reproduced in Table 6-4. A survey of three categories of baby food (formula, cereal, and puree) from the United States and China found the median concentrations of total PBDE (sum of BDE 17, BDE 28, BDE 47, BDE 49, BDE 100, BDE 153, BDE 183, and BDE 209) were 21 and 36 pg/g in foods purchased in the United States and China, respectively (Liu et al. 2014).

Table 6-4. PBDE Concentrations (pg/g Wet Weight) in 18 U.S. Meat and Fish Samples[a]

Sample	Lipid (%)	BDE 17	BDE 28	BDE 47	BDE 66	BDE 77	BDE 85	BDE 99	BDE 100	BDE 138	BDE 153	BDE 154	BDE 183	BDE 209	Total PBDEs[b]
U.S. meat samples															
Bacon A	52.3	ND (5.2)	ND (7.1)	ND (78.8)	ND (5.2)	ND (5.2)	ND (5.2)	ND (28.8)	ND (6.8)	ND (5.2)	ND (5.2)	ND (5.2)	ND (5.2)	ND (166.6)	165
Bacon B	43.4	ND (0.4)	ND (2.1)	ND (19.9)	ND (0.4)	ND (0.2)	NA	ND (15.6)	ND (2.8)	ND (0.4)	ND (1.1)	ND (0.9)	ND (1.7)	ND (32.8)	39
Bacon C	35.3	0.7	ND (2.0)	30.1	NA	NA	1.4	16.8	4.8	ND (0.7)	4.5	2.8	14.3	28.4	105
Beef (ground) A	30.7	ND (3.1)	59.7	87.5	ND (3.1)	ND (3.1)	ND (3.1)	35.5	6.2	ND (3.1)	6.8	4.6	ND (4.2)	ND (95.7)	258
Beef (ground) B	13.6	0.2	ND (0.7)	23.4	0.5	NA	NA	32.3	4.5	0.4	4.7	2.5	NA	9.7	79
Beef tenderloin	13.7	ND (1.4)	ND (1.5)	35.1	ND (1.4)	NA	1.7	40.3	6.9	ND (1.4)	4.9	3.7	3.8	ND (11.1)	105
Chicken breast	4.9	ND (0.04)	0.5	60.5	NA	NA	NA	128	17.1	2.2	12.0	10.8	3.2	48.5	283
Duck	75.1	ND (0.5)	ND (3.0)	286	2.7	ND (0.3)	15.2	609	122	7.3	52.3	42.9	31.6	113	1,283
Ground chicken	7.3	ND (0.7)	ND (1.5)	11.0	ND (0.7)	NA	ND (0.7)	18.9	4.6	ND (0.7)	4.1	2.6	5.8	80	129
Ground lamb	19.7	ND (2.0)	ND (2.1)	ND (23.0)	ND (2.0)	ND (2.0)	3.2	56.8	16.8	ND (2.0)	9.6	6.3	ND (2.0)	ND (150.6)	186
Ground pork	21.5	ND (2.2)	ND (3.5)	53.8	ND (2.2)	NA	3.1	74.2	12.9	4.3	18.7	15.0	19.9	ND (31.3)	221
Ground turkey	11.1	0.2	ND (0.5)	98	0.8	ND (0.1)	NA	217	54.4	3.9	32.9	24.1	36.8	245	713
Pork	8.9	0.1	ND (0.5)	6.9	NA	NA	NA	16.3	1.8	0.2	1.0	1.2	1.3	11.7	41
Pork sausage A	23.7	ND (1.3)	ND (6.9)	387	ND (1.0)	ND (0.3)	16.8	688	74.5	5.6	81.6	55.3	14.6	49.7	1,378
Pork sausage B	24.4	ND (2.4)	ND (3.4)	39.4	ND (2.4)	ND (2.4)	2.6	71.6	8.3	ND (2.4)	22.0	13.7	10.7	ND (139)	244
Sausage A	26.2	ND (2.6)	ND (5.5)	ND (34.8)	ND (2.6)	NA	3.1	40.1	6.4	ND (2.6)	5.9	4.9	6.9	ND (51.0)	1,426
Sausage B	28.5	ND (2.9)	ND (3.2)	94.1	ND (3.5)	ND (2.9)	ND (2.9)	43.7	8.3	ND (2.9)	8.5	9.2	ND (2.9)	ND (41.7)	195
Wieners	32.9	ND (0.3)	ND (1.5)	386	1.4	ND (0.2)	11.1	703	53.9	7.2	106	49.8	14.3	ND (28.7)	1,348
Mean	26.3	0.76	4.59	93.2	1.19	0.83	4.93	157	22.7	2.33	21.1	14	10.1	53.3	383
Median	24.1	0.66	1.03	39.4	1.08	0.57	2.62	42	7.57	1.37	7.68	5.63	5.83	38.1	190
Minimum	4.87	0.02	0.24	6.93	0.21	0.06	0.36	7.79	1.39	0.16	0.53	0.44	0.86	5.53	39
Maximum	75.1	2.62	59.7	387	2.74	2.62	16.8	703	121	7.28	106	55.3	36.8	245	1,426
U.S. fish samples															
Canned tuna A	0.3	0.1	0.6	5.1	0.2	NA	0.2	3.2	0.6	ND (0.0)	0.3	0.2	1.1	4.9	16.6
Canned tuna B	0.5	ND (0.1)	0.2	2.1	0.2	NA	ND (0.1)	1.1	0.4	ND (0.1)	0.2	0.3	2.1	8.8	15.5
Catfish A	11.1	4.6	6.4	372	4.3	NA	NA	589	116	5.1	37.1	39.6	7.3	1269	2,450
Catfish B	5.3	4.6	5.1	438	13.5	ND (0.1)	41.6	834	102	7.9	49.9	45.8	4.9	ND (15.9)	1,547
Catfish C	5.2	2.2	3.7	137	0.7	ND (0.5)	11.7	184	39.5	ND (2.7)	15.8	15.2	ND (1.6)	ND (49.4)	437

Table 6-4. PBDE Concentrations (pg/g Wet Weight) in 18 U.S. Meat and Fish Samples[a]

Sample	Lipid (%)	BDE 17	BDE 28	BDE 47	BDE 66	BDE 77	BDE 85	BDE 99	BDE 100	BDE 138	BDE 153	BDE 154	BDE 183	BDE 209	Total PBDEs[b]
Catfish fillet (farm)	5.7	1.1	3.7	197	6.3	NA	16.4	282	53.0	ND (4.1)	18.4	21.3	3.8	22.7	627
Halibut	0.2	0.6	4.1	76.6	2.8	NA	ND (0.1)	10.6	12.4	ND (0.1)	1.1	2.6	1.8	11.4	124
Herring	9.1	4.1	56.3	2,072	69.4	3.6	ND (0.9)	267	221	ND (0.9)	29.3	69.9	2.5	ND (26.4)	2,809
Mahi	0.5	0.6	ND (2.0)	24.1	2.0	NA	0.6	13.0	5.1	ND (0.8)	1.4	4.9	4.3	ND (16.6)	66
Salmon A	8.0	79.2	92.6	1,222	30.6	ND (0.2)	NA	93.2	348	ND (0.2)	27.7	98.8	1.4	ND (9.0)	1,999
Salmon B	13.9	118	142	2,081	59.1	ND (0.1)	NA	147	353	ND (0.2)	36.6	142	ND (1.2)	ND (7.0)	3,082
Salmon C	10.3	18.4	49.4	1,103	35.3	ND (0.1)	ND (0.1)	239	217	ND (0.1)	18.3	45.1	ND (1.3)	ND (11.2)	1,732
Salmon D	6.3	1.4	5.2	94.7	5.2	ND (0.9)	ND (0.6)	15.4	7.1	ND (0.6)	1.4	5.0	ND (0.8)	ND (9.1)	141
Salmon E	12.3	1.7	20.4	356	ND (2.1)	ND (1.2)	ND (1.2)	84.4	84.2	ND (1.2)	10.1	29.8	ND (1.4)	ND (29.2)	605
Salmon fillet (farm) A	7.4	11.1	50.5	1,000	63.1	NA	7.9	410	210	ND (1.4)	37.4	104	3.7	20.5	1,919
Salmon fillet (farm) B	6.9	2.3	27.9	517	24.3	NA	ND (0.7)	168	115	ND (0.7)	16.0	35.8	1.7	681	1,590
Sardines	9.6	3.3	53.6	2,748	85.6	ND (5.0)	ND (1.0)	358	257	ND (1.0)	51.9	139	ND (3.2)	ND (51.4)	3,726
Shark	0.4	1.1	29.8	784	29.5	0.3	NA	57.8	608	0.4	112	291	2.0	5.4	1,920
Shrimp	0.6	0.3	3.6	75.6	NA	NA	NA	9.4	14.3	ND (0.1)	1.2	2.6	0.2	ND (1.3)	108
Tilapia	1.0	ND (0.1)	ND (0.7)	5.9	NA	NA	0.1	1.3	0.6	ND (0.1)	0.2	0.5	ND (0.2)	ND (4.0)	11
Trout A	4.2	4.8	22.2	320	NA	NA	ND (0.2)	79.8	66.5	0.2	11.8	26.3	4.4	ND (26.7)	549
Trout B	10.1	4.3	49.3	826	ND (5.6)	ND (1.0)	ND (1.0)	128	198	ND (1.0)	24.7	61.3	2.5	ND (42.9)	1,319
Tuna	0.2	ND (0.1)	ND (1.0)	16.6	0.7	NA	ND (0.0)	ND (4.6)	2.9	ND (0.1)	ND (0.4)	ND (1.0)	0.5	23.4	48
Wild perch	1.2	ND (0.1)	0.7	10.2	0.4	NA	ND (0.1)	2.3	2.1	ND (0.1)	0.7	2.4	0.6	5.9	25
Mean	5.43	11.01	26.19	603	20.8	0.78	4.29	166	126	0.89	21	49.3	2.08	91.8	1,120
Median	5.52	1.97	5.77	338	5.23	0.30	0.35	88.8	75.3	0.33	15.9	28.	1.68	10.1	616
Minimum	0.15	0.03	0.20	2.11	0.18	0.06	0.02	1.15	0.43	0.02	0.21	0.21	0.12	0.63	11.14
Maximum	13.9	118	142	2,748	85.6	3.60	41.6	834	608	7.94	112	291	7.32	1,269	3,726

[a]Limits of detection (LODs) are shown in parentheses. Total PBDE concentrations and statistics for each congener were calculated by assuming that nondetected concentrations were one-half the LOD; for calculations, these were treated as zero.
[b]Totals rounded to the nearest whole number for hundreds and to the nearest decimal place for tens.

NA = not available; ND = not detected

Source: Adapted from Schecter et al. (2006)

Huwe et al. (2002a) reported total PBDE concentrations in farm chickens raised in two different regions of the United States. The total PBDE concentration of discrete samples of chickens raised in Arkansas was 39.4 ng/g whole weight, while one composite sample of chickens raised in North Dakota was 1.7 ng/g whole weight. In the United States, chickens fed ball clay (a sedimentary, kaolinite clay) and chickens bought in the grocery store were analyzed for total PBDEs (ENVIRON 2003b). BDE 99 was the dominant congener in all samples. Total PBDEs ranged between 4 and 35 ng/g lipid weight in chickens fed ball clay and 0.5 ng/g lipid weight in store-bought chicken. Ohta et al. (2002) determined the concentration of total PBDEs in vegetables and meat samples from Japan. The concentrations of PBDEs in spinach, potato, and carrot were 134, 47.6, and 38.4 pg/g fresh weight, respectively. The highest concentrations of total PBDEs and BDE 47 were found in spinach. Interestingly, different congener patterns were found among the vegetables analyzed. Compared to root vegetables, which had high concentrations of BDE 153, spinach (representing a leafy vegetable) might be strongly influenced by PBDE contamination in air. The concentrations of PBDEs in pork, beef, and chicken were 63.6, 16.2, and 6.25 pg/g fresh weight, respectively. PBDE concentrations were highest in pork samples; however, the reason for this is unknown (Ohta et al. 2002). Bocio et al. (2003) determined the concentrations of PBDEs in food samples from Catalonia, Spain during 2000. The highest concentration of total PBDEs was found in oils and fats (587.7–569.3 pg/g), followed by fish and shellfish (333.9–325.3 pg/g), meat and meat products (109.2–102.4 pg/g), and eggs (64.5–58.3 pg/g). In all of these food groups, a predominance of the tetra- and pentaBDE homologs, followed by hexaBDE, was observed in the sum total PBDEs. By contrast, PBDEs were not detected in the groups of fruits, cereals, or tubers. Four types of commercial fish oils sold in Sweden were found to contain PBDEs (0.2–28.1 ng/g lipid weight) (Haglund et al. 1997). The highest concentration of PBDEs was found in the cod liver oil. These oils were from products marketed as dietary supplements for humans. The concentrations of PBDEs in seafood from the Inland Sea of Japan were determined for samples collected in 1998 (Hori et al. 2000). BDE 28, BDE 47, BDE 66, BDE 99, BDE 100, BDE 153, and BDE 154 were detected in all analyzed seafood samples. BDE 47 was detected as the predominant congener, with concentrations ranging from 58 to 2,100 pg/g wet weight. Harrad et al. (2004) determined the concentrations of several PBDE congeners in omnivorous and vegan diet samples from the United Kingdom. Median concentrations of BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 in omnivorous diet samples were 66.8, 63.8, 10, 20, and 20 pg/g dry weight, respectively. In vegetarian samples, median concentrations of BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 were 47.2, 56.7, 10.0, 20, and 20 pg/g dry weight, respectively. Concentrations of BDE 47, BDE 99, and total PBDE were found to be statistically higher in omnivorous diet samples compared to vegetarian diet samples.

Biosolids and Effluents. The concentrations of PBDEs in biosolids (sewage sludge) and effluents are summarized in Table 6-5. PBDEs were detected in 11 biosolids obtained from Virginia, New York, Maryland, and California (Hale et al. 2001c). The total concentrations of pentaBDE in biosolids ranged from 1,100 to 2,290 ng/g dry weight. The concentration of decaBDE (BDE 209) varied widely among biosolids from the four states; the concentration of BDE 209 ranged from 84.8 to 4,890 ng/g dry weight in the biosolid samples.

Levels of PBDEs in biosolids were analyzed using samples from the EPA 2001 National Sewage Sludge Survey (NSSS) (Venkatesan and Halden 2014). Thirty-two PBDEs were detected in the samples analyzed. The total mean±standard deviation PBDE concentration detected in biosolids composites was 9,388±7,778 µg/kg dry weight. Deca, nona, and penta BDE congeners accounted for roughly 57, 18, and 13% of the total, respectively. Using these data and the estimated annual biosolids production and disposal figures in the United States, the annual mean loading rate of PBDEs was estimated to range from 47,900 to 60,100 kg/year. Analysis of samples collected between August 2006 and March 2007 (2–3 years after the voluntary phase-out of penta and octa PBDE formulations) indicated that the levels of 8 out of 11 major congeners in biosolids had declined approximately 10–57 % when compared to 2001 levels.

Sewage sludge in the vicinity of the Dan River (Virginia) were collected and analyzed for PBDEs (Hale et al. 2002). Congener patterns suggestive of both penta- and decaBDE commercial products were present at concentrations of 1,370 ng/g dry weight (sum of BDE 47 to BDE 154) and from 1,470 ng/g dry weight, respectively. While no known industrial source of pentaBDE discharged to this plant, the distribution pattern for lower-brominated congeners matched the pentaBDE commercial product.

Sewage sludge samples from 13 WWTPs in Germany were sampled (Hagenmaier et al. 1992). The mean concentration of tri- to heptaBDEs was 8.37 ng/g, with tri-, tetra-, penta-, hexa-, and heptaBDEs at concentrations of 0.65, 3.06, 3.02, 0.49, and 0.22 ng/g, respectively. Concentrations of penta- and hexaBDEs were highest in these samples. de Boer et al. (2000b) determined the concentration of PBDEs in sewage treatment plant effluents from the Netherlands. The concentration of total PBDEs (the sum of BDE 47, BDE 99, and BDE 100) ranged from 11 to 35 ng/g dry weight with the overwhelming majority as BDE 47, while the concentrations of BDE 209 ranged from 310 to 920 ng/g dry weight. Kohler et al. (2003) determined the concentrations of decaBDE in sewage sludge from Switzerland between 1993 and 2002. These authors reported that the average concentration of decaBDE increased with time from 220 to 1,100 ng/g dry weight, corresponding to an average increase of 560%.

Table 6-5. Concentrations (ng/g Dry Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Biosolids (Sewage Sludge) and Effluents

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Sewage sludge	Dan River, Virginia	No data	No data	No data	2,840*	1,470	Hale et al. 2002
Sewage sludge	11 biosolid samples from Virginia, New York, Maryland, and California	No data	No data	No data	1,100–2,290*	No data	Hale et al. 2001c
Sewage sludge	Gothenburg, Sweden	15	19	3.5	38	No data	Nylund et al. 1992
Sewage sludge	Klippan, Sweden	22	18	5.4	45.4	No data	Sellström et al. 1999; Sellström and Jansson 1995
Sewage Sludge	Rimbo, Sweden	53	53	13	119	No data	Sellström et al. 1999; Sellström and Jansson 1995
Sewage sludge	Three plants, Stockholm, Sweden	39–91	48–120	11–28	98–239	140–350	Sellström et al. 1999
Sewage sludge	Germany	No data	No data	No data	04–15*	No data	Hagenmaier et al. 1992
Sewage treatment plant effluents	Netherlands, several sites	11–35	<1	No data	11–35	310–920	de Boer et al. 2000b

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

BDE = brominated diphenyl ether

World Trade Center Site. In 2001, PBDEs were detected in dust and smoke samples taken near the World Trade Center disaster site (Lioy 2002). The highest concentration was for decaBDE (i.e., BDE 209), which was present in thermoplastics (e.g., computers). Concentrations of PBDE congeners were 107–174 µg/kg dry weight basis for BDE 47, 51.1–74.1 µg/kg dry weight basis for BDE 100, 155–293 µg/kg dry weight basis for BDE 99, 42.0–53.5 µg/kg dry weight basis for BDE 153, 219–305 µg/kg dry weight basis for BDE 154, and 1,330–2,660 µg/kg dry weight basis for decaBDE (BDE 209). Concentrations of PBDEs were found to be similar to concentrations found in sewage sludge (Lioy 2002).

Freshwater Fish. Monitoring data indicated that the concentrations of PBDEs were historically increasing in freshwater organisms, with higher concentrations near point sources. The congener profiles show the highest concentrations for BDE 47. The presence of PBDEs in freshwater aquatic organisms taken from remote regions suggests that diffuse sources of PBDEs are also important. A sampling of concentrations of PBDEs in freshwater fish samples in the United States are summarized in Table 6-6. Fish were sampled from two U.S. lakes, Hadley Lake, Indiana near a possible PBDE point source, and Lake of the Ozarks, Missouri, with no known sources (Dodder et al. 2000). Mean total PBDE concentrations (sum of BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154) were higher in crappie (*Pomoxis annularis*) and bluegill (*Lepomis macrochirus*) from Hadley Lake (1,500 and 1,900 ng/g lipid weight, respectively) than from Lake of the Ozarks (340 and 390 ng/g lipid, respectively). BDE 47, BDE 99, BDE 153, and BDE 154 were the primary congeners. From the Lake of Ozarks, BDE 47 was the dominant congener in fish. The total PBDE concentrations in smelt (*Osmerus mordax*) from Lakes Superior and Ontario were 150±9 and 240±30 ng/g lipid, respectively (Dodder et al. 2002). The dominant congeners in these fish were BDE 47 and BDE 99.

An analysis of fish tissue samples from selected locations in Washington State showed that total PBDE concentrations ranged from 29 ng/g lipid in rainbow trout from a remote spring-fed stream (Douglas Creek, Washington) to 19,000 ng/g lipid in rainbow trout from the urbanized Spokane River, Washington (Johnson and Olson 2001). The tetra- and pentaBDE isomers were the major compounds present.

TetraBDE to hexaBDE were found in carp (*Cyprinus carpio*) from the Buffalo River (New York), a polluted area around the Great Lakes (Loganathan et al. 1995). TetraBDEs dominated the congener pattern with 94–96% of total PBDEs. TetraBDE and pentaBDE concentrations ranged from 13 to 22 ng/g fresh weight. Asplund et al. (1999a) found tri- to hexaBDEs in steelhead trout (*Oncorhynchus mykiss*) sampled in 1995 from Lake Michigan. The combined concentration of BDE 47, BDE 99, BDE 100,

Table 6-6. Concentrations (ng/g Lipid Weight, Except as Noted) of Several Polybrominated Diphenyl Ethers (PBDEs) in Freshwater Fish Samples from the United States

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Lake trout	Lake Michigan	93–230	9.0–48	12–45	120–350*	No data	Streets et al. 2006
Lake trout	Lake Superior	22–79	8.5–53	5.2–19	39–180*	No data	Streets et al. 2006
Lake trout	Lake Huron	32–59	7.8–13	6.5–12	50–94*	No data	Streets et al. 2006
Lake trout	Lake Ontario	45–140	6.5–34	7.7–24	64–230*	No data	Streets et al. 2006
Lake Trout	Lake Ontario	4.3–114	59–680	7.4–1,285	269–3,339*	2.3–12	Ismail et al. 2009
Alewife	Grand Traverse Bay, Lake Michigan	16	No data	No data	36	No data	Stapleton and Baker 2003
Bloater chub	Grand Traverse Bay, Lake Michigan	11 (fw)	No data	No data	23 (fw)	No data	Stapleton and Baker 2003
Bluegill	Hadley Lake, Indiana	420	320	240	1,900	No data	Dodder et al. 2000
Bluegill	Lake of the Ozarks, Missouri	200	91	59	390	No data	Dodder et al. 2000
Burbot	Grand Traverse Bay, Lake Michigan	43 (fw)	No data	No data	86 (fw)	No data	Stapleton and Baker 2003
Carp	United States	No data	No data	No data	13–22* (fw)	No data	Loganathan et al. 1995
Carp	Detroit River, Grosse Isle, Michigan	3.0 (fw)	0.50 (fw)	0.48 (fw)	40.7*	No data	Rice et al. 2002
Carp	Des Plaines River, Joliet, Illinois	2.54 (fw)	0.5 (fw)	0.44 (fw)	281*	No data	Rice et al. 2002
Carp	Des Plaines River, Joliet, Illinois	1.34 (fw)	0.50 (fw)	0.49 (fw)	78.3*	No data	Rice et al. 2002
Carp (fillet)	Yakima River, Washington	No data	No data	No data	22 (fw)	No data	Johnson and Olson 2001
Crappie	Hadley Lake, Indiana	250	430	150	1,500*	No data	Dodder et al. 2000
Crappie	Lake of the Ozarks, Missouri	190	78	59	340*	No data	Dodder et al. 2000
Deepwater sculpin	Grand Traverse Bay, Lake Michigan	2.8 (fw)	No data	No data	3 (fw)	No data	Stapleton and Baker 2003
Lake trout	Grand Traverse Bay, Lake Michigan	75 (fw)	No data	No data	126 (fw)	No data	Stapleton and Baker 2003

Table 6-6. Concentrations (ng/g Lipid Weight, Except as Noted) of Several Polybrominated Diphenyl Ethers (PBDEs) in Freshwater Fish Samples from the United States

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Lake trout	Lake Ontario, United States	No data	No data	No data	540*	No data	Alaee et al. 1999
Lake trout	Lake Ontario, United States	58 (fw)	14 (fw)	5.7 (fw)	No data	No data	Luross et al. 2002
Lake trout	Lake Huron, United States	No data	No data	No data	240*	No data	Alaee et al. 1999
Lake trout	Lake Huron, United States	27 (fw)	7.7 (fw)	3.8 (fw)	No data	No data	Luross et al. 2002
Lake trout	Lake Superior, United States	No data	No data	No data	140*	No data	Alaee et al. 1999
Lake trout	Lake Superior, United States	29 (fw)	12 (fw)	4.1 (fw)	No data	No data	Luross et al. 2002
Lake trout	Lake Erie, United States	No data	No data	No data	117*	No data	Alaee et al. 1999
Lake trout	Lake Erie, United States	16 (fw)	2.0 (fw)	2.5 (fw)	No data	No data	Luross et al. 2002
Largescale sucker (whole)	Yakima River, Washington	No data	No data	No data	64 (fw)	No data	Johnson and Olson 2001
Largescale sucker (whole)	Spokane River, Washington	No data	No data	No data	105 (fw)	No data	Johnson and Olson 2001
Mountain whitefish (whole)	Spokane River, Washington	No data	No data	No data	1,250 (fw)	No data	Johnson and Olson 2001
Rainbow trout (whole)	Douglas Creek, Washington	No data	No data	No data	1.5 (fw)	No data	Johnson and Olson 2001
Rainbow trout	Spokane River, Washington	No data	No data	No data	20–174 (fw) (fillet) 297 (fw) (whole)	No data	Johnson and Olson 2001
Northern pike minnow	Spokane River, Washington	59–160	0.3–<0.4	17–47	No data	Not detected	Furl and Meredith 2010
Mountain whitefish	Spokane River, Washington	127–942.6	81–942.6	26.3–368.1	No data	Not detected	Furl and Meredith 2010
Largescale sucker	Spokane River, Washington	87–270	0.2–<4.4	13–45	No data	Not detected	Furl and Meredith 2010
Salmon	Grand Traverse Bay, Lake Michigan	34 (fw)	No data	No data	95 (fw)	No data	Stapleton and Baker 2003
Salmon	Lake Michigan, United States	52.1 (fw)	9.3 (fw)	9.7 (fw)	2,440	No data	Manchester-Neesvig et al. 2001
Smelt	Lake Superior, United States	5.7 (fw)	1.8 (fw)	0.98 (fw)	150	<1.5 (fw)	Dodder et al. 2002

Table 6-6. Concentrations (ng/g Lipid Weight, Except as Noted) of Several Polybrominated Diphenyl Ethers (PBDEs) in Freshwater Fish Samples from the United States

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Smelt	Lake Ontario, United States	10 (fw)	5.3 (fw)	1.6 (fw)	240	<1.6 (fw)	Dodder et al. 2002
Starry flounder (whole)	Columbia River, Washington	No data	No data	No data	30 (fw)	No data	Johnson and Olson 2001
Steelhead trout	Lake Michigan, United States	1,700	600	360	3,000*	No data	Asplund et al. 1999b
Whitefish	Columbia River, United States	No data	No data	No data	72 (fw)	No data	Rayne et al. 2003a
Whitefish	Grand Traverse Bay, Lake Michigan	9.8 (fw)	No data	No data	18 (fw)	No data	Stapleton and Baker 2003

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

BDE = brominated diphenyl ether; dw = dry weight; fw = fresh weight

BDE 153, and BDE 154 was 3,000 ng/g lipid weight (Asplund et al. 1999b). Lake trout (*Salvelinus namaycush*) from Lakes Ontario, Huron, and Superior were also found to have di- to heptaBDEs with combined concentrations of 545, 237, and 135 ng/g lipid weight, respectively (Alaee et al. 1999).

Lake trout from Lake Erie had 117 ng/g lipid weight (Luross et al. 2000). Variations in local sources, combined with atmospheric transport, may explain differences that were seen in congener profiles for the different lakes. A retrospective temporal study for the years 1978, 1983, 1988, 1993, and 1998 using archived trout samples from Lake Ontario show a dramatic increase in total PBDE concentrations over time (Luross et al. 2000). At 50 freshwater sites in Virginia, muscle samples from 253 fish samples were collected and analyzed for PBDEs (Hale et al. 2000, 2001b). Approximately 85% of the samples contained BDE 47, the predominant congener, at measurable concentrations. Concentrations were >1,000 ng/g lipid weight at 9 of 50 sites. The highest combined PBDE concentrations (up to 57,000 ng/g lipid weight) were observed in carp downstream of textile and furniture facilities. BDE 47 concentrations were greater than 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) concentrations in 58% of the samples analyzed. PBDEs were identified in fish collected from the Detroit River (Michigan) and Des Plaines Rivers (Illinois). In Detroit River fish (carp and largemouth bass), the congener patterns were dominated by BDE 47; however, in the Des Plaines River carp, the dominant congeners were heptaBDE congeners (BDE 181 and BDE 183), lesser amounts of BDE 190, and two hexaBDEs (BDE 154 and BDE 153). Possible sources for the heptaBDE congeners were not obvious Ozarks (340 and 390 ng/g lipid, respectively). BDE 47, BDE 99, BDE 153, and BDE 154 were the primary congeners. From the Lake of Ozarks, BDE 47 was the dominant congener in fish. The total PBDE concentrations in smelt (*O. mordax*) from Lakes Superior and Ontario were 150±9 and 240±30 ng/g lipid, respectively (Dodder et al. 2002). The dominant congeners in these fish were BDE 47 and BDE 99. An analysis of fish tissue samples from selected locations in Washington State showed that total PBDE concentrations ranged from 29 ng/g lipid in rainbow trout from a remote spring-fed stream (Douglas Creek, Washington) to 19,000 ng/g lipid in rainbow trout from the urbanized Spokane River, Washington (Johnson and Olson 2001). The tetra- and pentaBDE isomers were the major compounds present. TetraBDE to hexaBDE were found in carp (*C. carpio*) from the Buffalo River (New York), a polluted area around the Great Lakes (Loganathan et al. 1995). TetraBDEs dominated the congener pattern with 94–96% of total PBDEs. TetraBDE and pentaBDE concentrations ranged from 13 to 22 ng/g fresh weight. Asplund et al. (1999a) found tri- to hexaBDEs in steelhead trout (*O. mykiss*) sampled in 1995 from Lake Michigan. The combined concentration of BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 was 3,000 ng/g lipid weight (Asplund et al. 1999b). Lake trout (*S. namaycush*) from Lakes Ontario, Huron, and Superior were also

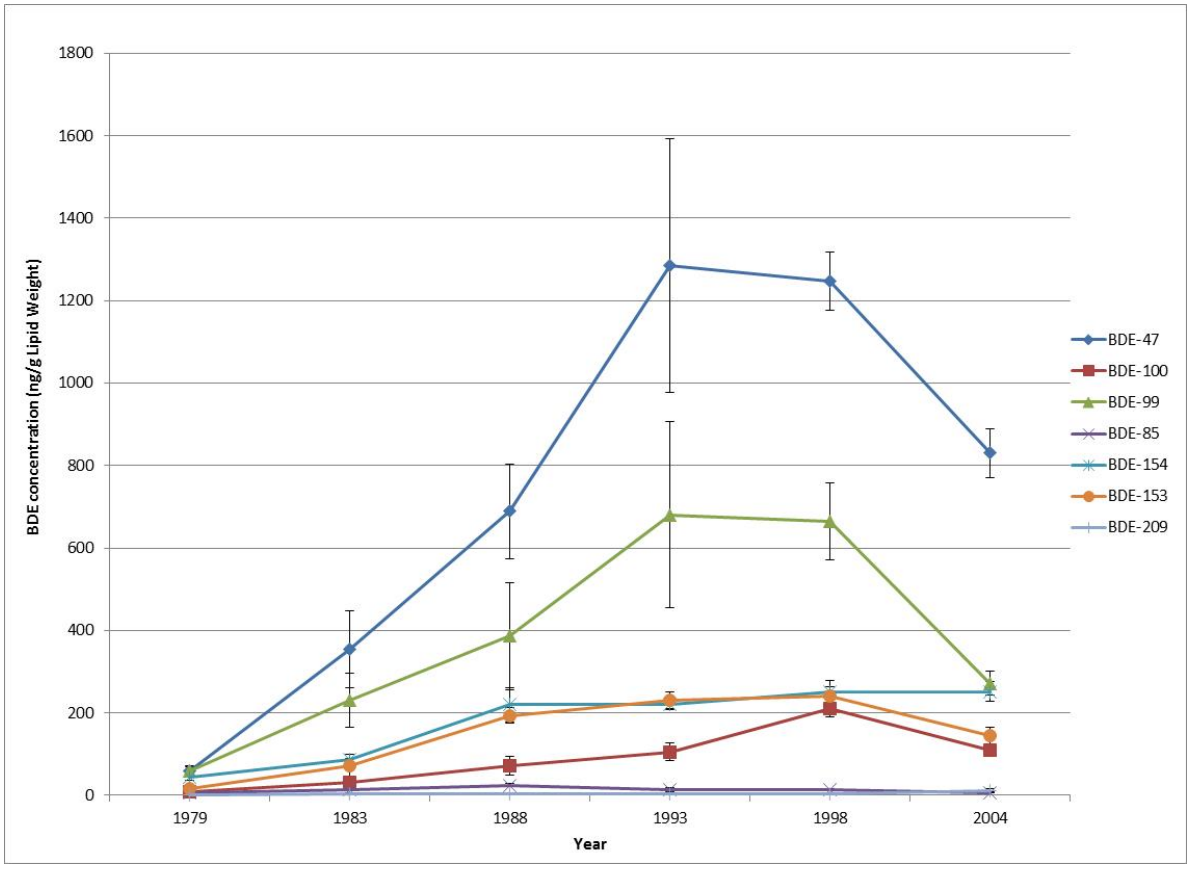
found to have di- to heptaBDEs with combined concentrations of 545, 237, and 135 ng/g lipid weight, respectively (Alaee et al. 1999).

The National Study of Chemical Residues in Lake Fish Tissue (1998–2009) is one of the statistically-based surveys conducted by EPA that analyzed the concentrations of PBDEs and other contaminants in fish from 500 lakes in the continental United States (EPA 2009c, 2013k). The most prevalent PBDE congeners detected in both predator and bottom dweller fish were reported as BDE 47, BDE 99, and BDE 100 (EPA 2013k).

Ismail et al. (2009) studied the temporal trends of PBDE congeners in trout obtained from Lake Ontario from 1979 to 2004. Concentrations of most PBDE congeners (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154) increased dramatically from 1979 to the mid-1990s and then either leveled off or decreased from 1998 to 2004; average concentration and standard error values are presented in Figure 6-2. The temporal trend of BDE 209 was different than for the other congeners, however. Concentrations of BDE 209 in lake trout increased more slowly from 1979 until the mid-1990s, but its concentrations increased dramatically from the late 1990s (3.3±0.8 ng/g in 1998) until 2004 (12±5.3 ng/g in 2004), corresponding to its increased use in consumer products.

The concentrations of PBDEs in freshwater fish samples from Europe are summarized in Table 6-7. Between 1986 and 1988, concentrations of BDE 47, BDE 99, and BDE 100 were measured in whitefish (*Coregonus spp*.) from a remote mountain lake in Northern Sweden (Lake Storvindeln), in Arctic char (*Salvelinus alpinus*) from a heavily populated lake (Lake Vättern) in south-central Sweden with numerous municipal and industrial point sources, and in trout (*Salmo trutta*) and pike (*Esox lucius*) from several sites along Dalslands Canal in west central Sweden (Jansson et al. 1993). No point sources of PBDEs were identified from these sites. Whitefish from the remote lake contained the lowest concentrations (26 ng/g lipid weight) of PBDEs, whereas the Arctic char, from a heavily populated lake, contained 520 ng/g lipid weight PBDEs. In both samples, BDE 47 was the predominant congener. PBDE concentration in pike and trout from the Dalslands Canal ranged from 180 to 210 ng/g lipid weight and from 280 to 1,200 ng/g lipid weight, respectively. The congener pattern in these samples was similar to the technical mixture, Bromkal 70-5DE, with equal quantities of both BDE 47 and BDE 99. The concentrations in pike and trout are of the same order of magnitude as in the Arctic char, indicating the spread of PBDEs from diffuse sources (de Wit 2002). In 1979 and 1980, high concentrations of tri- to hexaBDEs (range, 950–27,000 ng/g lipid weight in muscle tissues) were measured in fish sampled along a river in Sweden (Viskan) where numerous textile industries are located (Andersson and Blomkvist

Figure 6-2. Temporal Trends in the Concentrations (ng/g Lipid Weight) of PBDE Congeners in Lake Trout from Lake Ontario, Canada



Source: Ismail et al. 2009

Table 6-7. Concentrations (ng/g Lipid Weight Except as Noted) of Several Polybrominated Diphenyl Ethers (PBDEs) in Freshwater Fish Samples from Europe

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Freshwater fish	Pyrenees Mountains	0.40–0.51	0.24	0.16–0.18	No data	No data	Gallego et al. 2007
Freshwater fish	Tatras Mountains	0.20–0.26	0.17–0.21	0.043	No data	No data	Gallego et al. 2007
Arctic char	Lake Vättern, Sweden	400	64	51	520	No data	Sellström et al. 1993
Bream	Netherlands (several sites)	0.2–130 (dw)	Not detected	No data	No data	No data	de Boer et al. 2000b
Eels	Netherlands	<20–1,400	No data	No data	<50–1,700	No data	de Boer 1990
Osprey	Sweden	1,800	140	200	2,140	No data	Sellström et al. 1993
Pike	Dalslands canal, Sweden	94–98	60–79	25–36	180–210	No data	Sellström et al. 1993
Pike	River Viskan, Sweden, upstream and downstream	<46–2,000	<37–1,600	<14–1,000	<130–4,600	Trace	Sellström et al. 1998a
Several fish species	Germany	No data	No data	No data	19–983*	No data	Krüger 1988
Trout	Dalslands canal, Sweden	120–460	130–590	33–150	280–1,200	No data	Sellström et al. 1993
Whitefish	Lake Storvindeln, Sweden	15	7.2	3.9	26	No data	Sellström et al. 1993
Whitefish	Lake Geneva, Switzerland	26	13	2.5	44*	No data	Zennegg et al. 2003
Whitefish	Lake Greifen, Switzerland	96	52	9.1	165*	No data	Zennegg et al. 2003
Whitefish	Lake Biel, Switzerland	75.9	39	7.1	128*	No data	Zennegg et al. 2003
Whitefish	Lake Lucerne, Switzerland	56	46	10	121*	No data	Zennegg et al. 2003
Whitefish	Lake Zürich, Switzerland	56	25	4.5	89*	No data	Zennegg et al. 2003
Whitefish	Lake Nauchatel Switzerland	41	20	4.0	68*	No data	Zennegg et al. 2003
Whitefish	Lake Constance, Switzerland	32	15	2.9	52*	No data	Zennegg et al. 2003

Table 6-7. Concentrations (ng/g Lipid Weight Except as Noted) of Several Polybrominated Diphenyl Ethers (PBDEs) in Freshwater Fish Samples from Europe

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Whitefish	Lake Thun, Switzerland	19	12	2.5	36*	No data	Zennegg et al. 2003

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

BDE = brominated diphenyl ether

1981). These textile industries have used PBDEs in the production of textiles. BDE 47 was the predominant congener at 70–80% of the total PBDEs. In 1977, the PBDEs were not detected in fish sampled at the same sites. The elevated concentrations of BDE 47, BDE 99, and BDE 100 were later confirmed in a follow-up study in which fish were caught from approximately the same locations (Sellström et al. 1993). In the current study, BDE 47 was the predominant congener at 65–96% of total PBDEs. Several fish species were sampled (pike, perch, bream, eel, tench, and sea trout) in these studies. In 1995, fresh samples of pike and sediments were collected at four of eight sites along River Viskan in order to search for point sources of contaminants. The combined concentrations of BDE 47, BDE 99, and BDE 100 ranged from not detected to 4,600 ng/g lipid weight; with BDE 47 being the predominant congener (50–90% of total). DecaBDE (BDE 209) was found in a few fish at trace amounts. The lowest concentrations of the PBDEs were found upstream of the industries. The concentrations of PBDEs increased further downstream as more industries were passed (Sellström et al. 1998a). Concentrations of BDE 47 ranged from <20 to 1,700 ng/g lipid in eels (*Anguilla anguilla*) from Dutch rivers and lakes (at 10 locations); BDE 47 comprised 70% of the total PBDEs (de Boer 1990). Bream (*Abramis brama*) sampled from several sites in the Netherlands had concentrations of BDE 47 ranging from 0.2 to 130 ng/g dry weight (de Boer et al. 2000b). BDE 99 was below the detection limits. BDE 153 ranged from <0.04 to 4.1 ng/g dry weight. Allchin et al. (1999) conducted a study of PBDEs in plaice (*Pleuronectes platessa*), flounder (*Platichthys flesus*), and dab (*Limanda limanda*) collected in the estuaries of rivers in the United Kingdom. Suspected sources of PBDEs in the estuaries include a manufacturer of pentaBDE and octaBDE, several industries using pentaBDE, and several landfills receiving wastes suspected to contain PBDEs. Concentrations of BDE 47, BDE 99, pentaBDE (as technical mixture DE-71), and octaBDE (as technical mixture DE-79) in fish ranged from not detected to 9,500 ng/g lipid weight, not detected to 370 ng/g lipid weight, 47–1,200 ng/g lipid weight, and not detected to 1,200 ng/g lipid weight. The highest concentrations were at Tees Bay downstream from a manufacturing plant on the River Tees. These results are similar to the situation found in Sweden along the River Viskan (Andersson and Blomkvist 1981; Sellström et al. 1993). Freshwater mussels (*Dreissena polymorpha*) were collected at several locations in the Netherlands and analyzed for BDE 47, BDE 99, BDE 153, and BDE 209 (de Boer et al. 2000b). Concentration ranges for the congeners were 0.7–17, 0.4–11, and <0.1–1.5 ng/g dry weight for BDE 47, BDE 99, and BDE 153, respectively; BDE 209 was below the detection limit. Poma et al. (2014) analyzed freshwater zebra mussels in Lake Maggiore, Northern Italy for the presence of PBDEs and other brominated flame retardants. Total tri- to heptaBDE concentrations ranged from 1.0 ng/g for samples obtained in in May 2011 to 144.6 ng/g for samples collected in September 2012. The authors noted that even though penta- BDE was banned in Europe in 2004, increasing concentrations of tri- to heptaBDE congeners in mussels from 2011 to 2012 were observed in the samples obtained. Average

values of hepta to decaBDE congeners in zebra mussels ranged from 88.2 to 182.8 ng/g and tended to be dominated by BDE 209, with average concentrations of 71.2–144.7 ng/g (Poma et al. 2014). The presence of the lower brominated octa and hepta congeners was likely due to metabolism of BDE 209 within the organism or the environmental debromination of BDE 209 followed by uptake by the zebra mussels.

Saltwater Fish. Spatial trends show higher concentrations of lower-brominated BDE congeners found near human populated areas. The congener profiles show the highest concentrations for BDE 47. Representative concentrations of several PBDEs in marine aquatic species are summarized in Table 6-8. BDEs were detected in 10/10 white croakers and 8/8 shiner surfperch obtained from the San Francisco Bay at concentrations of (total PBDEs) 470–2, 260 and 730–3,930 ng/g lipid, respectively (Klosterhaus et al. 2012). Mean levels of total PBDEs in halibut, jack smelt, leopard shark, northern anchovy, shiner surfperch, striped bass white croaker, and white sturgeon collected from the San Francisco Bay in 2009 ranged from 1.5 to 8.3 ng/g wet weight (Sutton et al. 2015). In the year 2000, sole liver collected from five sites along the Canadian west coast (Crofton, Bamfield, Kitimat, Trincomali, and Vancouver) were analyzed for 14 BDE congeners (Ikonomou et al. 2002); the total PBDE concentrations were 64–340 ng/g lipid while the three highest congener concentrations were 27–160 ng/g lipid (BDE 47), 8.5–54 ng/g lipid (BDE 100), and 9.5–46 ng/g lipid (BDE 99). The highest concentrations were found in sole samples collected near Vancouver, Canada. DecaBDE was not detected in these samples at the level of procedural blank. Farmed salmon collected at two locations in Canada were analyzed for PBDE congeners (Easton et al. 2002). Forty-one congeners were detected with BDE 47 at the highest concentration (690 and 2,600 ng/g wet weight) followed by BDE 99 and BDE 100; total BDE congener concentrations were 1,188 and 4,147 ng/g wet weight for the two samples. Likewise, wild salmon from four locations in Canada were analyzed for BDE congeners. Concentrations were a factor of 10 lower for these samples compared to farmed salmon samples. The total PBDE concentration for the 41 detected congeners ranged from 38.7 to 485.2 ng/g wet weight. The concentration of the highest congener, BDE 47, ranged from 29 to 280 ng/g wet weight (Easton et al. 2002). PBDE concentrations in skipjack tuna from Asian offshore waters, off-Seychelles, off-Brazil, and open seas were determined for samples collected during 1996–2001 (Ueno et al. 2003). The concentration of total BDEs in muscles tissues ranged from not detected (<0.05 ng/g lipid) to 53 ng/g lipid. The concentration of the highest congener in muscle tissues, BDE 47, ranged from <0.1 to 15 ng/g lipid. BDE 99, BDE 100, BDE 153, and BDE 154 also were detected; BDE 209 was below the detection limit (<5.0 ng/g lipid) for these samples. Samples collected off the coast of the Seychelles (relatively pristine area) did not have detectable concentrations of any PBDEs, while samples collected in industrial areas of southeast Asia had the highest. Fall-caught

Table 6-8. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Aquatic Species

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
California halibut	San Francisco Bay	No data	No data	No data	1.8±0.5* (ww)	ND	Sutton et al.2015
Jack smelt	San Francisco Bay	No data	No data	No data	1.4±0.4* (ww)	ND	Sutton et al.2015
Leopard shark	San Francisco Bay	No data	No data	No data	5.0±1.2* (ww)	ND	Sutton et al.2015
Northern anchovy	San Francisco Bay	No data	No data	No data	7.9±2.9* (ww)	ND	Sutton et al.2015
Shiner surfperch	San Francisco Bay	No data	No data	No data	8.3±2.9* (ww)	ND	Sutton et al.2015
Striped bass	San Francisco Bay	No data	No data	No data	5.0±2.6* (ww)	ND	Sutton et al.2015
White croacker	San Francisco Bay	No data	No data	No data	4.3±2.5* (ww)	ND	Sutton et al.2015
White sturgeon	San Francisco Bay	No data	No data	No data	2.8±1.3* (ww)	ND	Sutton et al.2015
Winter Flounder	Northwest Atlantic	35	2.5	6.4	52*	ND	Shaw et al. 2009
Atlantic Herring	Northwest Atlantic	40	6.9	6.8	82*	ND	Shaw et al. 2009
American Plaice	Northwest Atlantic	42	4.0	7.0	69*	1.9	Shaw et al. 2009
White Hake	Northwest Atlantic	25	0.63	7.2	42*	0.91	Shaw et al. 2009
Alewife	Northwest Atlantic	8.3	3.6	1.7	18*	ND	Shaw et al. 2009
Atlantic Mackerel	Northwest Atlantic	20	7.5	4.1	69*	1.6	Shaw et al. 2009
Silver Hake	Northwest Atlantic	19	6.3	4.0	38*	ND	Shaw et al. 2009
Farmed Salmon	Canada	690; 2,600 (ww)	140; 390 (ww)	130; 470 (ww)	1,187; 4,147 (ww)	No data	Easton et al. 2002
Salmon (wild)	Canada	29–280 (ww)	ND–97 (ww)	4.2–43 (ww)	38.7–485.2 (ww)	No data	Easton et al. 2002

Table 6-8. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Aquatic Species

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Sole liver	West coast, Canada	27–160	9.5–46	8.5–54	64–340*	ND	Ikonomou et al. 2002
Skipjack tuna	Seychelles, Indian Ocean	<0.1	<0.05	<0.05	ND	<5.0	Ueno et al. 2003
Skipjack tuna	East China Sea	9.0–15	2.4–4.7	3.4–4.4	23–34	<5.0	Ueno et al. 2003
Skipjack tuna	Pacific Ocean	2.9–7.9	0.18–3.0	0.56–2.1	5.8–21	<5.0	Ueno et al. 2003
Herring	Baltic Sea	19–38	7.8–17	3.4–6	30–61	No data	de Wit 2002 Sellström et al. 1993
Herring	Baltic Sea	3.2–27	ND–2.9	1.3–1.9	3.2–32	No data	Haglund et al. 1997
Herring	Baltic Sea	7.6–24	4.3–3.9	No data	12.9–28.3*	No data	Strandman et al. 1999
Herring	Baltic Sea	6.3	0.6	0.8	12*	No data	Burreau et al. 1999
Herring	Kattegatt, Sweden	12	3.4	1.6	17	No data	de Wit 2002; Sellström et al. 1993
Herring	North Sea	8.4–100	No data	No data	No data	No data	de Boer 1990
Sprat (different age groups)	Baltic Sea	17.5–140.8	1.9–9.5	No data	21–149*	No data	Strandman et al. 1999
Sprat	Baltic Sea	4.3	0.7	0.8	8.4*	No data	Burreau et al. 1999
Cod liver	North Sea	170	No data	No data	1.9–360	No data	de Boer 1989
Salmon	Baltic Sea	167	52	44	220	No data	Haglund et al. 1997
Salmon	Baltic Sea	190	52	46	290	No data	Asplund et al. 1999b
Salmon	Baltic Sea	46	7.3	6.4	86*	No data	Burreau et al. 1999
Several fish species	Japan	No data	No data	No data	0.1–17*	No data	Watanabe et al. 1987
Yellowfin tuna	Japan	0.5	0.4	0.25	1.9*	No data	Ohta et al. 2000
Yellowtail	Japan	17	4.5	4.0	30.5*	No data	Ohta et al. 2000
Yellowtail (cultured)	Japan	29	3.3	5.3	44*	No data	Ohta et al. 2000
Salmon	Japan	22	8.1	5.3	46*	No data	Ohta et al. 2000

Table 6-8. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Aquatic Species

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Several flatfish	Seven river estuaries, Great Britain	73–9,500	16–790	No data	No data	ND	Allchin et al. 1999
Flounder	Netherlands, several sites	0.6–20 (dw)	<0.01–4.6	No data	No data	No data	de Boer et al. 2000b

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

BDE = brominated diphenyl ether; dw = dry weight; ND = not detected; ww = wet weight

herring (*Clupea harengus*) muscle from five sites along the Swedish coast was analyzed for BDE 47, BDE 99, and BDE 100; the combined concentration of these three congeners ranged from 17 to 61 ng/g lipid, with BDE 47 being the dominant congener (Sellström et al. 1993). Likewise, the concentration of BDE 47 in Baltic herring ranged from 3.2 to 27 ng/g lipid in different age groups; the combined concentration of BDE 47, BDE 99, and BDE 100 ranged from 3.2 to 32 ng/g lipid (Haglund et al. 1997); 2-year-old herring had the lowest concentrations and 5-year-old herring had the highest concentrations. Similarly, Strandman et al. (1999) observed increasing concentrations with age of BDE 47, BDE 99, and BDE 153 in Baltic sprat (*Sprattus sprattus*, age 3–13 years). However, this trend was not evident for herring. BDE 47 was the primary congener with concentrations ranging from 7.6 to 24 ng/g lipid weight for 1–3-year-old sprat, 17–140 ng/g lipid weight for 3–13-year-old sprat, and 7.6–24 ng/g lipid weight in herring. The concentrations of BDE 47, BDE 99, and BDE 100 in whole-body composites of herring were 6.21, 0.62, and 0.81 ng/g lipid, respectively; in sprat, the concentrations were 4.32, 0.71, and 0.80 ng/g lipid, respectively (Burreau et al. 1999). Baltic sea herring had similar concentrations of BDE 47 (46.3 ng/g lipid) compared to 8.4–100 ng/g lipid of BDE 47 found by de Boer (1990) for herring collected from three regions of the North Sea. BDE 47, BDE 99, and BDE 153 concentrations in Baltic salmon (*Salmo salar*) muscle were 167, 52, and 4.2 ng/g lipid, respectively (Haglund et al. 1997). BDE 47, BDE 99, and BDE 100 concentrations were 47, 7.2, and 6.3 ng/g lipid, respectively, in whole-body composites (Burreau et al. 1999). In another study, the concentrations of BDE 47, BDE 99, and BDE 100 were determined in muscle, ripe eggs, and blood plasma from Baltic salmon (Asplund et al. 1999a). The mean concentrations of PBDEs in tissues from Baltic salmon (ng/g lipid weight) were as follows: BDE 47 (muscle, 190; ripe eggs, 64; blood, 190), BDE 99 (muscle, 52; ripe eggs, 16; blood, 55), and BDE 100 (muscle, 46; ripe eggs, 18; blood, 59). Cod (*Gadus morhua*) liver samples at three locations of the North Sea had combined concentrations of BDE 47 and BDE 99 of 1.9–360 ng/g lipid (de Boer 1989). BDE concentrations in flounder were 0.6–20 ng/g dry weight for BDE 47 and <0.01–4.6 ng/g dry weight for BDE 99 from several sites in the Netherlands (de Boer et al. 2000b). Concentrations of BDE 153 and BDE 209 were below the detection limit. In 1996, de Boer et al. (2001) measured the concentrations of two BDE congeners in flounder liver samples from the Amsterdam and Rotterdam harbors, and off the Dutch coast; BDE 47 and BDE 99 ranged from 15 to 280 and from <2 to 24 ng/g lipid weight, respectively. Olsson et al. (1999) detected BDE 47 in perch (*Perca fluviatilis*) from Latvia in a study examining environmental contamination in coastal areas of the former Soviet Union; the concentration of BDE 47 ranged from 6.4 to 10 ng/g lipid weight in the perch.

Watanabe et al. (1987) detected PBDEs in numerous marine fish and shell fish in Japan. TetraBDE and pentaBDE concentrations ranged from 0.1 and 17 ng/g fresh weight, with tetraBDE being the major

congener. DecaBDE was also detected in a mussel sample from Osaka Bay (at 1.4 µg/kg wet weight). Japanese market fish were analyzed for PBDEs. The highest combined PBDE concentrations (BDE 28, BDE 47, BDE 66, BDE 99, BDE 100, BDE 153, and BDE 154) were in salmon, cultured yellowtail, and wild yellowtail muscle (46, 44, and 30.5 ng/g lipid weight, respectively) and lowest concentrations in yellowfin tuna (1.9 ng/g lipid weight) (Ohta et al. 2000). BDE 47 was major congener in all samples. In another study, several fish species from Japan were analyzed for 15 BDE congeners (Hori et al. 2000). The PBDE concentrations ranged from 0.00136 to 2.1 ng/g fresh weight, with BDE 47 as the predominant congener. Seven species of marine fish (conger eel, flounder, gray mullet, horse mackerel, red sea bream, sea bass, and yellowtail) were collected from the Inland Seas near Seto, Japan (Akutsu et al. 2001). Seven PBDEs (BDE 28, BDE 47, 2,3',4,4'-tetraBDE [BDE 66], BDE 99, BDE 100, BDE 153, and BDE 154) were detected in all samples, with BDE 47 being the most abundant congener. Concentrations of total PBDEs in gray mullets and yellowtails were 63 and 15 ng/g lipid weight, respectively.

Marine Aquatic Organisms. Marine mussels (*Mytilus edulis*) collected at several locations in the Netherlands and analyzed for BDE 47, BDE 99, BDE 153, and decaBDE (BDE 209) (de Boer et al. 2000b). Concentrations of BDE 47 and BDE 99 were 0.9–4.3 and 0.3–1.6 ng/g dry weight, respectively. BDE 153 and BDE 209 were not detected. Di- to heptaBDE were analyzed for in hepatopancreas samples from Dungenes crab from several sites on the Strait of Georgia, British Columbia, Canada (Ikonomou et al. 1999). The primary congener detected was BDE 47. The combined concentration of BDE 47 and BDE 99 was approximately 100–350 ng/g lipid weight.

Marine Animals. In marine animals, temporal trends show increasing concentrations of lower-brominated BDE congeners with higher concentrations found near human-populated areas. In all marine animal studies, the congener profiles show the highest concentrations for BDE 47. The concentrations of several PBDEs in marine animals are summarized in Table 6-9. Frouin et al. (2011) reported PBDE concentrations measured from serum and blubber samples obtained from six harbor seal pups (*Phoca vitulina*) live captured in May 2007, six harbor seal pups (*Phoca vitulina*) live captured in May 2008, six grey seal pups (*Halichoerus grypus*) live captured early January 2008, and six harp seal pups (*Phoca groenlandica*) live captured in March 2008 from the Gulf of St. Lawrence or the St. Lawrence Estuary. The ΣPBDEs in serum (BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 155) and blubber (BDE 28, BDE 47, BDE 49, BDE 66, BDE 99, BDE 100, BDE 153, BDE 154, BDE 155, and BDE 183) were strongly correlated. BDE 47 was detected in all serum samples and accounted for 66–73% of ΣPBDEs. ΣPBDE concentrations in lipid ranged from 21 to 530 ng/g lipid weight and from 34 to 600 ng/g lipid weight in serum. PBDEs have been detected in several species of seal from several

Table 6-9. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Animals

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Bottlenose dolphin	Gulf of Mexico	No data	No data	No data	8,000	No data	Kuehl and Haebler 1995
Harbor seal	Northwest Atlantic	904	134	49	1,385*	1.2	Shaw et al. 2009
Harbor seal	San Francisco Bay, California	No data	No data	No data	530–5,075*	No data	Klosterhaus et al. 2012
Cormorant eggs	San Francisco Bay, California	No data	No data	No data	3,425–5,550*	No data	Klosterhaus et al. 2012
Harbor seal	San Francisco Bay, California	46–6,682	17–303	No data	No data	No data	She et al. 2000
Cormorant eggs	Suisan Bay, CA (2002)	No data	No data	No data	19,000±4,000*	No data	Sutton et al. 2015
Cormorant eggs	Suisan Bay, California (2006)	No data	No data	No data	6,100±5,200*	No data	Sutton et al. 2015
Cormorant eggs	Suisan Bay, California (2009)	No data	No data	No data	440±170[8]	No data	Sutton et al. 2015
Cormorant eggs	Suisan Bay California (2012)	No data	No data	No data	1,300±900*	No data	Sutton et al. 2015
Cormorant eggs	Central Bay, California (2002)	No data	No data	No data	9,100±2200	No data	Sutton et al. 2015
Cormorant eggs	Central Bay, California (2004)	No data	No data	No data	3,700±500	No data	Sutton et al. 2015
Cormorant eggs	Central Bay, California (2006)	No data	No data	No data	1,800±400	No data	Sutton et al. 2015
Cormorant eggs	Central Bay, California (2009)	No data	No data	No data	1,800±300	No data	Sutton et al. 2015
Cormorant eggs	Central Bay, California (2012)	No data	No data	No data	1,100±200	No data	Sutton et al. 2015
Cormorant eggs	South Bay California (2002)	No data	No data	No data	4,200±400	No data	Sutton et al. 2015
Cormorant eggs	South Bay California (2004)	No data	No data	No data	3,300±300	No data	Sutton et al. 2015

Table 6-9. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Animals

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Cormorant eggs	South Bay California (2006)	No data	No data	No data	4,400±2,100	No data	Sutton et al. 2015
Cormorant eggs	South Bay California (2009)	No data	No data	No data	2,100±1,200	No data	Sutton et al. 2015
Cormorant eggs	South Bay California (2012)	No data	No data	No data	1,100±100	No data	Sutton et al. 2015
Harbor seal (blubber)	San Francisco Bay, California	1,304	112	87.1	1,730*	No data	She et al. 2002
Herring Gull Eggs	Lake Superior, United States	253–323 (fw)	202–284 (fw)	83.6–113 (fw)	664–887 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Lake Michigan, United States	522–602 (fw)	323–459 (fw)	167–203 (fw)	1,366–1,400 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Lake Huron, United States and Canada	146–291 (fw)	74.6–161 (fw)	37.3–89.5 (fw)	308–652 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Detroit River, United States	322 (fw)	130 (fw)	92.6 (fw)	639 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Lake Erie, United States	70–163 (fw)	52–55.9 (fw)	24.6–51.8 (fw)	192–340 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Niagara River, United States	168 (fw)	111 (fw)	53 (fw)	432 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	Lake Ontario, Canada	220–401 (fw)	113–322 (fw)	66.5–102 (fw)	530–1,003 (fw)*	No data	Norstrom et al. 2002
Herring Gull Eggs	St. Lawrence River, United States	220 (fw)	89.8 (fw)	56.6 (fw)	453 (fw)*	No data	Norstrom et al. 2002
Harbor seal	St. Lawrence Estuary and Gulf of St. Lawrence	52–408	No data	No data	72–530*	No data	Fouin et al. 2011
Grey seal	St. Lawrence Estuary and Gulf of St. Lawrence	41	No data	No data	69*	No data	Fouin et al. 2011
Harp seal	St. Lawrence Estuary and Gulf of St. Lawrence	14	No data	No data	21*	No data	Fouin et al. 2011
Beluga whale	Canadian Arctic	No data	No data	No data	81–160*	No data	Alaee et al. 1999
Beluga whale	Southeast Baffin, Canada	10	0.9	1.6	15*	No data	Stern and Ikonomou 2000

Table 6-9. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Animals

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Bottlenose dolphin	South Atlantic Ocean	No data	No data	No data	180–220	No data	Kuehl et al. 1991
Brunnich's guillemot	Svalbard, Sweden	No data	No data	No data	130	No data	Jansson and Asplund 1987
Cormorant	England, United Kingdom	170–3,500	50–250	50–1,500	300–6,400*	No data	Allchin et al. 2000
Cormorant liver	Rhine delta, Germany	No data	No data	No data	28,000 (fw)	No data	de Boer 1990
Galaucous gull	Bear Island, Norway (Arctic)	290–634	160	No data	No data	No data	de Wit 2002
Grey seal	Baltic Sea	650	40	38	730	No data	de Wit 2002; Sellström et al. 1993
Grey seal	Baltic Sea	308	54	57	419	No data	Haglund et al. 1997
Grey seal	Baltic Sea	No data	No data	No data	208	No data	Andersson and Wartanian 1992
Harbor porpoise	British Columbia, Canada	50–1,200	No data	No data	350–2,300*	No data	Ikonomou et al. 2000
Harbor porpoise	England and Wales, United Kingdom	227–6,790	No data	No data	440–7,670	No data	Law et al. 2000
Harbor seal	Baltic Sea	No data	No data	No data	90	No data	Jansson and Asplund 1987
Harbor seal	Skagerrak, Norway and Sweden	No data	No data	No data	230	No data	Andersson and Wartanian 1992
Harbor seal	North Sea	390–4,900	42–660	25–450	600–6,000	No data	de Boer et al. 1998b
Long-finned pilot whale	Faeroe Islands	410–1,780	160–600	87–280	843–3,160*	No data	Lindström et al. 1999
Long-finned pilot whale	Faeroe Islands	66–860	24–170	12–98	126–1,250*	No data	van Bavel et al. 1999
Minke whale	Netherlands	630	160	79	870	No data	de Boer et al. 1998b
Ringed seal	Baltic sea	256	33	61	350	No data	Haglund et al. 1997
Ringed seal	Baltic sea	No data	No data	No data	320	No data	Andersson and Wartanian 1992
Ringed seal	Svalbard, Sweden	47	1.7	2.3	51	No data	de Wit 2002; Sellström et al. 1993

Table 6-9. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Marine Animals

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Ringed seal	Canadian Arctic	No data	No data	No data	25.8–50*	No data	Alaee et al. 1999
Ringed seal	Holman Island, Northwest Territories, Canada	2.8	No data	No data	2.4–4.9*	No data	Ikonomou et al. 2000
Sperm whale	Netherlands	130–250	32–64	21–35	187–349	No data	de Boer et al. 1998b
White-beaked dolphin	Netherlands	5,500	1,000	1,200	7,700	No data	de Boer et al. 1998b

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

BDE = brominated diphenyl ether; fw = fresh weight

different sites. In San Francisco Bay, California, the concentrations of PBDEs in harbor seals have increased dramatically based on samples obtained from 1989 to 1998. The samples from 1998 had PBDE concentrations among the highest reported for this species (She et al. 2002). The concentration of total PBDEs (sum of BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154) in harbor seal blubber increased by over a factor of 50 from a concentration of 88 ng/g lipid for species samples collected in 1988 to a concentration of 2,985–8,325 ng/g lipid for species samples collected in 1998. The highest concentrations reported were for BDE 47, which increased from 45.6 ng/g lipid for blubber samples in 1989 to 2,343–6,682 ng/g lipid for blubber samples collected in 1998. The dominance of the tetraBDE congeners over other congeners may indicate that tetraBDEs bioaccumulate more than the higher-brominated congeners (She et al. 2002).

In the Baltic Sea, female grey seals (*Halichoerus grypus*) sampled in 1979–1985 contained 730 ng PBDE/g lipid in their blubber (sum of BDE 47, BDE 99, and BDE 100) (Jansson et al. 1993); male grey seals had 280 ng PBDE/g lipid weight (Andersson and Wartanian 1992). Male ringed seals (*Pusa hispida*) from the Baltic Sea had 320 ng PBDE/g lipid weight (Andersson and Wartanian 1992). Baltic gray and ringed seal blubber sampled between 1981 and 1988 contained 419 and 350 ng PBDEs/g lipid (total of BDE 47, BDE 99, and BDE 100), respectively (Haglund et al. 1997). In 1981, female ringed seals from Svalbard in the Swedish Arctic contained 40–51 ng PBDEs/g lipid in blubber (Jansson and Asplund 1987, Jansson et al. 1993; Sellström et al. 1993). Higher concentrations of PBDEs are generally evident in Baltic Sea ringed seals (320–350 ng/g lipid) (Andersson and Wartanian 1992; Haglund et al. 1997) compared to Arctic ringed seals (26–51 ng/g lipid) (Alaee et al. 1999; Jansson et al. 1987). The concentration of PBDEs in harbor seals from Skagerrak on the Swedish west coast was 230 ng PBDE/g lipid (Andersson and Wartanian 1992).

She et al. (2000) analyzed the concentration of BDE 47, BDE 99, and BDE 153 in harbor seals from the San Francisco Bay area. Mean concentrations for BDE 47, BDE 99, and BDE 153 were 1,124, 107, and 50 ng/g lipid weight, respectively. Alaee et al. (1999) found that ringed seals from the Canadian Arctic had mean PBDE concentrations (sum of di- to hexaBDEs) of 25.8 ng/g lipid weight (females) and 50.0 ng/g lipid weight (males). The lower concentrations in female seals suggest that PBDEs are transferred to young through breast milk. On Holman Island, Northwest Territory, Canada (Arctic) in 1996, ringed seals had total PBDE concentrations of 2.4–4.9 ng/g lipid for males. The concentrations of PBDEs were found to increase with age (Ikonomou et al. 2000). In a temporal trend study, archived samples of blubber from ringed seals from Holman Island, Northwest Territory, Canada were analyzed for PBDE concentrations. The concentration of PBDE in samples collected between 1981 and 1996

increased from approximately 0.3 ng/g lipid weight in 1981 to 3.6 ng/g lipid weight in 1996 (Ikonomou et al. 2000).

The concentrations of PBDEs have been determined in harbor porpoises (*Phocaena phocaena*) from British Columbia, Canada (Ikonomou et al. 2000) and from the coasts of England and Wales (Law et al. 2000). In British Colombia (Canada) samples, the total PBDE concentrations (sum of tri- to hepta-congeners) were 350–2,300 ng/g lipid weight; BDE 47 was found at the highest concentrations in these samples (range, 50–1,200 ng/g lipid weight) (Ikononmou et al. 2000). Concentrations of total PBDEs (sum of 13 congeners) along the coast of England and Wales, ranged from 450 to 7,670 ng/g lipid weight, with BDE 47 concentrations ranging from 227 to 6,790 ng/g lipid weight (Law et al. 2000).

During a mass mortality event on the south Atlantic coast in 1987–1988, blubber samples were collected from three bottlenose dolphins (*Tursiops truncatus*); these samples contained 180–220 ng PBDEs/g lipid (Kuehl et al. 1991). Blubber samples, taken from stranded bottlenose dolphins from several locations around the Gulf of Mexico in 1990, contained 3,110 ng PBDEs/g lipid (Kuehl and Haebler 1995). On the Dutch coast in early 1998, de Boer et al. (1998b) found PBDEs in blubber of one whitebeaked dolphin (*Lagenorhynchus albirostris*); the concentrations of BDE 47, BDE 99, and BDE 100 were 5,500, 1,000, and 1,200 ng/g lipid weight, respectively.

The concentration of 19 PBDEs was determined in long-finned pilot whale (*Globicephala melas*) from the Faeroe Islands in the north Atlantic (Lindström et al. 1999). Young males and females had the highest concentrations, ranging from 3,000 to 3,160 ng/g lipid; lower concentrations were observed for both adult females (840–1,050 ng/g lipid) and males (1,610 ng/g lipid). The predominant isomers in all samples were BDE 47 and BDE 99, accounting for 70% of the sum of 19 congeners. van Bavel et al. (1999) also studied the concentrations of PBDEs in long-finned pilot whales. They observed a similar trend with young animals having higher PBDE concentrations (740 ng/g lipid weight) and adult animals having lower concentrations (females, 230 ng/g lipid; males, 540 ng/g lipid). In Beluga whales sampled in 1997 from southeast Baffin (Cumberland Sound), the concentrations of total PBDEs and BDE 47 were 15 and 10 ng/g lipid weight, respectively (Stern and Ikonomou 2000). Between 1982 and 1997, total PBDE concentrations in archived blubber samples of beluga whales from southeast Baffin Canada increased significantly. For this time period, BDE 47, BDE 99, BDE 100, and BDE 154, and total PBDEs increased by factors of 6.5, 10.3, 7.9, 30.6, and 6.8, respectively (Stern and Ikonomou 2000). Three sperm whales (*Physeter macrocephalus*) and one minke whale (*Balaenoptera acutorostrata*) found stranded on the Dutch coast in early 1998 were analyzed for PBDEs (de Boer et al. 1998a, 1998b). Exposure to PBDEs for these animals occurred in the deep Atlantic through the food web. The

concentrations of PBDEs in these marine mammals were as follows: sperm whale (BDE 47, 130–250 ng/g lipid weight; BDE 99, 32–64 ng/g lipid weight; and BDE 100, 21–35 ng/g lipid weight) and minke whale (BDE 47, 630 ng/g lipid weight; BDE 99, 160 ng/g lipid weight; BDE 100, 79 ng/g lipid weight); BDE 209 (decaBDE) was below detection limits in all samples.

PBDEs, methoxylated (MeO-) PBDEs, and hydroxylated (OH-) PBDEs were evaluated in whole blood samples collected from northern fur seal (*Callorhinus ursinus*), spotted seal (*Phoca largha*), Steller sea lion (*Eumetopias jubatus*) and ribbon seal (*Phoca fasciata*) (Nomiyama et al. 2014), and harbor porpoise and Dall's porpoise (Ochiai et al. 2013) from northern Japanese coastal waters. The samples contained 3.9–280 pg/g median values of 6OH-BDE 47; <1.0–51 pg/g median values of 2'MeO-BDE 68; 2.9–1,020 pg/g median values of 6MeO-BDE 47; <1–18 pg/g median values of 6MeO-BDE 99; and <100–230 pg/g median values of total PBDEs.

Marine Birds. Increasing concentrations of PBDEs have been found in marine birds and eggs, with BDE 47 found at the highest concentrations. Di- and triBDE have been detected, but not quantified, in black skimmer (*Rynchops nigra*) tissues and eggs in the United States (Stafford 1983). In 2000, herring gull eggs collected from 15 locations around the Great Lakes (United States and Canada) were pooled and analyzed for PBDEs (Norstrom et al. 2002). A total of 25 di- to hepta-BDE congeners were identified in herring gull through the Great Lakes system. No mono-, octa-, nona-, or decaBDEs were found at the detection limit of the analysis (0.01–0.05 ng/g wet weight). Seven congeners, BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 184, constituted 97.5% of total PBDEs (192–1,400 ng/g wet weight). BDE 47 was the dominant congener (70–602 ng/g wet weight) followed by BDE 99 (52–459 ng/g wet weight). The highest concentrations (1,003–1,400 ng/g wet weight) were found in two Lake Michigan colonies and in Toronto Harbor, Lake Ontario (Norstrom et al. 2002). Muscle tissues from ospreys (*Pandion haliaetus*), found dead at various locations around Sweden, were pooled and analyzed for PBDEs (Jansson et al. 1993; Sellström et al. 1993). The ospreys' diet was freshwater fish. The combined concentration of BDE 47, BDE 99, and BDE 100 was 2,100 ng/g lipid in samples collected between 1982 and 1986; BDE 47 was the primary congener (86%) in these samples (n=35). High concentrations of PBDEs may reflect biomagnification and/or fish consumption along their migratory routes. The concentrations of PBDEs in common guillemots (*Uria aalge*) collected in 1979–1981 from the Baltic and North Seas were 370 and 80 ng/g lipid, respectively (Jansson and Asplund 1987). As part of the Swedish National Environmental Monitoring Program, guillemot eggs (St. Karlsö, Baltic Sea) are collected yearly and placed in the Swedish Natural History Museum's Environmental Specimens Bank. The concentrations of BDE 47, BDE 99, and BDE 100 in pooled egg samples from the specimen bank

showed a significant increase from 1969 to the beginning of the 1990s, with highs of 1,100 ng/g for BDE 47 in 1984 and 190 ng/g for BDE 99 in 1990 (Sellström et al. 1993, 1999). Between 1992 and 1997, PBDE concentrations started to decrease statistically. In 1997, the PBDE concentration (sum of BDE 47, BDE 99, and BDE 100) was 190 ng/g lipid, with BDE 47 as the predominant congener. Cormorant eggs obtained from the San Francisco Bay regions had total PBDE concentrations ranging from 3,425 to 5,550 ng/g (median, 5,500 ng/g) and was dominated by the penta (BDE 47, BDE 99, BDE 100) congeners (Klosterhaus et al. 2012). Sutton et al. (20015) noted decreasing levels of PBDEs in cormorant eggs obtained from three locations in northern California. Eggs collected from Suisun, Central, and South Bays in 2012 had total PBDE levels 93, 88, and 74% lower, respectively, when compared to the levels in eggs collected in 2002 (see Table 6-9).

Human Body Tissues and Fluids. The quantitative determination of the concentrations of PBDEs in body tissues and fluids is important in determining the human body burden of these chemicals. Increasing concentrations of lower-brominated PBDEs have been measured in blood and breast milk in temporal trend studies. Individuals who consumed fish had a somewhat higher concentration of total PBDEs in body fluids compared to individuals who ate less fish.

Lipid adjusted serum levels of 11 BDE congeners collected from the U.S. general population were reported in the Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables (CDC 2015). Serum levels for BDE 17, BDE 28, BDE 47, BDE 66, BDE 85, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 183 were evaluated in samples collected between 2003 and 2008; BDE 209 was evaluated in samples collected from 2005 to 2008. In the NHANES 2003–2004 survey years, congener BDE 47 was detected at a concentration of 20.5 ng/g lipid (geometric mean), the highest concentration for all samples. BDE 28, BDE 99, BDE 47, BDE 100, and BDE 153 were in >60% of participants (Sjödin et al. 2008). BDE 17 was not detected above the limit of detection of 1.0 and 0.6 ng/g lipid in survey years 2003–2004 and 2005–2008, respectively. BDE 209 was not detected above the limit of detection, 6.0 and 5.8 ng/g lipid, in survey years 2005–2006 and 2007–2008, respectively.

BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 were detected in 98, 100, 100, 96, and 48%, respectively, of serum samples collected from 48 mothers participating in the California Childhood Leukemia Study from 2006 to 2007 (Whitehead et al. 2015a). Median serum levels ranged from below the detection limit for BDE 154 to 35 ng/g lipid for BDE 47. BDE 47 and BDE 153 were detected in whole blood of 61 and 85%, respectively, of 191 children participating in the California Childhood Leukemia Study from 1999 to 2007 (Whitehead et al. 2015b). The median, 75th percentile, 90th

percentile, and maximum levels were 410, 820, 1,500, and 17,000 pg/mL, respectively, for BDE 47 and 130, 270, 460, and 6,500 pg/mL, respectively, for BDE 153.

Tables 6-10, 6-11, and 6-12 summarize representative concentrations of PBDEs found in blood (serum), adipose tissue, breast milk, and other body tissues or fluids, respectively. These studies indicate that concentrations of lower-brominated BDEs in body fluids are a factor of 10–100-fold higher for individuals living in the United States compared to individuals living in other regions of the world (e.g., Europe). Serum samples collected from 12 U.S. blood donors in 1988 were analyzed for PBDEs, and BDE 47, BDE 153, BDE 183, and BDE 209 were detected (Patterson et al. 2000; Sjödin et al. 2001b). Concentrations of these congeners were similar to those found in the Sjödin et al. (1999b) study for the control group. The median concentrations and ranges of BDE 47, BDE 153, BDE 183, BDE 209, and total PBDEs (sum of four congeners) were 0.63 (<0.4–24); 0.35 (0.08–2.0); 0.17 (0.09–1.3); <1 (<1–34); and 2.2 ng/g lipid weight, respectively (Sjödin et al. 2001b). DecaBDE was found at concentrations above the limit of quantification (1 pmol/g lipid) in 5 of 12 serum samples (Patterson et al. 2000).

Schecter et al. (2005) provided a summary of PBDE (BDE 17, BDE 28, BDE 47, BDE 66, BDE 77, BDE 85, BDE 99, BDE 100, BDE 138, BDE 153, BDE 154, BDE 183, and BDE 209) concentrations in blood from 29 adults residing in Mississippi and 10 adults in New York City. These blood samples were obtained in 2003. These data were then compared to archived blood samples from 100 individuals obtained in 1973 from the Dallas, Texas area and stored at the University of Texas Southwestern Medical Center. The 13 PBDE congeners were not detected in the blood samples from the 100 individual collected in 1973, but all congeners were detected in at least one of the blood samples obtained from the 29 residents of Mississippi collected in 2003. BDE 28, BDE 47, BDE 77, BDE 99, BDE 100, BDE 138, BDE 153, BDE 154, and BDE 183 were all detected in at least one of the blood samples obtained in 2003 from New York City residents. BDE 47 followed by BDE 99 were the predominant congeners detected in both the Mississippi and New York residents blood samples collected in 2003.

Rawn et al. (2014) analyzed data from nearly 5,000 serum samples collected from the Canadian Health Measures Survey (CHMS) from 2007 to 2009. PBDE congeners were detected in all samples tested, with a range of values of 27–130 ng/g lipid (total PBDEs) and a GM of 46 ng/g lipid. BDE 47 was the predominant congener with a GM of 22 ng/g lipid followed by BDE 153 (GM=9.4 ng/g lipid), BDE 99 (GM=4.6 ng/g lipid), BDE 100 (GM=4.1 ng/g lipid), and BDE 209 (GM 1.1 ng/g lipid) (Rawn et al. 2014).

Table 6-10. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Human Blood Samples[a]

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Human blood	United States (in 1988)	0.63	0.32	0.17	2.2*	<0.1	Sjödin et al. 2001b
Human blood	Mississippi and New York City (in 2003)	25 (mean)	11.1 (mean)	4.7 (mean)	52.6 (mean)	2.7 (mean)	Schecter et al. 2010
Maternal serum	Indiana	28 (9.2–310)	5.7 (2.4–68)	4.2 (1.9–110)	37 (15–580)	No data	Mazdai et al. 2003
Fetal serum	Indiana	25 (8.4–210)	7.1 (2.2–54)	4.1 (1.8–91)	39 (14–460)	No data	Mazdai et al. 2003
Maternal serum	Texas	14.9	3.0	2.8	27.8*		Schecter et al. 2010
Human serum	United States (in 2003–2004)	20.5 (geo-metric mean)	No data	3.93 (geo-metric mean)	No data	No data	CDC 2015
Human serum	United States (in 2005–2006)	21.2–74.9 (weighted arithmetic mean)	4.16–23.3 (weighted arithmetic mean)	4.06–14.2 (weighted arithmetic mean)	No data	No data	CDC 2015
Human serum	United States (in 2007–2008)	20.5–53.1 (weighted arithmetic mean)	4.30–10.7 (weighted arithmetic mean)	4.12–11.0 (weighted arithmetic mean)	No data	No data	CDC 2015
Human serum	Australia	2.6–55.1	0.9–24.2	0.6–14.1	24 (newborn); 31 (0–2 years); 41 (2–6 years); 26 (7–12 years); 20 (13–30 years); 9.4 (>31 ye ars) (mean)	No data	Toms et al. 2009
Maternal serum	France	2.831	1.939	0.365	No data	5.783	Antignac et al. 2009
Cord serum	France	No data	7.434	1.467	No data	27.110	Antignac et al. 2009
Maternal serum	Spain	2.3	0.35	No data	9.6	<0.7	Vizcaino et al. 2011
Cord serum	Spain	2.3	1.5	No data	9.6	<1.2	Vizcaino et al. 2011

Table 6-10. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Human Blood Samples[a]

Sample type	Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Human Serum	Canada	23 (mean)	5.4 (mean)	4.4 (mean)	48 (mean)	1.9 (mean)	Rawn et al. 2014
Maternal serum	China	0.75 (mean)	No data	No data	29.26 (mean)	2.12 (mean)	Li et al. 2013a
Cord serum	China	0.62 (mean)	No data	No data	41.12 (mean)	1.33 (mean)	Li et al. 2013a
Human blood	Sweden	No data	No data	No data	2.1*	No data	Klasson Wehler et al. 1997
Human blood	Japan	0.001	<LOQ	No data	No data	No data	Fujii et al. 2014
Human blood	Sweden, computer dis-assembly workers	2.9 (median)	No data	No data	26*	4.8	Sjödin et al. 1999a
Human blood	Sweden, cleaning personnel/office workers	1.5–1.6	No data	No data	3.3–4.1*	<0.7	Sjödin et al. 1999a
Human blood	Sweden, high fish intake	2.1	No data	No data	No data	No data	Bergman et al. 1999; Sjödin et al. 2000
Human blood	Sweden, no fish intake	0.40	No data	No data	No data	No data	Bergman et al. 1999; Sjödin et al. 2000
Maternal blood	Sweden	0.83 (0.3–5.1)	0.19 (<0.01–1.43)	0.17 (<0.01–0.52)	2.07 (0.71–8.39)	No data	Meironyte Guvenius et al. 2003
Cord blood	Sweden	0.98 (0.33–3.28)	0.07	0.07	0.46–4.28	No data	Meironyte Guvenius et al. 2003
Human blood	Germany	3.9	No data	No data	5.6*	No data	Schröter-Kermani et al. 2000

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

BDE = brominated diphenyl ether; LOQ = limit of quantitation

Table 6-11. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Human Adipose Tissue Samples

Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Northern California	7.0–28 (18, mean)	3.1–7.3 (4.9 mean)	No data	No data	No data	She et al. 2000
San Francisco, California	16.5 (5.2–196)	No data	No data	No data	No data	Petreas et al. 2003
Sweden	8.8	1.1	1.8	11.7	No data	Haglund et al. 1997
Sweden	2.2 (mean)	1.6 (mean)	0.1 (mean)	5* (mean)	No data	Meironyté Guvenius and Norén 1999
Finland	7.3 (mean)	2.3 (mean)	No data	6.2–22*	No data	Strandman et al. 1999
Finland	0.55	0.74	No data	No data	No data	Smeds and Saukko 2003
Spain	1.36 (mean)	0.42 (mean)		No data	No data	Meneses et al. 1999
Japan	0.459	0.118	0.250	1.288*	No data	Choi et al. 2003
France	0.651	0.166	0.168		0.752	Antignac et al. 2009

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

BDE = brominated diphenyl ether; ND = not detected

Table 6-12. Concentrations (ng/g Lipid Weight) of Several Polybrominated Diphenyl Ethers (PBDEs) in Human Breast Milk Samples

Location	BDE 47	BDE 99	BDE 100	ΣPBDEs[a]	BDE 209	Reference
Texas	18.4	5.7	2.9	34.0	8.24 (maximum)	Schecter et al. 2003
Texas	24.0	4.3	3.5	39.7*	No data	Schecter et al. 2010
California	29.7	6.40	5.65	54.5	1.41	Park et al. 2011
Pennsylvania	26	No data	4	No data	No data	LaKind et al. 2009
Philippines (mean)	0.9	0.22	0.19	1.8*	<0.05	Malarvannan et al. 2013
France	1.152	0.527	0.226		1.615	Antignac et al. 2009
Uppsala County, Sweden	1.78	0.43	0.27	3.15	No data	Lind et al. 2003
Sweden	1.8	0.442	0.340	3.373*	No data	Darnerud et al. 1998
Finland	0.85	0.35			No data	Strandman et al. 2000
Birmingham, United Kingdom	2.80	0.69	0.45	5.00*	0.25	Abdallah and Harrad 2014
Japan	0.18–0.57	0.09–0.13	0.07–0.18	0.65–1.48*		Ohta et al. 2000
Japan	No data	No data	No data	0.66–2.8*	No data	Ohta et al. 2002
Japan	0.57	0.33	No data	No data	No data	Fujii et al. 2014
Sweden	No data	No data	No data	0.07* (1972); 0.28 (1976); 0.48 (1980); 0.72 (1984-5); 1.21 (1990) 2.15 (1994); 3.11 (1996); 4.01 (1997)	No data	Norén and Meironyté 2000

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

BDE = brominated diphenyl ether

Serum samples were collected from a group of 50 Laotian immigrants (aged 19–40) participating in a reproductive outcome study in the San Francisco Bay area (Petreas et al. 2002). Participants were recruited and sampled in the late 1990s. The mean concentration of BDE 47 in serum was approximately 95 ng/g lipid. The contemporary samples were compared to serum samples taken from a group of over 400 women from the San Francisco Bay in the 1960s. Concentrations of BDE 47 in all archived samples were below the limit of detection. Petreas et al. (2003) expanded their investigation to include a diverse group of local women from the San Francisco Bay area sampled in the late 1990s. Their results confirmed earlier findings reported in Petreas et al. (2002). Mean concentrations of BDE 47 in serum samples taken from California women ranged from 5 to 510 ng/g lipid, with a median (16.5 ng/g lipid) 3–10 times higher than those reported from Europe (Petreas et al. 2003). In 2001, Mazdai et al. (2003) determined the concentration of six PBDE congeners (BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 183) and total PBDEs in maternal and fetal blood samples taken from subjects in Indianapolis, Indiana. Median concentrations of total PBDE (sum of six congeners) were 39 and 37 ng/g lipid for fetal and maternal serum, respectively. BDE 47 was the predominant congener reported at median concentrations of 25 and 28 ng/g lipid for fetal and maternal serum samples, respectively. When compared with serum PBDE concentrations for a similar population of Swedish mothers and newborns, the concentrations for the Indiana population were 20–69-fold higher for maternal blood and 30–106-fold higher for fetal blood. In fact, the median blood concentrations for this study were comparable to Swedish workers considered to have direct work-related exposures. These observations indicated that women in some areas of North America are exposed to much higher concentrations of lower-brominated BDEs (i.e., BDE 47) than European women. In general, the PBDE congener profile found in human serum was similar to that detected in environmental samples, except that there was an apparent decrease in the proportion of BDE 99. BDE 183 was detected in <17% of the samples even though it is the primary congener in octaBDE commercial mixtures (Mazdai et al. 2003). The conclusion that PBDE concentrations are higher in North America than in Europe is further supported by a study conducted in the Netherlands that analyzed maternal serum from 90 female volunteers collected at the 35th week of pregnancy, and in cord serum of a number of their infants (Meijer et al. 2008). Median concentrations of BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 in maternal serum were reported as 0.8, 0.2, 0.2, 1.6, and 0.5 ng/g lipid weight, respectively. Median concentrations of BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 in cord serum were 0.5, 0.1, 0.1, 0.9, and 0.3 ng/g lipid weight, respectively (Meijer et al. 2008). These concentrations are on the same order of magnitude as reported in other areas of Europe and much lower than concentrations typically detected in the United States (Vizcaino et al. 2011).

Six PBDE congeners (BDE 28, BDE 47, BDE 66, BDE 99, BDE 100, and BDE 153) were quantified in 40 human blood-plasma samples from Sweden. The highest concentrations in plasma were for BDE 47 and BDE 99; these congeners made up 70% of the total PBDE concentration. The mean concentration of total PBDE was 2.1±1.4 ng/g lipid weight (Klasson Wehler et al. 1997). Whole-blood samples from a German environmental specimen bank, collected in 1985, 1990, 1995, and 1999, contained measurable quantities of BDE 28, BDE 47, BDE 66, BDE 85, BDE 99, BDE 100, BDE 153, and BDE 154. An increasing temporal trend was also observed; the mean total PBDE concentration (sum of eight congeners) increased from 3.9 ng/g lipid weight in 1985 to 5.6 ng/g lipid weight in 1999. For the 1999 sample, BDE 47 was the major congener found, with a mean concentration of 3.9 ng/g lipid weight. The total PBDE concentrations were significantly lower in female blood samples (Schröter-Kermani et al. 2000). In a study of the influence of diet on concentrations of PBDEs, BDE 47 was measured in blood serum from persons with high fish intake and no fish intake (Bergman et al. 1999; Sjödin et al. 2000). High-fish-intake groups of Swedish and Latvian men had median BDE 47 concentrations of 2.2 and 2.4 ng/g lipid weight, respectively, whereas the no-fish-intake groups had median concentrations of 0.4 and 0.26 ng/g lipid weight, respectively (Sjödin et al. 2000).

Serum samples collected in 2006–2007 and analyzed for different age groups in Australia suggest that PBDE concentrations increase from infant to toddler and then gradually decrease over time (Toms et al. 2009). Mean total PBDE (sum of BDE 47, BDE 99, BDE 100, and BDE 153) concentrations in cord blood of 0–2 year olds, 2–6 year olds, 7–12 year olds, 13–30 year olds, and >31 year olds were 24, 31, 41, 26, 20, and 9.4 ng/g lipid, respectively. The peak mean concentration was observed in toddlers 2.6–3 years of age (51 ng/g lipid), which is later than when breastfeeding usually ceases, suggesting a lower capacity to eliminate PBDEs or greater exposure through unique exposure pathways more common for this age group (e.g., ingestion or dermal exposure of contaminated dust particles in carpeting).

BDE 47, BDE 153, BDE 154, BDE 183, and BDE 209 were measurable in blood plasma from three groups of workers (i.e., workers at a computer-disassembly plant, workers in a computerized office, and a control group) (Sjödin et al. 1999a). The median concentrations (sum of five congeners) were highest for the computer-disassembly plant workers (26 ng/g lipid weight); the office workers had a median concentration of 4.1 ng/g lipid weight and the control group had a median concentration of 3.3 ng/g lipid weight. The congener patterns for the control group and office workers were similar, with BDE 47 having the highest concentrations. For the computer disassembly plant workers, the median concentrations of BDE 183, BDE 153, BDE 154, BDE 47, and BDE 209 were 7.8, 4.5, 1.2, 2.9, and

4.8 ng/g lipid weight, respectively. Blood serum samples from 19 full-time computer technicians were analyzed (Hagmar et al. 2000a). The serum concentrations of BDE 153, BDE 183, and BDE 209 in these samples were found to be approximately 5 times higher than the control and office workers in the Sjödin et al. (1999a) study. The median concentration for total PBDEs (for the sum of five congeners) was 10.6 pmol/g (7.0 ng/g) lipid weight. The highest concentrations were of BDE 153. Two octaBDE congeners and one nonaBDE congener were also detected. Connections were observed between fish consumption and serum concentrations for congeners BDE 47, BDE 153, and BDE 183, and between worktime at the computer and congeners BDE 153 and BDE 183.

DecaBDE, as well as hexa- through nonaBDE, has been found in composite samples from the 1987 National Human Adipose Tissue Survey repository (Cramer at al 1990; Stanley et al. 1991). The concentrations ranged from not detected to 1 ng/g fat for hexaBDE, 0.001–2 ng/g fat for heptaBDE and not detected to 8 ng/g fat for octaBDE. NonaBDE concentrations were estimated to be >1 ng/g fat; decaBDE was estimated to range between not detected and 0.7 ng/g fat. In the late 1990s, breast adipose samples collected in northern California contained quantifiable amounts of BDE 47, BDE 99, and BDE 153 (She et al. 2000). Mean concentrations were 18 ng/g lipid weight for BDE 47, 4.9 ng/g lipid weight for BDE 99, and 2.2 ng/g lipid weight for BDE 153. Average total PBDEs concentrations (86 ng/g lipid) were the highest human concentrations reported to date. Petreas et al. (2003) expanded their investigation to include a diverse group of local women from the San Francisco Bay area sampled in the late 1990s. Their results confirmed earlier findings reported in She et al. (2000). Mean concentrations of BDE 47 in adipose tissues samples taken from California women were 28.9 ng/g lipid. In the adipose tissue of a 74-year-old Swedish male, the BDE 47 concentration was 8.8 ng/g lipid weight (Haglund et al. 1997).

Adipose and liver tissue from two Swedish males were examined for several PBDEs (BDE 28, BDE 47, BDE 85, BDE 99, BDE 100, BDE 153, and BDE 154) (Meironyté Guvenius and Norén 1999). The distribution of congener concentrations in the adipose and liver tissues for each individual were similar. BDE 47, BDE 99, and BDE 153 were the predominant congeners with adipose BDE 47 concentrations ranging from 2 to 2.4 ng/g lipid weight, BDE 99 concentrations of 1.6 ng/g lipid weight, BDE 100 concentrations of 0.1 ng/g lipid weight, and BDE 153 concentrations ranging from 1 to 1.3 ng/g lipid weight. The total PBDE concentration (i.e., the sum of the seven congeners) in adipose tissue was 5 ng/g lipid weight. Human liver and adipose tissues from one woman and four men autopsied in Sweden in 1994 were analyzed for PBDEs containing 3–6 bromine atoms (Meironyté Guvenius and Norén 2001). PBDEs were found in all of the tissue samples. The sums of nine congeners (BDE 17, BDE 28, BDE 47,

BDE 66, BDE 100, BDE 99, BDE 85, BDE 154, and BDE 153) were 5–18 and 4–8 ng/g lipids in liver and adipose tissue, respectively. The PBDE congeners BDE 47, BDE 99, and BDE 153 occurred at the highest concentrations and constituted 87–96 and 84–94% of the total sum in liver and adipose tissue, respectively. Strandman et al. (1999) measured the concentration of BDE 47, BDE 99, and BDE 153 in adipose tissue samples from 10 randomly selected individuals in Finland. Mean concentrations were 7.3 ng/g fat for BDE 47, 2.2 ng/g fat for BDE 99, and 2.3 ng/g fat for BDE 153. Concentrations of PBDEs were measured in adipose tissue samples from 13 individuals (3 women, 10 men) from Tarragona, Spain; the mean concentrations of BDE 47, BDE 99, and BDE 153 were 1.36, 0.42, and 1.83 ng/g lipid weight, respectively. The mean concentrations of pentaBDE and hexaBDE were 0.93 and 1.83 ng/g lipid weight, respectively (Meneses et al. 1999).

Human Milk. Schecter et al. (2003) reported the first findings on concentrations of PBDEs congeners in human milk from individuals in the United States. Forty-seven individual milk samples were analyzed from nursing mothers, 20–41 years age, from a milk bank in Austin, Texas, and a community health clinic in Dallas, Texas, both in the year 2001. The median concentration of the sum of PBDE congeners was 34.0 ng/g lipid. The predominant congener was BDE 47 (18.4 ng/g lipid); other congeners detected were BDE 17, BDE 28, BDE 66, 2, BDE 85, BDE 99, BDE 100, BDE 138, BDE 153, BDE 154, and BDE 183 at median concentrations of 0.01, 1.2, 0.14, 0.41, 5.7, 2.9, 0.09, 2.0, 0.22, and 0.07 ng/g lipid, respectively. DecaBDE was detected in 7 out of 47 samples with a maximum concentration of 8.24 ng/g lipid. PBDE concentrations in breast milk from this study were similar to concentrations found in U.S. blood and adipose tissue lipid from California and Indiana and are 10–100 times greater than human tissue concentrations in Europe (Schecter et al. 2003). These data have been updated to include 2001–2004 samples and are provided in Table 6-13 (Schecter et al. 2005).

Median concentrations of BDE 47, BDE 100, and BDE 153 were 26, 4, and 3.5 ng/g lipid, respectively, in breast milk samples collected from 10 mothers in Pennsylvania (LaKind et al. 2009). The detection frequency was 100% for each congener in all 35 samples collected.

Norén and Meironyté (1998, 2000) examined the temporal trends of PBDE concentrations in pooled breast milk samples from mothers in Stockholm, Sweden. Between 1972 and 1997, the concentration of PBDEs in human breast milk increased, with a doubling rate of 5 years. In the 1997 sample, the concentration of PBDEs (sum of eight congeners) was 4 ng/g lipid, whereas the 1972 sample contained 0.07 ng/g lipids (Meironyté et al. 1999). The authors suggest that the current exposure of humans to PBDEs may not be only diet; other exposure routes may result from the presence of PBDE in both work

Table 6-13. Concentrations of PBDE Congeners in Human Milk from Nursing Mothers in the United States (2001–2004) (ng/g Lipid)

				BDE congener													
Female	Lipid (%)	Age (years)	Nursing (weeks)	17	28	47	66	77	85	99	100	138	153	154	183	209	Sum
1[a]	4.8	31	3	ND	0.2	2.9	0.02	ND	0.08	0.7	0.7	ND	1.5	0.06	ND	ND	6.2
2[a]	1.3	29	3	ND	0.3	3.5	ND	ND	0.08	0.7	0.5	ND	0.9	0.06	0.06	ND	6.2
3[a]	2.1	23	74	ND	0.2	3.9	0.06	ND	0.11	1.5	0.6	ND	0.4	0.08	ND	ND	6.9
4[b]	4.8	32	21	—	0.3	3.5	0.14	—	0.08	1.6	0.7	0.09	1.4	0.09	0.04	—	8
5[a]	2.6	22	40	0.01	0.3	6.3	0.05	ND	0.23	2.8	1.2	ND	0.7	0.2	0.05	ND	11.8
6[a]	3.6	36	109	ND	0.4	7.8	0.09	ND	0.23	2.4	1.1	0.01	0.4	0.11	ND	ND	12.5
7[a]	1.9	32	20	ND	0.7	8.2	0.04	ND	0.22	1.3	1.7	ND	0.9	0.12	0.08	ND	13.3
8[a]	6.3	25	2	ND	0.4	7.9	0.02	ND	0.38	2.3	2.7	ND	0.8	0.15	0.06	ND	14.7
9[b]	2.1	35	29	—	0.7	8.8	0.19	—	0.17	1.5	1.7	0.16	2	0.06	0.03	—	15.2
10[a]	5.5	32	30	ND	0.4	8	0.01	ND	0.44	2.9	2	ND	0.9	0.14	0.24	0.48	15.6
11[b]	5	20	2	0.01	1.1	10.9	0.05	ND	0.18	2	2.4	ND	1.3	0.17	0.04	ND	18.1
12[a]	3.4	23	3	0.01	0.4	8	0.03	ND	0.35	3.1	2.7	ND	2	0.21	0.61	0.93	18.3
13[b]	1.3	32	16	—	0.8	10.5	ND	—	0.35	2.5	2.2	0.19	2	0.12	0.03	—	18.6
14[a]	3.4	25	NA	0.02	1.1	12	0.13	ND	0.23	2.5	1.8	ND	1.3	0.15	0.08	1.85	21.1
15[a]	2.9	21	29	0.03	0.5	10.7	0.09	ND	0.27	5.5	2.1	ND	0.9	0.35	0.07	2.74	22.4
16[b]	3.5	30	30	—	0.7	6.9	ND	—	0.12	1.3	4.6	0.41	8.5	0.19	0.06	—	22.8
17[a]	1	23	2	ND	0.9	14.2	0.11	ND	0.37	3.7	2.6	ND	1.3	0.24	0.09	ND	23.5
18[b]	3.7	23	19	—	0.7	13.2	0.57	—	0.29	3.7	2.5	0.29	1.9	0.17	0.06	—	23.5
19[a]	3.2	26	2	ND	1.3	17.4	0.19	ND	0.35	4	2.1	ND	0.7	0.18	ND	ND	26.2
20[b]	3.5	34	22	—	1	14.3	0.29	—	0.46	5.7	3.6	0.25	1.4	0.2	0.1	—	27.3
21[b]	3.1	33	60	—	1.4	18.4	ND	—	0.25	4.1	1.8	0.09	2.1	0.16	0.06	—	28.3
22[b]	4.9	38	26	—	1.2	17.4	ND	—	0.34	7.1	2.3	0.14	0.6	0.3	0.12	—	29.6
23[a]	3.4	30	2	0.01	0.7	15.2	0.06	ND	0.42	4.2	2.3	ND	3	0.22	0.03	3.97	30.1
24[a]	5.1	28	53	0.01	1.1	20	0.18	ND	0.53	5.1	3.9	0.01	2.7	0.32	0.11	ND	34
25[b]	4.7	35	NA	—	1.3	20.9	0.56	—	0.31	6.3	2.9	0.14	1.2	0.22	0.17	—	34.1
26[a]	1.1	41	38	0.02	1.5	19.5	0.11	ND	0.41	3.4	3.3	ND	7.7	0.18	ND	ND	36.1
27[b]	6.1	37	25	—	7.6	17.2	1.19	—	0.35	6.1	2.3	0.18	1.7	0.27	0.05	—	36.8
28[b]	3	27	51	—	1.4	28.2	ND	—	0.51	7.5	2.9	0.25	0.7	0.2	0.75	—	42.4
29[b]	4.8	25	NA	—	1.8	21.6	0.94	—	0.5	9.4	4.4	0.47	5.8	0.6	0.06	—	45.5
30[b]	2.2	39	11	—	1.1	26.8	ND	—	0.75	8.9	5.3	0.58	2	0.45	0.1	—	46
31[b]	5.6	34	NA	—	2.7	31.8	ND	—	0.42	7.8	3.1	0.09	0.8	0.22	0.1	—	47
32[b]	3.4	27	10	—	2.6	30.1	0.75	—	0.57	5.9	6.5	0.32	2.5	0.34	0.09	—	49.6
33[a]	2.8	20	13	0.02	1.1	31.3	0.17	ND	0.13	10.2	5.9	0.02	1.5	0.48	0.11	2.96	53.9
34[b]	4	20	13	—	3.4	33.5	2.32	—	0.49	5.8	5.8	0.27	2.6	0.32	0.06	—	54.6
35[b]	3.3	26	17	—	1.4	32.3	0.7	—	0.66	9.6	5.7	0.46	12.4	0.51	0.05	—	63.8
36[b]	2.2	20	16	—	1.4	25.5	0.75	—	0.76	8	18.3	1.75	18.3	0.94	0.08	—	75.8
37[a]	1.1	22	51	0.04	2.2	44.3	0.55	0.03	0.64	10.8	8.1	0.02	14.7	0.56	ND	ND	81.9
38[b]	4.3	29	38	—	5.2	34.8	0.61	—	1.94	9.8	29.2	1.2	14.5	0.96	0.1	—	98.2

Table 6-13. Concentrations of PBDE Congeners in Human Milk from Nursing Mothers in the United States (2001–2004) (ng/g Lipid)

				BDE congener													
Female	Lipid (%)	Age (years)	Nursing (weeks)	17	28	47	66	77	85	99	100	138	153	154	183	209	Sum
39[a]	1	26	22	0.02	1.7	54.7	0.54	ND	1.63	23.6	10	ND	4.8	1.15	0.07	ND	98.2
40[b]	4.9	32	38	—	3.4	49.7	1.21	—	1.2	7.7	21.1	1.4	16.3	0.93	0.15	—	103.1
41[b]	3.4	30	9	—	3.9	63.1	3.13	—	2.81	30.1	16.2	3.29	17.2	1.94	0.08	—	141.6
42[b]	1.2	21	2	0.1	10.1	120.9	1.68	0.06	2.64	30.3	20.1	0.13	16.4	2.07	ND	ND	204.3
43[b]	1.2	33	15	—	8	139.6	ND	—	4.12	44.6	23	4.47	21.8	2.76	0.18	—	248.5
44[a]	1	23	2	0.06	3.6	172.4	1.14	ND	6.28	69.8	31.9	0.08	8.4	3.07	0.16	ND	296.9
45[b]	2.1	34	13	—	7.5	199.6	6.67	—	7.73	108.5	31.7	4.12	6.9	3.62	0.36	—	376.7
46[a]	1.7	33	47	0.18	6.1	196.2	2.07	0.16	6.46	111	31	0.27	15.5	7.21	1.32	8.24	385.5
47[b]	5.1	29	28	—	16.1	271.5	3.16	—	6.29	50.4	47.4	6.86	14.1	2.87	0.12	—	418.8
48	3.18	NA		0.011	0.6	9.9	0.058	NA	NA	2.7	1.3	0.022	0.62	0.13	0.072	2.4	17.81
49	3.28	NA		0.016	1.2	25	0.12	NA	NA	11	4.5	0.092	3.1	0.57	0.092	0	45.69
50	3.9	NA		0.016	4.4	41	0.098	NA	1.3	11	11	0.15	6.1	0.71	0.14	0	75.91
51	3.12	NA		0.015	2.3	37	0.11	NA	0.49	6.7	6.9	0.086	11	0.39	0.11	0	65.10
52	6.31	NA		0.01	1.8	14	0.084	NA	NA	2.9	2.9	0.033	2.1	0.17	0.1	0	24.1
53	7.04	37		0.02	0.71	16	0.13	NA	0.46	5.8	2.5	0.03	2.2	0.28	0.057	0.02	28.21
54	3.29	33		0.014	0.76	9	0.056	NA	0.14	1.5	2.1	0.01	2.6	0.094	0.051	0.05	16.37
55	2.44	38		0.02	1.2	19	0.18	NA	0.35	5	2.7	0.02	2.4	0.27	0.051	2.5	33.69
56	6.5	NA		0.005	0.9	6.1	0.088	NA	0.082	1	1.2	0.01	6.7	0.077	0.029	0.03	16.22
57	5.55	NA		0.005	0.9	6.1	0.088	NA	0.082	1	1.2	0.01	3.4	0.077	0.029	0.03	12.92
58	6.75	NA		0.046	1.5	24	0.18	NA	0.38	4.8	2.7	0.02	2.1	0.22	0.57	0.05	36.57
59	3.08	NA		0.016	1.2	10	0.086	NA	0.18	2	1.3	0.01	4	0.15	0.096	0.1	19.14

[a]Austin milk bank sample.
[b]Dallas milk bank sample.

NA = not available; ND = not detected

Source: Schecter et al. 2005

and home environments. PBDE concentrations were studied in breast milk obtained from mothers pregnant for the first time (n=39, ages 22–36 years old) from Uppsala County, Sweden (Darnerud et al. 1998). The mean value of total PBDEs (sum of eight congeners) was 4.4 ng/g fat; the major congener was BDE 47, contains ca. 55% of the total PBDEs. Lind et al. (2003) reported concentrations of PBDEs in human breast milk sampled from Uppsala County, Sweden. Total PBDEs, BDE 47, BDE 99, and BDE 100 concentrations were 4.01, 2.35, 0.62, and 0.38 ng/g lipid, respectively. In human breast milk from 25 German mothers, the concentrations of PBDEs ranged from 0.6 to 11 ng/g lipid (de Wit 2002). In 1992, the mean concentration of total PBDEs (sum of BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, and BDE 183) was 5.8 ng/g lipid weight for samples (n=6) from mothers from Ontario and Quebec, Canada (Ryan and Patry 2000). Combined samples from 1992 representing four regions of Canada and one representing all Canadian provinces had total PBDE concentrations ranging from 2.6 to 19 ng/g lipid weight; the highest concentrations were observed in the New Brunswick, Nova Scotia, and Prince Edward Island. Breast milk samples from Finland, collected between 1994 and 1998, had concentrations of total PBDEs (sum of BDE 28, BDE 47, BDE 99, and BDE 153) ranging from 0.88 to 5.9 ng/g lipid weight (Strandman et al. 2000). In Japan, breast milk samples had total PBDE concentrations (sum of BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154) ranging from 0.66 to 2.8 ng/g lipid weight (Ohta et al. 2002). Women who consumed fish had a somewhat higher concentration of total PBDEs (range, 1.4–2.8 ng/g lipid weight) compared to women who ate less fish (range, 0.67–0.87 ng/g lipid weight). BDE 47 was the major congener in most of the samples; BDE 153 concentrations were analogous to BDE 47 concentrations in some samples (Ohta et al. 2002).

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

correlation between the concentrations of BDE congeners and methoxy-brominated diphenyl ethers was observed, indicating sources other than PBDEs for these compounds.

Biomonitoring Historical Trends and Future Projections. Concentrations of PBDE in human and animal tissues have increased since their development and widespread use as flame retardants in commercial products. Blood samples collected from U.S. residents in 1973 did not contain measurable concentrations of PBDE congeners; however, many congeners have been identified at varying concentrations in U.S. blood samples since the widespread use of PBDEs as flame retardants (Schecter et al. 2005). For example, the CDC reported BDE congener concentration in serum collected in 2003–2004 from the general U.S. population (CDC 2015). The total geometric mean concentrations ranged from below the limit of detection for BDE 17 to 20.5 ng/g lipid for BDE 47. In general, body burden concentrations of PBDEs in North America are higher than in Europe due to higher historical demand and usage. Since all production and use of penta-, octa-, and now decaBDE have ceased in the United States, future biomonitoring results will likely show a gradual decline in body burden concentrations of these substances in U.S. residents as products containing PBDEs ultimately become rare. Age-dependent data on PBDE levels indicate several sources of human exposure. Serum samples collected in Australia suggest that PBDE levels increase from infant to toddler and then gradually decrease over time (Toms et al. 2009). Peak average concentrations were observed in toddlers 2.6–3 years of age (51 ng/g lipid), which is later than when breastfeeding usually ceases, suggesting a lower capacity to eliminate PBDEs or greater exposure through unique exposure pathways more common for this age group (e.g., ingestion or dermal exposure of contaminated dust particles in carpeting). The EPA Exposure Assessment of Polybrominated Diphenyl Ethers published in May of 2010, summarizes many other biomonitoring studies not discussed here and the reader is encouraged to consult this assessment for additional analysis of the environmental fate and biomonitoring of PBDEs (EPA 2010).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Humans are exposed to PBDEs by a wide variety of routes including ingestion of contaminated foods inhalation of air, ingestion of contaminated dusts/soils, and dermal exposure routes. The EPA published an exposure assessment of the U.S. population to PBDEs and determined that the overall weight-of-evidence suggested that bulk of U.S. exposures occur in indoor environments through ingestion and contact with house dust. It concluded that house dust accounts for between 80 and 90% of total exposures of the general population, with the remainder due primarily to food ingestion. Watkins et al. (2011)

determined that regular hand washing decreases the mass of PBDEs on hands from dust samples and is thus expected to reduce intake from hand-to-mouth activities.

Intake doses of BDE 47, BDE 99, BDE 100, and BDE 153 from all exposure pathways for the North American population were modeled by Wong et al. (2013). The model assumed intake of PBDEs increased exponentially to a peak in 2004, and has since exponentially declined. The intakes of BDE 47, BDE 99, BDE 100, and BDE 153 were estimated as 3.88–54, 1.59–2.39, 1.17–2.98, and 1.37–2.44 ng/kg body weight/day depending upon how the intakes were fit to measured body burden data using different elimination half-lives. Trudel et al. (2011) used eight different exposure pathways (oral uptake of food, dust, soil, and organic films; inhalation of air; and dermal uptake of dust, soil, and organic films) to model intakes of PBDEs for different age/gender groups in North American and European populations. The mean intakes for total PBDEs in the North American population were 210.0, 80.0, 79.0, 69.0, 43.0, 28.0, and 22.0 ng/kg body weight/day for infants, toddlers, children, female teenagers, male teenagers, female adults, and male adults, respectively. These concentrations are about 3–8 times greater than the estimated intakes for European populations. Lorber (2008) also estimated PBDE intake of the U.S. population through similar exposure routes. The adult intake of total PBDEs was estimated as 7.7 ng/kg body weight/day, while the intake of children aged 1–5 years was 49.3 ng/kg body weight/day. The intakes for 6–11 year olds and 12–19 year olds were estimated as 14.4 and 9.1 ng/kg body weight/day, respectively (Lorber 2008). Exposure from indoor house dust accounted for about 82% of the intake (66% from soil/dust ingestion, 16% from soil/dust dermal contact) of total PBDEs, while inhalation and ingestion of food and water accounted for <20% of the total intake. BDE 47, BDE 99, BDE 100, and BDE 209 were the predominant congeners, accounting for 26, 28, 11, and 27%, respectively, of the total intake (Lorber 2008). The EPA 2010 Exposure Assessment of Polybrominated Diphenyl Ethers calculated the adult intake dose of total PBDEs to be 7.1 ng/kg body weight/day (EPA 2010). The largest source contributing to PBDE exposure in the United States was reported to be house dust (ingestion and dermal exposure), contributing about 90% of the overall estimated intakes. The EPA exposure assessment estimated children intakes as 47.2 ng/kg body weight/day for 1–5 year olds, 13.0 ng/kg body weight/day for 6–11 year olds, and 8.3 ng/kg body weight/day for 12–19 year olds. Intake modeling using a breastfeeding pathway, which used measured milk concentrations and infant ingestion rates of human milk, led to estimated infant intakes of 141 ng/kg body weight/day (EPA 2010). While exposure to dust appears to be the predominant exposure pathway for the general population of North American residents, PBDE exposure through dietary routes appears to be more important for European communities (Abdallah and Harrad 2014; Law et al. 2008).

Breast adipose samples collected in northern California in the late 1990s contained quantifiable amounts of BDE 47, BDE 99, and BDE 153 (She et al. 2000). Mean concentrations were 18 ng/g lipid weight for BDE 47, 4.9 ng/g lipid weight for BDE 99, and 2.2 ng/g lipid weight for BDE 153. In studies of the general populations of other countries, it has also been shown that exposure to lower-brominated PBDE congeners by the general population is widespread (see Section 6.4.4; Haglund et al. 1997; Meneses et al. 1999). In general, concentrations of decaBDE in human tissues and body fluids are lower than for the lower-brominated congeners, presumably due to a more rapid elimination half-life (Trudel et al. 2011).

Consumption of fish has been associated with elevated concentrations of PBDEs in tissues from the Swedish population (Bergman et al. 1999). In Sweden, fish consumption is about 30 g/day; this translates to an estimated 0.1 μg of pentaBDE and 0.3 μg of total PBDEs from fish that is ingested by humans daily (WHO 1994a). The fish of greatest concern to humans are bottom feeders like carp and catfish. Harrad et al. (2004) estimated the daily dietary intakes of PBDEs in omnivorous and vegan diet samples from the United Kingdom. In this study, the median lower bound estimates of dietary exposure (i.e., where a congener is below the detection limit, the concentration is assumed to be zero) for BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, and total PBDEs were 46.4, 42.6, 0, 0, 0, and 90.5 ng/day, respectively (Harrad et al. 2004). The International Polar Year Inuit Health Survey in 2007–2008 evaluated PBDE blood concentration for 2,172 Inuit adults in Canada (Laird et al. 2013). The sum concentration of BDE 47, BDE 99, and BDE 100 in the general population ranged from 0.04 to 10.6 μg/L in blood plasma. Like PCBs, there may be a higher risk of exposure to PBDEs in Native Americans who reside in the Arctic region and consume whale and seal blubber (Jaret 2000).

Workers involved in the production and manufacture of PBDE-containing plastics and plastic products are exposed to PBDEs. Body burden data indicate higher concentrations for workers exposed to PBDEs than for the general population. Occupational exposure to PBDEs also occurs in workers at plants that dismantle electronic equipment, computer monitor repair technicians, and automobile drivers, as well as other professions (Lindström 1999). Occupational exposure occurs primarily by inhalation. Inhalation of vapor-phase PBDEs is expected to be low due to the low vapor pressures of PBDEs (see Table 4-4); however, the inhalation of particulate phase PBDEs is possible during plastic reprocessing where grinding or shredding of polymers with PBDEs occurs. Occupational exposure may also likely involve oral exposure to particulate PBDEs as a result of hand-to-mouth activity.

Air samples were taken from an electronics dismantling plant, an office with computers, and outdoors and then analyzed for PBDEs (Sjödin et al. 1999a, 2001a). The electronics dismantling plant had the highest

concentrations of PBDEs, with mean concentrations of 2.5 pmol/m^3 (1.25 ng/m^3) for BDE 47, 4.6 pmol/m^3 (2.6 ng/m^3) for BDE 99, 6.1 pmol/m^3 (3.93 ng/m^3) for BDE 153, 26 pmol/m^3 (18.8 ng/m^3) for BDE 183, and 38 pmol/m^3 (36.5 ng/m^3) for decaBDE (BDE 209) (Sjödin et al. 1999a, 2001a). Air samples were found to be 4–10 times higher in PBDE concentrations near a plastic shredder when compared to other locations in the plant (range, 0.42–200 ng/m^3). Concentrations of PBDEs in the office (range, <0.002–0.09 ng/m^3) were 400–4,000 times lower than in the plant, and PBDEs were not detected in outside air (Sjödin et al. 1999a, 2001a).

Lipid adjusted serum levels of 11 BDE congeners collected from the US general population were reported in the Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables (CDC 2015; also see http://www.cdc.gov/biomonitoring/). Serum levels for BDE 17, BDE 28, BDE 47, BDE 66, BDE 85, BDE 99, BDE 100, BDE 153, BDE 154, and BDE 183 were evaluated in samples collected between 2003 and 2008; BDE 209 was evaluated in samples collected from 2005 to 2008. In the NHANES 2003–2004 survey years, congener BDE 47 was detected at a concentration of 20.5 ng/g lipid (geometric mean), the highest concentration for all samples. BDE-153 had the second highest geometric mean concentration of 5.7 ng/g lipid. BDE 28, BDE 99, BDE 47, BDE 100, and BDE 153 were in ≥60% of participants (Sjödin et al. 2008). The serum levels of BDE 47, BDE 99, and BDE 153 were highest in the youngest age group (12–19 years old) and decreased for the older age groups (from 20–39 to 40–59 years old) and then increased in the ≥60 years old age group.

BDE 47, BDE 153, BDE 154, BDE 183, and decaBDE (BDE 209) were measurable in blood plasma from three groups of workers (i.e., workers at a computer disassembly plant, workers in a computerized office, and a control group) (Sjödin et al. 1999b). The median concentrations (sum of five congeners) were highest for the computer disassembly plant workers (26 ng/g lipid weight); the office workers had a median concentration of 4.1 ng/g lipid weight and the control group had a median concentration of 3.3 ng/g lipid weight. The congener patterns for the control group and office workers were similar, with BDE 47 having the highest concentrations. For the computer disassembly plant workers, the median concentrations of BDE 183, BDE 153, BDE 154, BDE 47, and BDE 209 were 7.8, 4.5, 1.2, 2.9, and 4.8 ng/g lipid weight, respectively. Blood serum samples from 19 full-time computer technicians were analyzed (Hagmar et al. 2000a). The serum concentrations of BDE 153, BDE 183, and BDE 209 in these samples were found to be approximately 5 times higher than the control and office workers in the Sjödin et al. (1999b) study. The median concentration for total PBDEs (for the sum of five congeners) was 10.6 pmol/g (7.0 ng/g) lipid weight. The highest concentrations were for BDE 153. Two octaBDE congeners and one nonaBDE congener were also detected.

6.6 EXPOSURES OF CHILDREN

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

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Body burden data, as well as intake modeling, suggest that infants and toddlers have higher exposures to PBDEs as compared to older children or adults. PBDE concentrations increase from infant to toddler and then gradually decrease over time. PBDE intake values for children have been estimated using several models (EPA 2010; Lorber 2008; Trudel et al. 2011; Wong et al. 2013). Using the model developed by the EPA, total PBDE intakes for children residing in the United States were estimated as 47.2 ng/kg body weight/day for 1–5 year olds, 13.0 ng/kg body weight/day for 6–11 year olds, and 8.3 ng/kg body weight/day for 12–19 year olds. Data from fetal tissue and several studies, including measurements of PBDE congeners from umbilical cord blood, indicate that the fetus is exposed to PBDEs through the mother.

Schecter et al. (2003, 2005) reported the first findings on concentrations of PBDEs congeners in human milk from individuals in the United States. The median concentration of the sum of PBDE congeners was 34.0 ng/g lipid with BDE 47 (18.4 ng/g lipid) as the predominant congener. DecaBDE was detected in 7 out of 47 samples with a maximum concentration of 8.24 ng/g lipid. The concentrations of PBDEs in breast milk from this study were 10–100 times greater than human tissue concentrations in Europe (Schecter et al. 2003). Guo et al. (2016) found that PBDE levels in breast milk samples declined in females from California over two sampling periods (2003–2005 and 2009–2012). The geometric mean of total PBDE congeners (sum of BDE 28, 47, 99, 100, 153, and 154) in breast milk was 67.8 ng/g lipid in the 2003–2005 sampling period (n=82) and 45.7 ng/g lipid in the 2009–2012 sampling period (n=66).

PBDE levels were shown to increase in human milk samples collected from different regions of Canada from 1992 to 2002, but declined slightly from 2002 to 2005 (Ryan and Rawn 2014). The median and geometric mean levels of total PBDEs (sum of BDE 28, 47, 99, 100, 153, 154, and 183) in collected milk samples were 2.992 and 3.536 ng/g lipids in 1992, respectively, and 22.104 and 25.162 ng/g lipid, respectively, in 2002. The median and geometric mean of total PBDEs in milk samples collected in March and April 2005 were 19.948 and 21.082 ng/g lipid, respectively.

PBDEs were detected in human placental tissues (n=102) collected between 2010 and 2011 in Durham County, North Carolina (Leonetti et al. 2016). The geometric mean concentration of total PBDE (sum of BDE 47, 99, 100, 153, 154, and 209) was 17.6 ng/g lipid. The detection frequencies of the individual congeners were: BDE 47, 91.2%; BDE 99, 68.6%; BDE 100, 88.2%, BDE 153, 93.1%; BDE 154, 83.3%; and BDE 209, 52.9%.

PBDEs were detected at a median concentration of 53,000 ng/g in a variety of toys such as hard plastic toys (racing cars, vehicles, toy weapons, etc.), foam toys, rubber/soft plastic toys (dolls and teethers), and stuffed toys that were purchased in China from 2007 to 2008 (Chen et al. 2009). These findings suggest additional possible exposure routes to children and toddlers through mouthing activities and dermal contact with toys.

PBDE congeners (predominantly BDE 47, 99, and 209) were detected in 100% of dust samples collected from 40 California daycare and preschool centers (Bradman et al. 2014). The mean and median total PBDE (BDE 47, 99, 100, 118, 153, 154, 183, 190, 197, 203, 205, 206, 207, and 209) levels in dust samples were 7,956.6 and 4,225 ng/g, respectively. Individual congeners (BDE 47, 99, 100 153, 154, and 209) were detected in indoor air samples at the facilities at mean levels ranging from 0.001 to 1.63 ng/m^3.

Hoffman et al. (2016) analyzed serum levels and handwipe samples from 83 children aged 12–36 months residing in the state of North Carolina. Correlations between serum and handwipe levels of PBDE congeners and behavioral patterns were observed. For example, increased age and increased activity was positively correlated to levels of PBDEs in serum and handwipe samples, while time spent sleeping (a measure of inactivity) was negatively correlated with PBDE levels in serum. It was reported that for each additional hour of sleep, BDE 47, BDE 99, BDE 100, and BDE 153 serum levels decreased by 12, 15, 9, and 10%, respectively, in the children. BDE 47, BDE 99, BDE 100, and BDE 153 levels in handwipes decreased 30, 31, 30, and 23% for each additional hour of sleep.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers who were involved in the production and manufacture of PBDE-containing plastics and plastic products were exposed to higher concentrations of PBDEs than the general population. Body burden data indicate higher concentrations for workers exposed to PBDEs than for the general population. Occupational exposure to PBDEs also occurs in workers at plants that dismantle electronic equipment, computer monitor repair technicians, and automobile drivers, as well as other professions (Lindström 1999). Occupational exposure occurs primarily by inhalation and ingestion of dust containing PBDEs.

Stapleton et al. (2008) examined PBDE serum concentrations in workers involved with foam recycling and carpet installation in the United States. Serum PBDE concentrations in foam recyclers (median, 160 ng/g lipid) and carpet installers (median, 178 ng/g lipid) were significantly greater than a non-occupationally exposed control group (median, 19.3 ng/g lipid).

Firefighters appear to have higher exposure potential to PBDEs and other types of flame retardants because they are exposed to the combustion products of the flame retardants as well as the original forms of the chemicals. In a study conducted to examine exposure to PBDEs in 101 firefighters from Southern California, the median and geometric mean for total PBDEs (sum of BDE 28, 47, 99, 100, and 153) in the serum of the firefighters were 59.1 and 66.2 ng/g lipid, respectively (Park et al. 2015). These levels are approximately 40% greater when compared to the general population. The median and geometric mean for the same total PBDE congeners obtained from a subset of the NHANES survey with similar age and gender as the firefighters were 36 and 40.8 ng/g lipid, respectively.

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 PBDEs is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PBDEs.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Many of the relevant physical and chemical properties of the PBDEs are available (see Tables 4-3 and 4-4). Very limited data are available on the physical and chemical properties for the individual congeners (Braekevelt et al. 2003; Tittlemier et al. 2002). Important data, such as K_{ow}, K_{oc}, vapor pressure, and Henry's Law constant, are necessary for the prediction of the environmental fate and transport of PBDEs.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2014, became available in March 2016. This database is updated yearly and should provide a list of industrial production facilities and emissions.

There are no current manufacturers of technical PBDEs in the United States. PentaBDE and octaBDE mixtures were voluntarily withdrawn from the U.S. marketplace by their manufacturers at the end of 2004, leaving only decaBDE being marketed for use in commercial products in the United States (EPA 2010). In December of 2009, the two remaining U.S. producers of decaBDE, Albemarle Corporation and Chemtura Corporation (formerly known as the Great Lakes Chemical Corporation), and the largest U.S. importer, ICL Industrial Products, Inc., announced commitments to phase out manufacture and importation of decaBDE for most uses in the United States by December 31, 2012, and to end manufacture and import for all uses by the end of 2013 (EPA 2013j). Many consumer goods enter the United States from other countries such as China. OctaBDE was never produced in China, and manufacture of the commercial pentaBDE mixture stopped in 2004; however, there are currently no restrictions on the use of decaBDE, which had a production volume of 20,500 metric tons in 2011 (Ni et al. 2013). It is unclear if items being treated with decaBDE are still entering U.S. markets from other parts of the world.

Given the importance assigned to dust ingestion as an exposure pathway to Americans, more data are needed on human bioavailability of PBDEs from external matrices, such as dust, as well as food for

exposure characterization. Characterization of the quantity of dust containing PBDEs, ingested by humans, and in particular young children, would improve exposure estimates.

Environmental Fate. Based on limited data, photolysis appears to be the dominant transformation process for some PBDEs (e.g., decaBDE) (Hua et al. 2003). PBDEs absorb light in the environmental spectrum. Hua et al. (2003) found that decaBDE and the commercial octaBDE absorbed light up to 325 nm, which indicates that these compounds may be susceptible to photodegradation at environmental wavelengths. However, the importance of photochemical transformation reactions in the environment cannot be determined due to lack of quantitative rate information (EU 2002, 2003a). Better data on degradation via hydroxyl radical reaction and photolysis are needed. Based on a very limited number of studies, biodegradation does not appear to be significant for commercial mixtures of PBDEs (EU 2002, 2003a). Limited studies have been done on biodegradation of PBDEs in the environment under both aerobic and anaerobic conditions, especially studies investigating dehalogenation mechanisms (EU 2002, 2003a). More studies are needed to determine conclusively if commercial PBDE mixtures, such as decaBDE, are degraded to lower-brominated congeners (e.g., BDE 47), which appear to bioaccumulate in fish, animals, and humans (see Section 6.4). Additional data on degradation via hydroxyl radical reaction and photolysis are needed. Since the toxicity and the environmental fate of PBDEs depend on specific PBDEs congeners, development of more data regarding congener-specific fate and transport of PBDEs in the environment are needed.

Bioavailability from Environmental Media. The absorption and distribution of PBDEs as a result of inhalation, ingestion, and dermal exposure are discussed in Sections 3.4.1 and 3.4.2. PBDEs will exist in both the vapor and particulate phase in both indoor and outdoor air, and more data are needed regarding the bioavailability of these substances in these two phases (Harrad et al. 2004) and the bioavailability of PBDEs from PBDE-contaminated toys (Chen et al. 2009).

Food Chain Bioaccumulation. An abundance of monitoring data illustrates the uptake of lower-brominated diphenyl ethers by aquatic organisms, which results in bioconcentration (see Section 6.4.4; Hardy 2002b). Congener components of the pentaBDE commercial product tend to bioconcentrate to different extents. DecaBDE and octaBDE commercial products do not bioconcentrate to the extent of the penta mixtures; however, monitoring data clearly show that even the higher-brominated congeners are taken up. More information on bioaccumulation and biomagnification of PBDE and its congeners is needed in assessing human health risks.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of PBDEs in contaminated media at hazardous waste sites are needed so that the information obtained on levels of PBDEs in the environment can be used in combination with the known body burden of PBDEs to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

More monitoring data on the concentrations of total PBDEs and PBDE congeners in air in remote, rural, and urban areas, as well as areas near hazardous waste sites and incinerators, are needed. Although concentrations are predicted to be low, monitoring data on PBDE concentrations in finished drinking water nationwide would be helpful. Sediment concentrations of PBDEs tend to be dominated by higher-brominated congeners (e.g., decaBDE or BDE 209) (deWit 2002; Dodder et al. 2002; Hale et al. 2001b, 2002). Monitoring data indicated that the concentrations of PBDEs are increasing in aquatic organisms with higher concentrations near point sources (Alaee et al. 1999; Dodder et al. 2000; Johnson and Olson 2001; Loganathan et al. 1995; Luross et al. 2000). Additional monitoring data on environmental concentrations of PBDEs would to useful to determine the extent of contamination in environmental media, and also the mechanisms of human exposure to this class of chemicals.

Exposure Levels in Humans. Body-burden data indicate that there are low-level exposures to lower-brominated PBDEs for the general population. Information about the average daily intake of PBDEs is available (Bergman et al. 1999; EPA 2010; Lindström 1999; Lorber 2008; WHO 1994a). PBDE concentrations are reported in the current literature for serum, blood, breast milk, and adipose tissue of the general population and occupationally exposed individuals (CDC 2015; EPA 2010; WHO 1994a). Additional data regarding the concentrations of PBDEs in body fluids or tissues of people who reside near hazardous waste sites are needed. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. The most important exposure pathway for infants to PBDEs likely occurs through ingestion of breast milk (EPA 2010). PBDE intakes for infants and young children are typically greater than older children and adults (EPA 2010; Lorber 2008; Trudel et al. 2011; Wong et al. 2013). Since children tend to spend more time playing in carpeting, this leads to the potential to greater exposure to PBDEs through indoor dust. PBDEs have been detected in a variety of toys such as hard plastic toys (racing cars, vehicles, toy weapons, etc.), foam toys, rubber/soft plastic toys (dolls and teethers), and stuffed toys that were purchased in China from 2007 to 2008 (Chen et al. 2009). These findings indicate additional possible exposure routes to children and toddlers through mouthing activities and dermal contact with toys. Although there has been a gradual phase-out of pentaBDE, octaBDE, and now

decaBDE, products are still in households that contain these substances. Therefore, continued biomonitoring data of infants and children is needed.

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

Exposure Registries. No exposure registries for PBDEs were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

A prospective study of 316 mothers enrolled during pregnancy being conducted at the Icahn School of Medicine at Mount Sinai, New York will examine prenatal exposure to complex mixtures of endocrine-disrupting compounds including PBDEs (RePORTER 2016).

A study being conducted at the University of California, Berkeley is designed to examine exposures and health effects in vulnerable populations, such as pregnant women and children living in California, where stricter flammability standards have resulted in very high flame retardant exposures (RePORTER 2016).

The Center for Children's Environmental Health Research at the University of California, Berkeley will examine novel methods of examining prenatal exposure to PBDEs and other compounds using shed deciduous teeth and geographic information system (GIS) methods with remote sensing (RePORTER 2016).

A study at the University of Cincinnati is investigating two groups of persistent organic chemicals for their associations with adverse effects in child neurobehavior: PBDEs and perfluoroalkyl chemicals (including perfluorooctane sulfonic acid [PFOS] and perfluorooctanoic acid [PFOA]). The research project will provide novel information to the public about the developmental neurotoxicity of these chemicals. It will also generate new data regarding PBDE exposure routes to aid in future prevention initiatives (RePORTER 2016).

A study is being conducted at the University of California, San Diego that is collecting and analyzing sediment and biota sample in the in the Southern California Bight for PBDEs (RePORTER 2016).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring PBDEs, their metabolites, and other biomarkers of exposure and effect to PBDEs. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

PBDEs are analyzed in environmental and biological samples by methods quite similar to those used for PCBs (de Kok et al. 1977; Fries 1985b; Pomerantz et al. 1978). The analytical methods for PBDEs were developed relatively recently. There have been many advances in the technology and costs of analytical instruments used in the efforts directed at PBDE analysis. GC/MS with capillary columns (i.e., congener specific) is the primary analytical technique now used for PBDEs.

Covaci et al. (2003) and Stapleton (2006) reviewed the determination of brominated flame retardants, with emphasis on PBDEs in environmental and human samples. The analysis methodology for PBDEs includes several steps: sample collection and storage, sample pretreatment, extraction, cleanup and fractionation, and analytical determination. Care must be taken to assure that the sample collection follows quality-assurance protocols and that equipment and containers are free from contamination. It is important that laboratories utilize blanks when reporting trace concentrations of PBDEs. This practice will minimize the influence of trace contamination samples that can originate from a variety of sources.

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

PBDEs are typically separated from the biological and environmental media by extraction with organic solvents. Liquid-solid extraction (e.g., Soxhlet apparatus) remains a widely used technique for solid

samples despite recent advances in other extraction techniques. Typical solvents are hexane, toluene, hexane/acetone mixtures, or dichloromethane. New extractions techniques, such as accelerated solvent extraction (ASE) or microwave-assisted extraction (MAE), are also currently used by a number of laboratories. The advantage of these techniques is lower solvent consumption and reduced extraction time. Supercritical fluid extraction with solid-phase trapping has been used for the extraction of brominated flame retardants from sediment with CO_2 as the supercritical fluid. Extraction with pressurized hot water (PHWE) has been used for the analysis of brominated analytes from sediment. Liquid-liquid extraction has been applied for river and seawater samples, using hexane/acetone mixtures. Solid-phase extraction 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 PBDEs. Lipids (e.g., oils and fats) may be destroyed with concentrated sulfuric acid treatment either directly to the extract or using impregnated silica columns. Chromatography (e.g., gel permeation, silica gel, Florisil) is used to remove other matrix interferences and to fractionate samples (Covaci et al. 2003).

The identification and quantitation of PBDEs are most often accomplished by GC techniques. Capillary or high-resolution gas chromatography (HRGC) columns capable of separating a substantial proportion of the congeners are indispensable, and GC detectors possessing high selectivity and sensitivity for the PBDEs are required. Historically, flame-ionization detectors (FID) or electron-capture detectors (ECD) were used. However, the MS detectors have become the main detection tool for PBDEs. MS detectors have selectivity for PBDEs and can distinguish and individually measure homologs that may co-elute on a particular HRGC column. The use of MS is indispensable in the definitive identification of PBDE congeners. One method of detection is ECNI as an ionization technique in combination with GC/MS analysis (de Boer et al. 2000a). This method is advantageous because it offers a high sensitivity for compounds with four or more bromine atoms. However, ECNI, although generally more sensitive and less costly than other ionization methods for PBDE analysis, does not provide information on the molecular ion cluster (as required for qualitative identification). It is also more subject to brominated interferences and does not allow the use of ^{13}C-labeled standards for quantification (Ikonomou and Rayne 2002). Conversely, electron ionization (EI) methods suffer from fragmentation of the molecular ions, creating difficulties in both identification and quantitation of congeners in full-scan and single ion monitoring (SIM) modes, respectively. For example, loss of bromine atoms from PBDE congeners during EI may lead to incorrect identification of the parent ion as a lower-brominated congener. In

addition, the relatively unpredictable fragmentation during EI restricts the utility of applying relative response factors (RRFs) of one congener for which an analytical standard is available (e.g., 2,2,4,4'-tetraBDE or BDE 47) for other members of its homolog group (e.g., tetraBDEs). This can result in either under- or overestimating concentrations of congeners for which analytical standards are not available (Ikonomou and Rayne 2002). In general, hepta- through decaBDE congeners are difficult to determine accurately by GC analysis, especially in biological samples (Ikonomou and Rayne 2002).

The analysis of BDE 209 and BDE 154 has some analytical difficulties. For example, BDE 209 (1) is not stable at high temperatures in the GC injector and GC column; (2) is sensitive to degradation by UV light (i.e., both sunlight and fluorescent light); (3) behaves differently in the MS source from those of chlorinated and lower-brominated compounds (de Boer and Cofino 2002); and (4) may easily adsorb to small dust particles in the laboratory, which may result in sample contamination (Covaci et al. 2003). Thermal decomposition of BDE 209 can be avoided using a short GC column and a thermally inert GC injection port (Beser et al. 2014). In contrast, BDE 154 usually co-elutes from most gas chromatographic columns with 2,2',4,4',5,5'-hexabromobiphenyl (PBB-153). In order to ensure the separation of BDE 154 and PBB 153, analysts need to use a sufficiently long GC column. Thus, in order to accurately determine the concentrations of BDE 209 and BDE 154 in analytical samples, analysts are required perform two separate GC measurements under different operating conditions. The difficulties in the determination of BDE 209 have been addressed through the use of liquid chromatography (LC)/MS/MS (Abdallah et al. 2009). The analytes, BDE 47, BDE 85, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, BDE 196, BDE 197, BDE 203, BDE 206, BDE 207, BDE 208, and BDE 209, were separated and ionized in a single run using an isotope dilution method for indoor dust samples.

7.1 BIOLOGICAL MATERIALS

Methods for the determination of organobromine compounds such as PBDEs generally consist of the following steps: extraction of the analyte from the sample matrix; cleanup to remove interfering compounds; and analysis (separation and quantitation). The primary method of analysis is GC coupled with MS. Analytical methods have been developed for the determination of PBDEs in blood or serum, urine, feces, adipose tissue, liver, breast milk, and hair. The methods for determining PBDE residues in biological samples are provided in Table 7-1.

Table 7-1. Analytical Methods for Determining Polybrominated Diphenyl Ethers (PBDEs) in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Animal tissues (muscle, fat, and egg)	Extraction with sulfuric acid; clean up with GPC/ silica column/carbon column	GC/MS (NCI)	No data	No data	Sellström et al. 1993
Animal serum	Extraction with CH_2Cl_2 in hexane; H_2SO_4 to remove lipids; washed with NaOH followed by distilled water, then dehydrated through anhydrous Na_2SO_4	ELISA (specific for BDE 27)	0.2 µg/L	82–138	Ahn et al. 2009
Human adipose tissue	Soxhlet extraction; clean up using 2 solid-phase extraction cartridges	Capillary GC-EILR-MS	0.05–0.30 ng/g lipid	81–103	Covaci et al. 2002
Human adipose tissue	Extraction with methylene chloride; evaporate; clean up on silica gel followed by clean up on alumina and on a carbon/silica gel column	HRGC/ HRMS	0.73–120 pg/g	No data	Cramer et al. 1990
Human liver/ adipose tissue	Extract with 2-propanol/ hexane; clean up with Lipidex 5000, column chromatography/GPC	GC/MS (NCI)	5 pg/g lipids	83 (54–116) liver; 71 (51–95) adipose	Meironyté Guvenius et al. 2001
Human milk	Extract with potassium oxalate/ethanol/diethyl ether/pentane; GPC; clean up on Florisil; elute with hexane	GC/MS (NCI/SIM)	<0.6 ng/g fat	No data	WHO 1994a
Human milk	Extract by column chromatography using hexane/dichloromethane/ hexane; clean up using GPC	GC/MS (SIM)	5 pg/g lipids	86–102	Meironyté et al. 1999
Human milk	Extract with n-hexane; clean up using multi-layer column	HRGC-LRMS or LRGC-HRMS (EI-SIM)	No data	>80	Ohta et al. 2002
Human plasma	Extract with formic acid, 2-propanol, and water on a SPE column; derivatized using diazomethane	GC/MS (NCI)	1–10 pg/g plasma	72	Thomsen et al. 2001
Human serum	Extraction with hexane/ MTBE (1:1); clean up silica gel/sulfuric acid column	GC-ECD; GC/MS (NCI)	0.7 ng/g lipid weight	69–104 (low spike); 77–104 (high spike)	Sjödin et al. 1999a

Table 7-1. Analytical Methods for Determining Polybrominated Diphenyl Ethers (PBDEs) in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human serum	Extraction with ethyl acetate, evaporated to dryness, and dissolved in DMSO	ELISA (specific for BDE 27)	0.2 µg/L	83–90	Ahn et al. 2009
Human serum	Denaturation with formic acid followed by SPE	GC/MS	140–1,300 pg/g (lipid weight)	40–106	Butt et al. 2016
Human hair	Physical extraction followed by washing with 0.3% polyoxyethylene lauryl ether and rinse with tap and distilled water; extraction using hexane/ dichloromethane	GC/MS	0.02 ng/g	No data	Malarvannan et al. 2013
Human hair	Extraction with 4 N HCl and hexane (4:1); clean up on $NaSO_4$/Florisil SPE columns (1:1); elute with hexane	GC/MS (SIM)	0.025 pg/mg hair (lower-brominated) 2.5 pg/mg hair (BDE 209)	70–90	Aleksa et al. 2012a

BDE = brominated diphenyl ether; DMSO = dimethyl sulfoxide; ECD = electron capture detection; EI = electron impact; EILR = electron impact low-resolution; ELISA = enzyme-linked immunosorbent assay; GC = gas chromatography; GPC = gel permeation chromatography; HRGC = high resolution gas chromatography; HRMS = high resolution mass spectrometry; LRGC = low resolution gas chromatography; LRMS = low resolution mass spectrometry; MS = mass spectrometry; MTBE = methyl-*tert*-butyl either; NCI = negative chemical ionization; SIM = selected ion monitoring; SPE = solid phase extraction

Determination of hydroxylated PBDEs metabolites were reported by Malmberg et al. (2005). The methylated derivatives of PBDE-OH metabolites were identified by GC-MS ECNI and EI analysis after extraction from the sample matrix, cleanup to remove interfering compounds, and methylation of the hydroxyl group. In plasma samples, the internal standard, BDE 138, had 71 and 98% recovery (relative standard deviation, 8 and 2%) on days 1 and 5 after dosing, respectively.

Residues in biological samples can be extracted using sulfuric acid, 2-propanol/hexane, methylene chloride, *n*-hexane, formic acid/2-propanol/water, or hexane/methyl *t*-butyl ether (Cramer et al. 1990; Meironyté Guvenius et al. 2001; Ohta et al. 2002; Sellström et al. 1993; Sjödin et al. 1999a; Thomsen et al. 2001). Samples are cleaned up to remove interferences using Florisil, silica gel, alumina or activated-charcoal column chromatography, gel permeation chromatography (GPC), and/or LC (Cramer et al. 1990; Meironyté Guvenius et al. 2001; Sellström et al. 1993; Sjödin et al. 1999a). Most techniques are based on analysis by GC coupled with MS (WHO 1994a). Capillary columns and temperature programming allow the separation of the different PBDE congeners. High recoveries (69–104%) of PBDE residues are obtained by the available analytical methods. Typically, the limit of quantitation for PBDE residues is about 0.7 ng/g lipid in blood serum, 5 pg/g lipid in human milk, 0.3 ng/g lipid in adipose tissue, and 0.025 pg/mg in hair (Aleksa et al. 2012a; Covaci et al. 2002; Meironyté Guvenius et al. 1999; Sjödin et al. 1999a). Additionally, a selective competitive enzyme-linked immunosorbent assay (ELISA) has been developed to detect BDE 47 (Ahn et al. 2009). This method also reports high recoveries (83–90%) and a limit of quantitation for BDE 47 in blood of 0.2 µg/L.

7.2 ENVIRONMENTAL SAMPLES

Most environmental analyses have been performed using multi-residue methods involving solvent extraction of the analytes from the sample matrix, cleanup to remove interfering compounds, determination by GC with confirmation using MS. New methods and technologies are evolving, and this has resulted in lower detection limits. Analytical methods for the determination of PBDEs in environmental samples are given in Table 7-2.

Like PCBs, air samples containing PBDEs are usually collected by pumping air through a sampler containing a glass-fiber filter and adsorbent trap to separate the particle-bound and vapor-phase fractions, respectively (Dodder et al. 2000; Hillery et al. 1997). The filters and adsorbents are then Soxhlet extracted with acetone/hexane, and the extracts are cleaned up and analyzed by high-resolution GC techniques. Beser et al. (2014) discussed a GC/MS method to quantify PBDEs that used microwave-

Table 7-2. Analytical Methods for Determining Polybrominated Diphenyl Ethers (PBDEs) in Environmental Samples

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Air pumped through glass fiber filter and adsorbent trap; filters and adsorbents are Soxhlet extracted with acetone/hexane; cleaned-up by column chromatography	GC/MS	No data	No data	Dodder et al. 2000
Air	Samples collected using a large-volume active sampler at 30 m^3/hour for 24 hours onto filters followed by microwave assisted extraction using hexane/acetone.	GC/MS	0.063–0.210 pg/m^3	80–120%	Beser et al. 2014
Air	Passive samplers set out with PUF disks; PUF disks were collected at 10-day intervals over 50 days; active samplers had low volume pump with PUF plugs housed in a glass holder; solvent extraction (collected hexane layer); washed with H_2SO_4 back extraction using dimethyl sulfoxide followed by column elution containing Florisil, hexane, and anhydrous Na_2SO_4	GC/MS	No data	41–78% (passive samplers) 42–80% (active samplers)	Hazrati and Harrad 2007
Dust	Samples collected from vacuum cleaner bags; extracted using hexane by an accelerated solvent extraction system, concentrated, treated with H_2SO_4, liquid/liquid back extraction using dimethyl sulfoxide, column elution	GC/MS	0.03 ng/g	No data	Harrad et al. 2006
Dust	Samples collected from vacuum cleaner bags; extracted using microwave-assisted solvent extraction (collected hexane layer); washed with H_2SO_4, then deionized water, and dried with anhydrous Na_2SO_4	ELISA (specific for BDE 47)	0.2 µg/L	105±22.7	Ahn et al. 2009

Table 7-2. Analytical Methods for Determining Polybrominated Diphenyl Ethers (PBDEs) in Environmental Samples

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Clean up by GFF followed by PUF plugs; extraction with dichloromethane	GC/MS	0.2–1.4 pg/L	No data	Yang et al. 2014
Water	Clean up by disk-type C18 solid-phase extraction	Capillary GC-ECD	0.12 pg/L	103±8.6 (river water); 87±10.7 (sea water)	Yamamoto et al. 1997
Sewage	Soxhlet extraction acetone:hexane (1:1, v/v), clean-up with liquid-liquid extraction with fuming sulfuric acid, GPC and silica gel column, and a basic alumina column	HRGC/MS	No data	No data	Zennegg et al. 2013
Sewage	Extract with chloroform; evaporate and dissolve residue in ethanol	GC/MS	0.06 µg/g	No data	WHO 1994a
Sediment	Extract with hexane and dichloromethane (1:1 v/v), treat with copper, sulfonate with sulfuric acid, clean and fraction using neutral, acid, and alkaline silica gel chromatography	GC/MS	1.93–227 pg/g	88.8−138	Tang et al. 2014
Sediment	Clean up by cartridge-type Florosil extraction	Capillary GC-ECD	9.7 ng/g	91±6.3	Yamamoto et al. 1997
Sediment	Pressurized hot water extraction coupled with clean up by LC	LC-GC/MS/ FID	0.71 ng/g	No data	Kuosmanen et al. 2002
Sediment	Extract with acetone; clean up on Florisil	NAA; GC/EC	<5 ng/g; <5 ng/g	No data	Watanabe et al. 1987
Fish	Extract with dichloromethane:n-hexane (1:1, v/v) column chromatography on silica and Al_2O_3	GC/MS	No data	58–106	Yang et al. 2008
Fish	Extract with acetone-hexane + hexane-ethyl ether; treatment with sulfuric acid or clean up on alumina; chromatography on silica gel	GC/EC; GC/MS	0.1 µg/g fat	No data	Andersson and Blomkvist 1981

Table 7-2. Analytical Methods for Determining Polybrominated Diphenyl Ethers (PBDEs) in Environmental Samples

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish	SE, ASE, and MAE performed followed by evaporation to dryness; dissolved in n-hexane; added silica gel, column filtered; concentrated; silica gel column followed by a basic alumina column eluted with n-hexane/ dichloromethane (1:1, v/v)	HRGC/ HRMS	24.8 pg/g	79–118 (SE) 50–96 (MAE)	Wang et al. 2010
Fish	Extract with dichloromethane on chromatography column; clean-up using GPC; fractionation using silica gel column	GC-HRMS (NCI)	5–93 pg/g	No data	Alaee et al. 2001
Fish	Extract clean up with GPC and mini-column chromato-graphy; concentration	GC/MS (NCI)	0.01–0.2 ng/g lipid	88–128	Akutsu et al. 2001
Animal tissues	Homogenize; extract with n-hexane-acetone; treatment with sulfuric acid; GPC; chromatography or silica gel chromatography or activated charcoal	GC/MS (NCI)	10 pg/g	No data	Jansson et al. 1991
Vegetables	Homogenize; MAE; extract clean up with Florisil or silica cartridge; elute with n-hexane:toluene (80:20, v/v)	GC/MS	1-3 ng/g	99–106	Bizkarguenaga et al. 2014
Vegetables	Extract with acetone/ n-hexane (1:1 v/v)	GC/MS (ion trap)	1 ng/kg dry weight	82–98 (mean)	Parolini et al. 2012

ASE = accelerated solvent extraction; BDE = brominated diphenyl ether; EC = electron capture; ECD = electron capture detection; ELISA = enzyme-linked immunosorbent assay; GC = gas chromatography; GFF = glass fibre filter; GPC = gel permeation chromatography; HRGC = high resolution gas chromatography; HRMS = high resolution mass spectrometry; LC = liquid chromatography; MAE = microwave-assisted extraction; MS = mass spectrometry; NAA = neutron activation analysis; NCI = negative chemical ionization; PUF = polyurethane foam; SE = soxhlet extraction

assisted extraction (MAE) rather than the traditional Soxhlet extraction technique in order to shorten the extraction time and quantity of solvents used. For a sampling rate of 30 m^3 per hour over a sampling duration of 24 hours, they achieved low limits of quantification (0.063 pg/$m^3$for BDE 28, BDE 49, BDE 47, BDE 66, and BDE 100; 0.105 pg/m^3 for BDE 119 and BDE 99; and 0.210 pg/m^3 for BDE 155, BDE 154, BDE 153, BDE 139, and BDE 183). Sampling of PBDEs is also performed using passive or diffusive samplers (Covaci et al. 2003). Hazrati and Harrad (2007) describe passive sampling with polyurethane foam disks (PUF) of BDE 28, BDE 47, BDE 99, and BDE 100 with mean recoveries of 57 and 62% for passive and active samplers, respectively. Harrad and Hunter (2006) performed passive air sampling with PUF disks in the United Kingdom. BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, and BDE 154 were detected using GC/MS. The detection limit for individual BDEs were approximately 0.05 pg/m^3.

Passive air sampling techniques have been developed to monitor both vapor- and particulate-phase PBDEs in indoor air through the use of a PUF disk and glass fiber filter (GFF) sampling media (Abdallah 2010). The PUF disks and GFFs were evaluated independently by initial soxhlet extraction with dichloromethane, concentration of extracts, and purification with SPE cartridge. Elution with hexane:dichloromethane (1:1, v/v), evaporation, reconstitution in methanol, and analysis using LC/MS/MS followed. BDE 47, BDE 85, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, BDE 196, BDE 197, BDE 203, BDE 206, BDE 207, BDE 208, and BDE 209 were evaluated using this technique. The octaBDE to decaBDE analytes were detected on the GFF media only, indicating that these congeners are expected to primarily be found in the particulate phase.

Residues in environmental samples can be extracted using chloroform, acetone, acetone-hexane, hexane-acetone, and hexane-ether (Andersson and Blomkvist 1981; Jansson et al. 1991; Watanabe et al. 1987; WHO 1994a). Samples are cleaned up to remove interferences using Florisil, silica gel, alumina or activated charcoal column chromatography, GPC, and/or LC (Akutsu et al. 2001; Alaee et al. 2001b; Andersson and Blomkvist 1981; Jansson et al. 1991; Watanabe et al. 1987; Yamamoto et al. 1997). Vegetable and soil samples have been prepared for analysis using, focused ultrasound solid-liquid extraction (Bizkarguenaga et al. 2014).

As for biological samples, quantitation of environmental samples is also usually done by GC. Capillary columns are required for the separation of the individual congeners in a mixture (WHO 1994a). High recoveries (88–128%) of PBDE residues in environmental samples are obtained by the available analytical methods (Akutsu et al. 2001). Typically, the limit of quantitation for PBDE residues is about

0.12 ng/mL in water, 9.7 µg/kg in sediment, and 0.2 µg/kg lipid in fish (Akutsu et al. 2001; Yamamoto et al. 1997). The first inter-laboratory study on PBDEs in environmental samples showed that there is good agreement for quantification of BDE 47 and BDE 100 congeners. Additionally, a selective competitive ELISA has been developed to detect BDE 47 in dust (Ahn et al. 2009). This method also reports high recoveries (105%) and a limit of quantitation for BDE 47 in blood of 0.2 µg/L.

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 PBDEs is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PBDEs.

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods used as biomarkers for exposure to PBDEs are available (Ahn et al. 2009; Aleksa et al. 2012a; Brilliant et al. 1978; Covaci et al. 2002; Eyster et al. 1983; Landrigan et al. 1979; Meironyté Guvenius et al. 1999; Sjödin et al. 1999a; Wolff et al. 1982). Analytical methods of sufficient precision and accuracy are presently available for the determination of PBDEs in adipose tissue, serum, breast milk, and hair (Ahn et al. 2009; Aleksa et al. 2012a; Burse et al. 1980; Covaci et al. 2002; Domino et al. 1980; Fawkes et al. 1982; Fehringer 1975a; Meironyté Guvenius et al. 1999; Sjödin et al. 1999a; Willet et al. 1978; Wolff et al. 1979a, 1979b). Additional congener standards are needed for PBDEs analysis. Only 30–40 congener standards are currently available for identification and quantification of PBDEs (Eljarrat et al. 2002; Sjödin et al. 1998). Metabolites are also important biomarkers for exposure to PBDEs. Ryden et al. (2012) discussed a GC/MS method for the analysis of hydroxylated PBDE metabolites in

human blood. GC/MS has been used to identify hydroxylated-BDE metabolites from recombinant cytochrome P450 by Simpson et al. (2015), and Gross et al. (2015) used GC/MS and GC/MS/MS.

Effect. No studies have been conducted to determine if known effects of PBDEs exposure can be quantitatively correlated with PBDE exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods of sufficient sensitivity are presently available for the determination of PBDEs in environmental samples (Akutsu et al. 2001; Andersson and Blomkvist 1981; Covaci et al. 2003; Stapleton 2006; Yamamoto et al. 1997).

Methods for determining degradation products and metabolites of PBDE are needed. There is no information in the literature of detectable biodegradation of PBDEs in the environment under aerobic or anaerobic conditions. The analysis of PBDE pyrolysis degradation products, such as PBDD/PBDF, is often disturbed by the presence of PBDEs. Ebert et al. (1999) demonstrated that by using a Florisil column in a sample clean-up process, almost complete separation of PBDEs and PBDDs/PBDFs is achieved before analysis by GC/MS.

7.3.2 Ongoing Studies

Analysis of PBDEs and other anthropogenic pollutants in marine mammals by a novel application of comprehensive two-dimensional gas chromatography with time- of-flight mass spectrometry (GCxGC/TOF-MS) is being studied at the University of California, San Diego (RePORTER 2016).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an intermediate-duration inhalation MRL of 0.006 mg/m^3 for lower-brominated PBDEs based on a NOAEL for changes in thyroid hormones in rats (Great Lakes Chemical Corporation 2000).

ATSDR has derived an acute-duration oral MRL of 0.00006 mg/kg/day for lower-brominated PBDEs based on a LOAEL for endocrine effects in rat dams and reproductive and neurobehavioral effects in F1 offspring from a series of reports (Kuriyama et al. 2005, 2007; Talsness et al. 2005). ATSDR has derived an intermediate-duration oral MRL of 0.000003 mg/kg/day for lower-brominated PBDEs based on a minimal LOAEL for decreased testosterone in male rats (Zhang et al. 2013b).

ATSDR has derived an acute-duration oral MRL of 0.01 mg/kg/day for decaBDE based on a NOAEL for neurobehavioral effects in mice (Johansson et al. 2008). ATSDR has derived an intermediate-duration oral MRL of 0.0002 mg/kg/day for decaBDE based on a minimal LOAEL for increased serum glucose in rats (Zhang et al. 2013a).

IARC has classified PBDE as a Group 3 carcinogen (*not classifiable as to its carcinogenicity to humans*) based on inadequate evidence of carcinogenicity in humans and inadequate or limited evidence in experimental animals (IARC 2014). The EPA assigns the cancer category Group D (*not classifiable as to human carcinogenicity*) to mono-, di-, tri-, tetra-, penta-, hexa-, octa-, and nonaBDEs (IRIS 2003a, 2003b, 2003c, 2003d, 2003e, 2004, 2005, 2006) and reports "*inadequate information*" to classify the specific congeners 2,2',4,4'-tetraBDE, 2,2',4,4',5-pentaBDE, and 2,2',4,4',5,5'-hexaBDE (IRIS 2008b, 2008c, 2008d). However, EPA assigns a classification of "*suggestive evidence of carcinogenic potential*" for decaBDE (IRIS 2008a). The Department of Health and Human Services has not classified PBDEs as carcinogens (NTP 2011). ACGIH has no data regarding cancer classifications for PBDEs (ACGIH 2014).

The EPA's reference doses (RfDs) for penta-, octa-, and decaBDEs are $2x10^{-3}$, $3x10^{-3}$, and $7x10^{-3}$ mg/kg/day, respectively (IRIS 2003c, 2004, 2008a). For the specific congeners 2,2',4,4'-tetraBDE, 2,2',4,4', 5-pentaBDE, and 2,2',4,4',5,5'-hexaBDE, the RfDs are $1x10^{-4}$, $1x10^{-4}$, and

$2x10^{-4}$ mg/kg/day, respectively (IRIS 2008b, 2008c, 2008d). No reference concentrations (RfCs) were derived for PBDEs.

OSHA has not set PELs to protect workers against adverse health effects resulting from exposure to PBDEs (OSHA 2013a, 2013b). No guidelines for worker exposure limits have been recommended by ACGIH (2014) or NIOSH (2014).

WHO has not established any air quality guidelines for PBDEs (WHO 2010). PBDEs are not designated as hazardous air pollutants, and no acute exposure guidelines (AEGLs) have been derived (EPA 2013a, 2014a). The Department of Energy (DOE) has established values for responding to potential releases of airborne monoBDE for use in community emergency planning. The values established by the DOE (2012) are the Protective Active Criteria (PAC-1, -2, and -3). The PAC-1, -2, and -3 values are 0.29, 3.2, and 19 mg/m^3, respectively, and represent increasing severity of effects (mild, irreversible, and life threatening, respectively) for a 1-hour exposure (DOE 2012). The American Industrial Hygiene Association (AIHA) has no Emergency Response Planning Guidelines (ERPGs-1, -2, -3) for PBDEs (AIHA 2014).

WHO has not established any drinking water guidelines for PBDEs (WHO 2011) and the EPA has not set drinking water standards for PBDEs (EPA 2009a, 2009b, 2012, 2013c, 2013d, 2014c). The FDA has not set allowable levels for PBDEs in bottled water (FDA 2013).

Under the Toxic Substances Control Act (TSCA), mono-, penta-, octa-, and decaBDEs are on the list of chemicals that manufacturers and importers must report for each plant site at which they manufactured or imported PBDEs during the reporting period specified (EPA 1998a). MonoBDE (represented by CAS Registry Number 101-55-3) has been designated as a hazardous substance pursuant to CERCLA of 1980 (EPA 2013g). The owner and operator of any facility that produces, uses, or stores a CERCLA hazardous substance is required to immediately report releases to any environmental media, if the amount released is equal to or exceeds the specified “reportable quantity” assigned to the substance. The reportable quantity for monoBDE is 100 pounds (45 kg) (EPA 2013g). However, PBDEs are no longer manufactured or imported in the United States as of January 2014 (EPA 2013j)

The Emergency Planning and Community Right-to-Know Act (EPCRA) has identified decaBDE as a toxic chemical and monoBDE as hazardous waste, and the Master Testing list includes penta-, octa-, and decaBDEs (EPA 2006, 2013e, 2014d). MonoBDE is on the Resource Conservation and Recovery Act

(RCRA) waste minimization persistent, bioaccumulative, and toxic (PBT) priority chemical list and the groundwater monitoring list (EPA 1998b, 2013f).

The international and national regulations, advisories, and guidelines regarding PBDEs in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to PBDEs

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2014
	DecaBDE	Group 3[a]	
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA	No data	ACGIH 2014
AIHA	ERPGs	No data	AIHA 2014
DOE	PACs		DOE 2012
	MonoBDE		
	PAC-1	0.29 mg/m^3	
	PAC-2	3.2 mg/m^3	
	PAC-3	19 mg/m^3	
EPA	AEGLs	No data	EPA 2013a
	Regulated toxic and flammable substances under Section 112(r) of the Clean Air Act	No data	EPA 2013b 40 CFR 68.130
	Hazardous Air Pollutants	No data	EPA 2014a
	NAAQS	No data	EPA 2014b
NIOSH	REL	No data	NIOSH 2014
	IDLH	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2013a 29 CFR 1910.1000, Table Z-1
	Highly hazardous chemicals	No data	OSHA 2013b 29 CFR 1910.119, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2013c 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories	No data	EPA 2012
	National primary drinking water regulations	No data	EPA 2009b

Table 8-1. Regulations, Advisories, and Guidelines Applicable to PBDEs

Agency	Description	Information	Reference
NATIONAL (cont.)			
	National recommended water quality criteria	No data	EPA 2014c
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2013d 40 CFR 117.3
c. Food			
FDA	Allowable levels for contaminants in bottled water	No data	FDA 2013 21 CFR 165.110
	EAFUS[b]	No data	FDA 2014
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2014
EPA	Carcinogenicity classification		
	MonoBDE	Group D[c]	IRIS 2006
	DiBDEs	Group D[c]	IRIS 2005
	TriBDEs	Group D[c]	IRIS 2003e
	TetraBDEs	Group D[c]	IRIS 2003d
	PentaBDEs	Group D[c]	IRIS 2004
	HexaBDEs	Group D[c]	IRIS 2003a
	OctaBDEs	Group D[c]	IRIS 2003c
	NonaBDEs	Group D[c]	IRIS 2003b
	DecaBDE	Suggestive evidence of carcinogenic potential	IRIS 2008a
	2,2',4,4'-tetraBDE	Inadequate information	IRIS 2008b
	2,2',4,4',5-pentaBDE	Inadequate information	IRIS 2008c
	2,2',4,4',5,5'-hexaBDE	Inadequate information	IRIS 2008d
	RfC	No data	
	RfD		
	PentaBDEs	2×10^{-3} mg/kg/day	IRIS 2004
	OctaBDEs	3×10^{-3} mg/kg/day	IRIS 2003a
	DecaBDE	7×10^{-3} mg/kg/day	IRIS 2008a
	2,2',4,4'-tetraBDE	1×10^{-4} mg/kg/day	IRIS 2008b
	2,2',4,4',5-pentaBDE	1×10^{-4} mg/kg/day	IRIS 2008c
	2,2',4,4',5,5'-hexaBDE	2×10^{-4} mg/kg/day	IRIS 2008d
	Chemical substances subject to proposed or final TSCA rules or orders		EPA 1998a
	MonoBDE	TSCA Section 5(a)(2)	
	PentaBDEs	TSCA Section 4	
	OctaBDEs	TSCA Section 4	
	DecaBDE	TSCA Section 4	
	EPCRA Section 313 Toxic Chemicals		EPA 2006
	DecaBDE	Yes	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to PBDEs

Agency	Description	Information	Reference
NATIONAL (cont.)			
	Identification and listing of hazardous waste		EPA 2013e 40 CFR 261,
	MonoBDE	Yes	Appendix VIII
	Master Testing List		EPA 2014d
	PentaBDEs	Yes	
	OctaBDEs	Yes	
	DecaBDE	Yes	
	RCRA waste minimization PBT priority chemical list		EPA 1998b 63 FR 60332
	MonoBDE	Yes	
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list		EPA 2013f 40 CFR 264, Appendix IX
	MonoBDE	Yes	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity		EPA 2013g 40 CFR 302.4
	MonoBDE		
	Statutory code	2,4	
	Final RQ pounds	100	
	Effective date of toxic chemical release reporting		EPA 2013h 40 CFR 372.65
	DecaBDE	1/1/87	
	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2013i 40 CFR 355, Appendix A
DHHS	Carcinogenicity classification	No data	NTP 2011

[a]Group 3: Not classifiable as to its carcinogenicity to humans
[b]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[c]Group D: Not classifiable as to human carcinogenicity

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; BDE = brominated diphenyl ether; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; EPCRA = Emergency Planning and Community Right-To-Know Act; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBDE = polybrominated diphenyl ether; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; RQ = reportable quantity; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

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

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

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

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

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

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.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that 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 OR 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 dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology 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 Diphenyl Ethers (PBDEs)
[lower-brominated diphenyl ethers]
CAS Numbers: 32536-52-0 (octaBDE)
Date: March 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 2
Species: Rat

Minimal Risk Level: 0.006 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Great Lakes Chemical Corporation. 2000. A 90-day inhalation toxicity study of octabromodiphenyl oxide in albino rats, dated 04/04/02. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0574171-1.

Experimental design: This is an unpublished study in which a commercial octaBDE product (Lot No. 9525DA23B, bromine content 78.7%, composition and purity not otherwise specified) was administered to groups of 10 male and 10 female Crl:CD(SD)IGS BR rats, via nose-only inhalation as a dust aerosol, in measured concentrations of 0 (filtered air-only), 1.1, 16, or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks. The mean MMADs in the low to high level groups were 2.0, 2.7, and 2.8 microns; the corresponding mean GSDs were 3.37, 3.72, and 3.01. Clinical and physical signs, body weight, food consumption, and survival were evaluated throughout the study. Ophthalmic, hematology (11 indices), serum chemistry (18 indices), and serum thyroid hormone (TSH, total T_3, and total T_4) evaluations were performed near the end of the exposure period. Urinalyses were not conducted. Comprehensive necropies, organ weight measurements, and histological examinations (including respiratory tract and thyroids) were performed following exposure termination.

Effects noted in study and corresponding doses: Hepatic, nasal, lung, thyroid, and ovarian effects were observed. The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at $\geq$16 mg/m^3 and liver weight (absolute and relative) at 202 mg/m^3. Total incidences of centrilobular hepatocellular hypertrophy in the 0, 1.1, 16, and 202 mg/m^3 groups were 1/10 (minimal), 0/10, 3/10 (all minimal), and 10/10 (6 minimal, 2 mild, 2 moderate) in males, and 0/10, 0/10, 3/10 (all minimal), and 6/10 (3 minimal, 3 mild) in females. Changes in nasal goblet cells were increased at 202 mg/m^3, but showed no clear dose-related increasing trends for incidence or severity. Total incidences of goblet cell hypertrophy (minimal or mild) were slightly increased in nasal level II of both sexes at $\geq$1.1 mg/m^3; incidences in 0, 1.1, 16, and 202 mg/m^3 exposure groups were 4/10 (all minimal), 9/10 (7 minimal, 2 mild), 6/10 (all minimal), and 10/10 (9 minimal, 1 mild) in males, and 2/10 (all minimal), 6/10 (all minimal), 4/10 (all minimal), and 8/10 (all minimal) in females. Goblet cell hypertrophy was also slightly increased in nasal level IV in males at 202 mg/m^3 (4/10, 0/10, 1/10, and 8/10, all minimal severity, not increased in females). Histological changes in the lungs included alveolar histiocytosis and chronic active inflammation that were only clearly induced at 202 mg/m^3. Total incidences of alveolar histiocytosis at 0, 1.1, 16, and 202 mg/m^3 were 3/10 (2 mild, 1 minimal), 5/10 (all minimal), 5/10 (all minimal), and 10/10 (5 minimal, 3 mild, 2 moderate) in males, and 0/10, 5/10 (all minimal), 2/10 (all minimal), and 10/10 (1 minimal, 7 mild, 2 moderate) in females. Corresponding total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10 (both minimal), and 10/10 (5 minimal, 4 mild, 1 moderate) in males, and 0/10, 1/10 (minimal), 1/10 (minimal), and 10/10 (2 minimal, 5 mild, 3 moderate) in females. Gross lung changes also occurred in both sexes at 202 mg/m^3; these included lung firmness and white discoloration and/or enlargement in the bronchial

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

Other findings included some hematological alterations in 202 mg/m^3 females that were not considered to be exposure-related (slightly increased mean activated partial thromboplastin time, and decreased mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration without effects on red blood cell counts, hematocrit, or hemoglobin levels). Serum chemistry evaluations showed that cholesterol was significantly increased (66.2% more than controls, $p<0.01$) in 202 mg/m^3 females, but the magnitude of the elevation was not considered toxicologically significant. Some other statistically significant serum chemistry alterations (increased mean globulin and total protein, decreased albumin/globulin ratio) also occurred in the 202 mg/m^3 females, but were not considered exposure-related due to small magnitudes of changes and lack of similar findings in the males.

Dose and end point used for MRL derivation: 1.1 mg/m^3

[X] NOAEL [ ] LOAEL

Considering the unclear adversity of minimal severity goblet cell hypertrophy, lack of clear dose-related increasing trends for incidence and severity of this nasal effect, identification of both a NOAEL (1.1 mg/m^3) and LOAEL (16 mg/m^3) for changes in thyroid hormones, and abundant evidence for thyroid effects of PBDEs in oral studies, the NOAEL for effects on thyroid hormones is the most appropriate basis for derivation of the MRL.

Uncertainty factors used in MRL derivation:

[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability
[X] 3 modifying factor for incomplete database

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

Was a conversion used from intermittent to continuous exposure? The NOAEL was adjusted to continuous exposure as follows: 1.1 mg/m^3 x 6 hours/24 hours x 5 days/7 days = 0.196 mg/m^3

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The human equivalent NOAEL ($NOAEL_{HEC}$) was calculated from the duration-adjusted NOAEL ($NOAEL_{ADJ}$) using EPA RfC methodology as follows:

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

The RDDR for the extrathoracic region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculate the RDDR of 2.7: MMAD of 2.0 μm with a

mean GSD (sigma g) of 3.37; default human body weight of 70 kg, and a default female F344 rat body weight of 180 g.

Based on these values, the MRL for lower brominated diphenyl ethers is derived as follows:

$$MRL = NOAEL_{HEC} \div (UF \times MF) = 0.53 \div (30 \times 3) = 0.006 \text{ mg/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: This is the only intermediate-duration inhalation study of PBDEs.

The thyroid is a sensitive target of lower-brominated BDEs in orally exposed animals. A LOAEL for reduced serum T_4 hormone levels in rat dams that were exposed to 2,2',4,4',5-pentaBDE (BDE 99) (Kuriyama et al. 2007) was used as a co-critical end point for the basis for the acute oral MRL for lower-brominated BDEs. This study is supported by numerous studies that report reduced serum T_4 levels in adult, nonpregnant mice and rats following acute exposure to commercial pentaBDE mixtures (Bromkal 70, Bromkal 70-5 DE, DE-71), and the commercial octaBDE mixture DE-79, or 2,2',4,4'-tetraBDE (BDE 47), indicating significant reductions of 19–92% following gavage exposure at doses ≥10 and ≥0.8 mg/kg/day in rats and mice, respectively, for 1–14 days (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998, 2002; Hallgren et al. 2001;Hoppe and Carey 2007; Richardson et al. 2008; Stoker et al. 2004, 2005; Zhou et al. 2001). In developing animals, numerous studies have reported decreased serum T_4 and/or T_3 levels in pups after gestational and lactational exposure to commercial pentaBDE mixtures (DE-71, Bromkal 70-5 DE), BDE 99, or BDE 47 at doses as low as 0.3 mg/kg/day in rats and 452 mg/kg/day in mice (Blanco et al. 2013; Bondy et al. 2011, 2013; Ellis-Hutchings et al. 2006; Kodavanti et al. 2010; Kuriyama et al. 2007; Miller et al. 2012; Poon et al. 2011; Shah et al. 2011; Skarman et al. 2005; Szabo et al. 2009; Wang et al. 2011a; Zhou et al. 2002).

Hepatic effects observed in critical study also support the selected point of departure (POD), as a dose-related increased centrilobular hepatocellular hypertrophy was observed in males and females exposed to octaBDE at concentrations ≥16 mg/m^3; however, this end point was not selected as a co-critical effect, as the increase in incidence was only significant at 202 mg/m^3 (Great Lakes Chemical Corporation 2000).

Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polybrominated Diphenyl Ethers (PBDEs)
[lower-brominated diphenyl ethers]
CAS Numbers: 60348-60-9 (2,2',4,4',5-pentaBDE)
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 24, 60, 63
Species: Rat

Minimal Risk Level: 0.00006 ($6x10^{-5}$) [X] mg/kg/day [ ] ppm [ ] mg/m^3

References: Kuriyama SN, Talsness CE, Grote K, et al. 2005. Developmental exposure to low dose PBDE 99: effects on male fertility and neurobehavior in rat offspring. Environ Health Perspect 113(2):149-154.

Talsness CE, Shakibaei M, Kuriyama SN, et al. 2005. Ultrastructural changes observed in rat ovaries following in utero and lactational exposure to low doses of a polybrominated flame retardant. Toxicol Lett 157(3):189-202.

Kuriyama SN, Wanner A, Fidalgo-Neto AA, et al. 2007. Developmental exposure to low-dose PBDE-99: Tissue distribution and thyroid hormone levels. Toxicology 242(1-3):80-90.

Experimental design: In the first study (Kuriyama et al. 2005), pregnant rats (16–20/group) were given a single dose of 2,2',4,4',5-pentaBDE (BDE 99, 98% purity) at 0, 0.06, or 0.3 mg/kg via gavage in peanut oil vehicle on GD 6. Dams were allowed to deliver, and litter size was not artificially altered. Emergence of postnatal reflexes and developmental landmarks (eruption of incisors, fur development, eye opening, and testes descent) was evaluated in all pups (163–200/group). Locomotor activity was evaluated over 24-hour periods on PNDs 36 and 71 in one male and female per litter (16–20 litters/group). F1 male offspring were sacrificed as adults (~PND 140, 12 males/group) and the thymus, spleen, liver, testis, epididymis, seminal vesicle, and ventral prostate were weighed. The right testis and caudal epididymis were retained for spermatid and sperm counts and morphology, respectively. Additionally, blood was collected for analysis of testosterone and LH levels. In 15–19 F1 males/group, reproductive function was assessed at ~PND 150. F1 males were mated with untreated females in a 1:1 ratio for 14 days. The ability of males to impregnate unexposed females was assessed, and pregnant dams were sacrificed on GD 21 for assessment of the number of implantations, resorptions, and fetuses in the F2 generation. Uterine and fetal weight was recorded, and fetuses were sexed and examined for external anomalies. In a separate group of F1 males, male sexual behavior was assessed in 20 males/group at ~PND 160. F1 males were mated with untreated females in estrus (1:1) and the sexual behavior of each mating was recorded for 20 minutes.

In the second study (Talsness et al. 2005), pregnant rats (14–17/group) were exposed to BDE 99 according to the exposure protocol for Study 1. The F1 offspring were weaned on PND 22. The female offspring were necropsied in estrus (based on vaginal cytology) on approximately PND 90. Histological evaluation of the ovary (10/group), uterus (5–7/group), and vagina (5–9/group) was performed. Ovarian follicles were counted in 10 ovaries from each group. One ovary from one female offspring in each group was analyzed by transmission electron microscopy. Twenty virgin F1 females per group were mated with non-exposed males to evaluate fertility. The F1 dams were sacrificed on GD 21 and the uterus was excised. The uterine and F2 fetal weights and the number of implantations, resorptions, and fetuses were

determined. The F2 fetuses were examined for external anomalies and when present, they were stained and examined for skeletal anomalies.

In the third study (Kuriyama et al. 2007), pregnant rats (15–20/group) were exposed to BDE 99 according to the exposure protocol for Study 1. On PND 1, approximately half of the dams (8–10/group) and their offspring were sacrificed. Liver samples were collected for enzyme activity (EROD, UDPGT) and blood was collected for determination of thyroid hormones (T_3, free-T_3, T_4, free-T_4). In pups, blood and liver tissue were pooled by gender on a litter basis. On PND 14, 2 pups/sex/litter (7–11 litters/group) were sacrificed, and liver samples and blood were collected for analysis. On PND 22, remaining dams (7–11/group) and 2 pups/sex/litter were sacrificed, and liver samples and blood were collected for analysis.

Effects noted in study and corresponding doses:

Study 1 (Kuriyama et al. 2005): No exposure-related effects were observed for the age at fur development or eye opening, testes descent, or the ability to master the rotating rod test. However, significant delays in the eruption of incisors in F1 pups and the development of the cliff-drop aversion reflex were observed in F1 males in the 0.3 mg/kg group, compared with controls. Total activity, time spent active, the duration of activity per active phase, and the total activity per active phase were all significantly increased in F1 offspring on PND 36 in the 0.3 mg/kg group, compared with controls. On PND 71, the increased total activity and time spent active persisted in the 0.3 mg/kg group, and was also significantly increased in the 0.06 mg/kg group. In the group sacrificed on PND 140, no exposure-related changes were observed in body weight, liver weight, or thymus weight; however, absolute spleen weight was significantly increased by 9% in the 0.06 and 0.3 mg/kg groups, and relative spleen weight was significantly increased by 12% in the 0.06 mg/kg group. Compared with controls, significantly altered male reproductive organ weights at PND 140 included a 10 and 11% decrease in relative testes and epididymis weight, respectively, in the 0.3 mg/kg group and a 5% decrease in relative epididymis weight in the 0.06 mg/kg group; no significant changes were observed in absolute organ weights. In both dose groups, the number of spermatids and sperm and daily sperm production were significantly decreased, compared with controls. No exposure-related effects were observed for sperm morphology. No changes were observed in serum testosterone or LH levels. Despite sperm alterations, no significant exposure-related effects were observed in male reproductive function or the majority of male sexual behaviors. The only significantly altered male sexual behavior was a 32% decrease in the percent of males with two or more ejaculations.

Study 2 (Talsness et al. 2005): No statistically significant, exposure-related histological changes were observed at the light microscopic level in the ovary, uterus, or vagina of female offspring, and no exposure-related effects were observed in the number of ovarian follicles. However, multiple ultrastructural changes were noted in the ovaries of PND 90 female offspring from dams exposed to 0.06 or 0.3 mg/kg, including destruction of the surface of the serosal epithelial cells, necrosis, and numerous vesicular structures with dense granular material within the cytoplasm. Additional changes observed in the 0.3 mg/kg group included degenerative changes and aggregates of small and large vesicles filled with homogeneously dense granular material in the cytoplasm and clumped chromatin within the condensed nucleus. No exposure-related changes were found for F1 female pregnancy rate, total implantation sites, implantation sites/dam, F2 fetuses/gravid dam, or total number of live F2 fetuses. However, the resorption rates were 12 and 15% in the 0.06 and 0.3 mg/kg groups, respectively, compared with the control rate of 9%. Statistics were not reported; however, the resorption rates in the exposed rats were also reportedly increased compared with historical controls (average control resorption rate=5.4%, with rates up to 10% considered to be within normal limits). In addition, the percentage of litters with resorptions was higher in the exposed females, being 47% in the control group and 69 and 72% in the 0.06 and 0.3 mg/kg groups, respectively. In F2 pups, mean fetal weight was significantly increased by 5% in the 0.06 mg/kg group, but not in the 0.3 mg/kg group, compared with controls. Three fetuses from different litters in the 0.3 mg/kg/day group showed skeletal anomalies (tail, skull, vertebrae); however,

this incidence of anomalies in 3/18 litters is not significantly elevated compared with the control incidence of 0/19 (Fisher's exact test, performed for this review).

Study 3 (Kuriyama et al. 2007): Serum T_4 levels were significantly decreased by 23–33% in the 0.06 and 0.3 mg/kg dams, sacrificed on PND 1. No changes were observed in T_3, free-T_3, or free-T_4 at PND 1 or any thyroid hormone levels at PND 22 in dams. In pups, no dose-related changes were observed at PND 1 or 14. At PND 22, serum T_4 was significantly decreased by in F1 males and females and serum free-T_4 was significantly decreased in F1 females from the 0.3 mg/kg group (19–23% reductions). Hepatic EROD activity was significantly decreased in PND 22 dams from the 0.3 mg/kg group; no other changes in hepatic enzyme activity were observed in dams. In F1 offspring, hepatic UDPGT activity was significantly increased in females at PND 1 and EROD activity was significantly elevated in males at PND 22; no other changes in hepatic enzyme activity were observed in F1 offspring.

Dose and end point used for MRL derivation: 0.06 mg/kg

[ ] NOAEL [X] LOAEL

Collectively, these studies indicate a LOAEL of 0.06 mg/kg for endocrine effects in F0 dams (reduced serum T_4) and reproductive and neurobehavioral effects in F1 adult offspring (impaired spermatogenesis, ultrastructural changes in ovaries, increased resorptions in F1 females mated to unexposed males, and increased spontaneous motor activity). A NOAEL was not identified.

Uncertainty factors used in MRL derivation:

[X] 10 for extrapolation from a LOAEL to a NOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable (gavage studies).

Was a conversion used from intermittent to continuous exposure? Not applicable (single exposure studies).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL:

Support for reproductive effects in F1 animals as a co-critical end point: In a companion study to the critical studies described above, pregnant rats (8/group) were administered 2,2´,4,4´-tetrabromodiphenyl ether (BDE 47, 98% purity) at 0, 0.14, or 0.7 mg/kg via gavage in peanut oil vehicle on GD 6 (Talsness et al. 2008). As observed in pentaBDE-exposed F1 females, ultrastructural changes (accumulation of vesicular structures with homogeneously dense granular material in the cytoplasm of the stromal cells, large vacuoles) were observed in the ovaries of F1 females from both dose groups on PND 100. No exposure-related changes were observed in F1 female fertility or F2 litter parameters. F1 males were not evaluated for developmental reproductive effects following tetraBDE exposure.

Support for altered open-field activity in F1 animals as a co-critical end point: Alterations in open-field activity have been consistently reported in mice exposed to BDE 99 at doses ≥0.8 mg/kg on PND 3 or 10 and evaluated at 2–8 months of age, characterized by decreased activity during the first 20-minute period

followed by increased activity during the third 20-minute period (Eriksson et al. 2002b, 2006; Fischer et al. 2008; Sand et al. 2004; Viberg et al. 2002, 2004a, 2004b). These findings indicate an initial decrease in activity, but also a lack of habituation to new surroundings. The study authors noted that this nonhabituating behavior profile (i.e., decreased activity early in the test period and increased activity late in the test period) has also been reported in adult mice neonatally exposed to certain PCB congeners. Several other 1-day exposure studies have reported similar findings in rats and mice following exposure to various lower-brominated PBDEs. Decreased spontaneous activity and/or impaired habituation was observed in rats exposed to BDE 99 at 8 mg/kg on PND 10, mice exposed to 2,2',4,4',5,5'-hexaBDE (BDE 153) at ≥0.45 mg/kg on PND 10, mice exposed to BDE 47 at 10.5 mg/kg on PND 10, mice exposed to the 2,2',3,4,4',5',6-heptaBDE (BDE 183) at 15.2 mg/kg on PND 3, and mice exposed to the 2,2',3,4,4',5,5',6-octaBDE (BDE 203) at 16.8 mg/kg on PND 3 or 10 (Eriksson et al. 2001; Viberg et al. 2003a, 2005, 2006). Increased vertical activity was significantly increased at 4 months, but not at 2 months, in mice exposed to BDE 47 at ≥1 mg/kg on PND 10; no changes were observed in horizontal activity or habituation (Gee and Moser 2008). No changes in open-field behavior were observed in mice exposed to BDE 183 at 15.2 mg/kg or 2,2',3,3',4,4',5,5',6-nonaBDE (BDE 206) at 18.5 on PND 10 (Viberg et al. 2006).

Additional neurobehavioral changes observed in the studies described above included learning and memory impairments in the Morris water maze or radial arm maze in mice exposed to BDE 99 at 0.8 mg/kg on PND 10, mice exposed to BDE 153 at ≥0.9 mg/kg on PND 10, and mice exposed to BDE 203 at 16.8 mg/kg on PND 10, and in rats exposed to BDE 47 at ≥1 mg/kg on PND 10 (Fischer et al. 2008; He et al. 2009, 2011; Viberg et al. 2003a, 2006).

Support for decreased serum T_4 in F0 dams as a co-critical end point: Numerous studies report reduced serum T_4 levels in adult, nonpregnant mice and rats following acute exposure to commercial pentaBDE mixtures (Bromkal 70, Bromkal 70-5 DE, DE-71), the commercial octaBDE mixture DE-79, or BDE 47. Significant reductions of 19–92% have been reported following gavage exposure at doses ≥10 and ≥0.8 mg/kg/day in rats and mice, respectively, for 1–14 days (Darnerud and Sinjari 1996; Fowles et al. 1994; Hallgren and Darnerud 1998, 2002; Hallgren et al. 2001;Hoppe and Carey 2007; Richardson et al. 2008; Stoker et al. 2004, 2005; Zhou et al. 2001).

Toxicokinetic considerations: Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polybrominated Diphenyl Ethers (PBDEs)
[lower-brominated diphenyl ethers]
CAS Numbers: 5436-43-1 (2,2',4,4'-tetraBDE)
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 164
Species: Rat

Minimal Risk Level: 0.000003 ($3x10^{-6}$) [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Zhang Z, Zhang X, Sun Z, et al. 2013b. Cytochrome P450 3A1 mediates 2,2',4,4'-tetrabromodiphenyl ether-induced reduction of spermatogenesis in adult rats. PLoS ONE 8(6):e66301. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0066301. August 14, 2014.

Experimental design: Male rats (20/group) were administered 2,2',4,4'-tetrabromodiphenyl ether (BDE 47; ≥98.7%) at 0, 0.001, 0.03, or 1 mg/kg/day via gavage in corn oil 6 days/week for 8 weeks. Twenty-four hours after the final BDE 47 treatment, rats were sacrificed. Testes were fixed for histological analysis and labeling of apoptotic cells or prepared for analysis of sperm production. Daily sperm production was estimated by dividing the total number of mature spermatids per testis by 6.1 (i.e., the days of the seminiferous cycle that the spermatids are present in the seminiferous epithelium). Testicular samples were examined for ROS and mRNA expression of apoptosis related proteins (ser15, ser473, p53, PTEN, AKT, BAD, caspase 3, FAS, FASL). Serum levels of E2, FSH, LH, and testosterone were measured.

Effects noted in study and corresponding doses: Histological examination of the testes showed a significant increase in the number of multinucleated giant cells (arising from spermatocytes that aborted meiosis) at ≥0.03 mg/kg/day and abundant vacuolar spaces in the seminiferous epithelium at 1 mg/kg/day (quantitative data not reported). Additionally, the number of apoptotic cells was significantly increased by 1.9- and 3-fold in the testes of rats from the 0.03 and 1 mg/kg/day groups, respectively, and the mRNA levels of several apoptosis genes were elevated in a dose-related manner. Daily sperm production was significantly decreased by 23% in the 1 mg/kg/day group, compared with controls. Serum testosterone was significantly decreased by ~34, 53, and 62% in the 0.001, 0.03, and 1 mg/kg/day groups, respectively, compared with controls. No exposure-related changes were observed in serum E2, FSH, or LH levels. Testicular ROS levels were significantly elevated at 1 mg/kg/day, compared with controls.

Dose and end point used for MRL derivation: 0.001 mg/kg/day

[ ] NOAEL [X] LOAEL [ ] $BMDL_{1SD}$

BMD modeling was performed on the serum testosterone data to assess suitability of this approach for determining the POD. Since testosterone data were presented graphically, GrabIt! software was used to extract the means and standard deviations. The data are shown in Table A-1.

Table A-1. Digitally Extracted Serum Testosterone Levels Following Exposure to BDE 47 (Zhang et al. 2013b)

Dose (mg/kg)	Mean testosterone level (ng/mL)	Standard deviation (ng/mL)
0	9.8	0.8
0.001	6.5	1.6
0.03	4.6	1.1
1	3.7	1.5

Modeling was performed using the reference benchmark response (BMR) of 1 standard deviation change from the mean (1SD). Results are shown in Table A-2 and Figure A-1.

Table A-2. Modeling Results for Decreased Serum Testosterone Levels Following Exposure to BDE 47 (Zhang et al. 2013b)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c]			AIC	BMD_{1SD} (mg/kg)	$BMDL_{1SD}$ (mg/kg)
				Dose below BMD	Dose above BMD	Overall largest			
Constant variance									
Exponential (model 2)[d]	<0.0001	0.14	<0.0001	-3.34	0.20	3.96	108.73	0.54	0.32
Exponential (model 3)[d]	<0.0001	0.14	<0.0001	-3.34	0.20	3.96	108.73	0.54	0.32
Exponential (model 4)[d]	<0.0001	0.14	0.11	0.00	0.00	1.13	66.79	0.0003	0.0002
Exponential (model 5)[d]	<0.0001	0.14	N/A	0.00	0.00	1.13	68.79	0.0003	0.0002
Hill[d]	<0.0001	0.14	0.18	0.02	-0.10	1.00	66.09	0.0002	0.0001
Linear[e]	<0.0001	0.14	<0.0001	-3.34	0.10	3.99	109.09	0.65	0.45
Polynomial (2-degree)[e]	<0.0001	0.14	<0.0001	-3.34	0.10	3.99	109.09	0.65	0.45
Polynomial (3-degree)[e]	<0.0001	0.14	<0.0001	-3.34	0.10	3.99	109.09	0.65	0.45
Power[d,e]	<0.0001	0.14	<0.0001	-3.34	0.10	3.99	109.09	0.65	0.45

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BDE = brominated diphenyl ether; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation

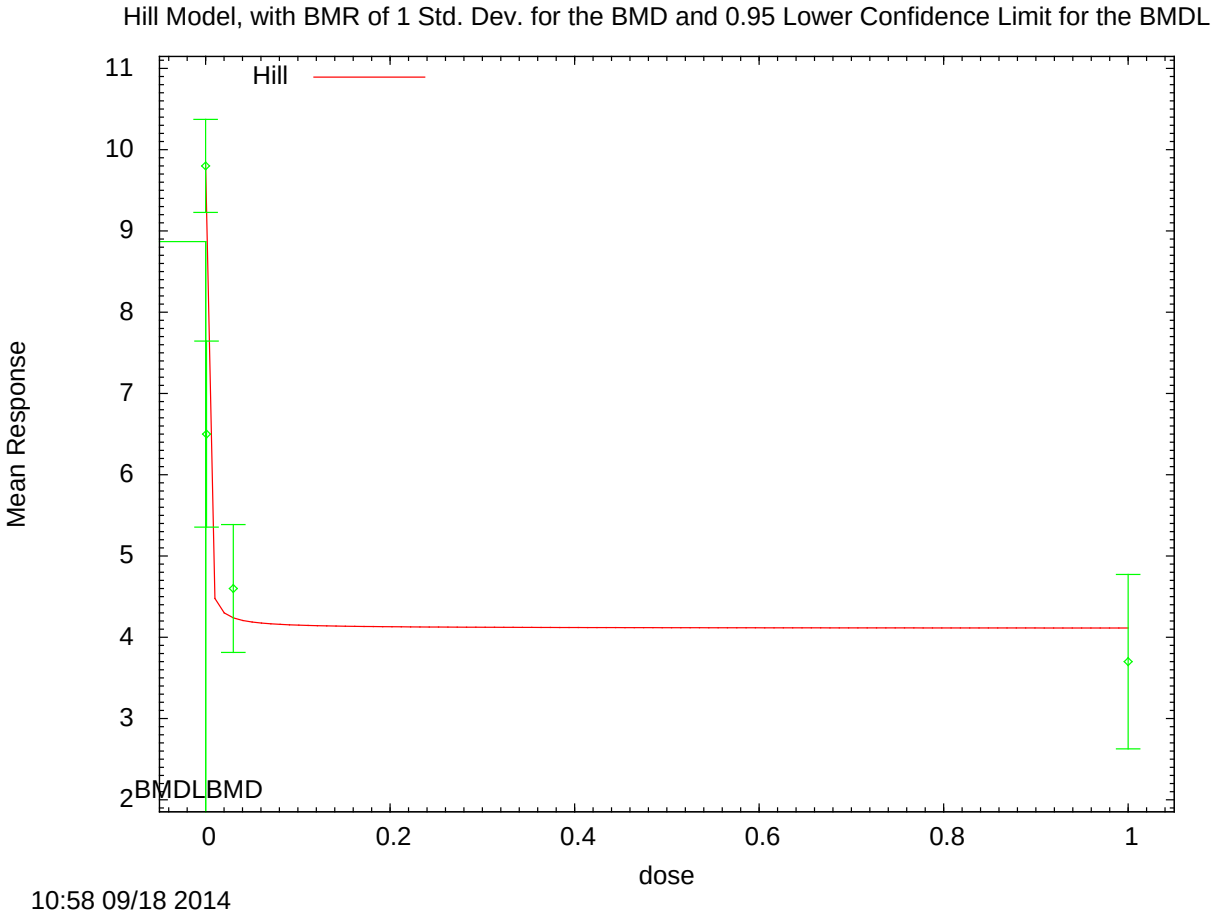

Figure A-1. Fit of Hill Model to Data for Decreased Serum Testosterone Levels Following Exposure to BDE 47 (Zhang et al. 2013b)

Goodness-of-fit statistics indicate inadequate fit to the data for all models except the Exponential 4 and Hill models, which were considered unsuitable for use in MRL derivation because they did not provide reliable information about the shape of the dose-response curve. For example, using the BMR of 1SD, the BMD, which should be within the range of the data points for best model performance, is a full order of magnitude lower than the lowest dose used in the study. When an alternate BMR of 50% change from the mean (50RD) was used in order to get the BMD within the range of observation, the BMDL calculation failed (data not shown). The observed instability in the BMD and BMDL calculations indicates that the model is not suitable for use in MRL derivation.

In the absence of a suitable model, the minimal LOAEL of 0.001 mg/kg/day for decreased serum testosterone was chosen as the POD for MRL derivation; no NOAEL was identified. The change in testosterone is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, this statistically significant reduction in serum testosterone is considered an early indication of damage to the male reproductive system, considering the additional effects observed at ≥0.03 mg/kg/day (histological lesions in testes, sperm effects).

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable (gavage study).

Was a conversion used from intermittent to continuous exposure? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: One additional rat study and a mouse study reported histopathological changes in the testes following intermediate-duration exposure to tetraBDE at ≥0.03 mg/kg/day; neither study evaluated serum testosterone levels (Huang et al. 2015; Wang et al. 2013). In the rat study, a NOAEL of 0.001 mg/kg/day and a LOAEL of 0.03 mg/kg/day were identified for increased epithelial thickness and spermatocyte apoptosis in the testes of males exposed to BDE 47 for 8 weeks via gavage (Huang et al. 2015). In the mouse study, a NOAEL of 0.0015 mg/kg/day and a LOAEL of 0.045 mg/kg/day were identified for germ cell loss and increased apoptosis in the testes of males exposed to BDE 47 for 30 days via gavage (Wang et al. 2013). Testis sections in control and 0.0015 mg/kg/day groups were normal. In the 0.045, 0.15, and 30 mg/kg/day groups, "some" seminiferous tubules exhibited complete germ cell loss and had a Sertoli cell-only phenotype (no incidence data reported). No exposure-related changes were observed in Leydig cells. The TUNEL assay showed a significant, dose-related increase in the number of apoptotic cells. Quantitative data were not reported; however, from the qualitative figures, it appears that apoptotic cells were observed at doses ≥0.045 mg/kg/day.

No other study evaluated testicular histopathology or serum testosterone levels in male laboratory animals following exposure to tetraBDE (BDE47). Following intermediate exposure to other congeners, no changes in testicular histology were observed in rats exposed to commercial pentaBDE mixtures (Bromkal 70-5 DE; DE-71) at gavage doses up to 250 mg/kg/day for 15–28 days (Becker et al. 2012; Oberg et al. 2010), commercial penta- or octaBDE mixtures (DE-71, unspecified octa mixture) at dietary doses up to 750 mg/kg/day for 28–90 days (IRDC 1976, 1977; WIL Research Laboratories 1984), or a dietary PBDE mixture containing 52.1% pentaBDE (DE-71), 44.2% decaBDE (BDE 209), and 0.4% octaBDE (DE-79) at doses up to 20 mg/kg/day for 70 days (Ernest et al. 2012). However, testicular apoptosis was not evaluated in any of these studies. Serum testosterone was significantly decreased by 40–45% in rats exposed once to BDE 99 at 0.06 or 1.2 mg/kg (Alonso et al. 2010). Other studies evaluating serum testosterone levels after intermediate-duration exposure to lower-brominated PBDEs mixtures (DE-71, dietary PBDE mixture described above) did not report exposure-related decreases (Becker et al. 2012; Ernest et al. 2012; Stoker et al. 2005). These data suggest that individual congeners (BDE 47, BDE 99) may have a greater capacity to alter serum testosterone levels than PBDE mixtures.

One-generation studies of the BDE 47 congener reported developmental effects at ≥0.03 mg/kg/day, including:

- Impaired spatial learning in the Barnes maze in PNW 8 offspring of mouse dams fed cornflakes dosed with BDE 47 from pre-mating day 28 through PND 21 (Koenig et al. 2012).

- Decreased center-field activity in an open field (indicating increased anxiety) in PND 60 female offspring from mouse dams fed cornflakes dosed with BDE 47 from pre-mating day 28 through PND 21 (Ta et al. 2011).

- Decreased pre-weaning weight, decreased pup vocalizations on PNDs 8–10, and decreased sociability on PND 72 in female offspring of mouse dams exposed to BDE 47 via gavage from pre-mating day 28 through PND 21 (Woods et al. 2012)

Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Polybrominated Diphenyl Ethers (PBDEs) [decabromodiphenyl ether (decaBDE)]
CAS Numbers:	1163-19-5
Date:	February 2017
Profile Status:	Final
Route:	[ ] Inhalation [X] Oral
Duration:	[X] Acute [ ] Intermediate [ ] Chronic
Graph Key:	12
Species:	Mouse

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm [ ] mg/m^3

References: Johansson N, Viberg H, Fredriksson A, et al. 2008. Neonatal exposure to deca-brominated diphenyl either (PBDE 209) causes dose-response changes in spontaneous behavior and cholinergic susceptibility in adult mice. Neurotoxicology 29:911-919.

Buratovic S, Viberg H, Fredriksson A, et al. 2014. Developmental exposure to the polybrominated diphenyl ether PBDE 209: Neurobehavioural and neuroprotein analysis in adult male and female mice. Environ Toxicol Pharmacol 38(2):570-585.

Experimental design: In the first study (Johansson et al. 2008), neonatal male mice (3–4 litters/group) were given single doses of 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209, 98% purity) at 0, 1.34, 2.22, 13.4, or 20.1 mg/kg via gavage in a 20% fat emulsion vehicle (1:10 mixture egg lecithin and peanut oil) on PND 3. Mice were observed for clinical signs of toxicity and body weight was measured at PND 3 and PNW 4. Spontaneous motor behavior (locomotion, rearing, total activity) was evaluated in an open field at 2 months (10 mice/group) and 4 months (16 mice/group). Motor activity was measured during a 60-minute period, divided into three 20-minute intervals. Nicotine-induced behavior was evaluated at 4 months following single subcutaneous injections of 80 µg nicotine/kg (8/group) or 10 mL 0.9% NaCl/kg (8/group). Anxiety was assessed at 4 months using the elevated plus maze.

In the second study (Buratovic et al. 2014), neonatal male mice (6 litters/group; 31–40 males and 23–34 females per group) were administered 2,2',3,3',4,4',5,5',6,6'-decaBDE (BDE 209, >95% purity) at doses of 0, 1.34, 5.76, or 13.4 mg/kg via gavage in a 20% fat emulsion vehicle (1:10 mixture egg lecithin and peanut oil) on PND 3. Mice were observed for clinical signs of toxicity and body weight changes throughout the study (no further details were provided). Spontaneous motor behavior (locomotion, rearing, total activity) was evaluated in an open field at 2 months (18/sex/group). Motor activity was measured during a 60-minute period, divided into three 20-minute intervals. Directly after spontaneous motor evaluation, 9/sex/group were injected with a cholinergic agent (0.25 mg/kg paraoxon in males, 80 µg/kg nicotine in females), while the other 9/sex/group were injected with 0.9% saline, for evaluation of cholinergic-induced locomotion. At 4 months, spontaneous behavior was assessed again in the saline-injected animals only (9 males/group at all doses and 9 females/group in the control and high-dose group only). Learning and memory was assessed using the Morris water maze at 5 and 7 months in 13–15 males from the 0, 5.76, and 13.4 mg/kg groups only (the same mice were evaluated at each time point). Male and female mice were sacrificed at 7 months. The cerebral cortex and hippocampus from control and high-dose males and females were removed and processed for neuroprotein analysis using Western blot.

Effects noted in study and corresponding doses:

Study 1 (Johansson et al. (2008): No clinical signs of toxicity or body weight effects were observed. At 2 months, significantly decreased locomotion, rearing, and total activity were observed during the first 20-minute interval of the open field assessment in mice exposed to ≥2.22 mg/kg, compared with controls. However, during the third 20-minute interval, when activity should decrease due to habituation, locomotion, rearing, and total activity were significantly increased in mice exposed to ≥13.4 mg/kg. None of the end points measured were significantly altered at 1.34 mg/kg. At 4 months, significantly decreased locomotion, rearing, and total activity were observed during the first interval of the open field assessment in mice exposed to ≥2.22 mg/kg, compared with controls. During the third interval, significantly increased locomotion, rearing, and total activity were observed in mice exposed to ≥2.22 mg/kg. Additionally, total activity, but not rearing or locomotion, was significantly decreased during the first 20-mintue interval in the 1.34 mg/kg group; no significant changes were observed during the third interval in the 1.34 mg/kg group. Statistical analysis shows that habituation ability declined in mice exposed to ≥2.22 mg/kg from 2 to 4 months of age. At 4 months, nicotine exposure caused significantly decreased activity during the first interval in mice exposed to ≥13.4 mg/kg, compared with saline-injected mice from the same decaBDE exposure group. This finding is the opposite of the expected increase in activity due to nicotine exposure, which was observed in controls and lower dose decaBDE groups. During third interval, mice exposed to ≥13.4 mg/kg and nicotine showed impaired habituation. No exposure-related effects were observed in the elevated plus maze assessment.

Study 2 (Buratovic et al. 2014): No clinical signs of toxicity or body weight effects were observed. In spontaneous activity assessment, a dose-related decrease in locomotion, rearing, and total activity was observed during the first 20 minutes of open field testing in a novel environment at 2 months. Decreases were significant at all doses tested in both sexes; however, findings were only dose-related for total activity. However, during the third 20-minute interval, when activity should decrease due to habituation, locomotion, rearing, and total activity were significantly increased in males and females at ≥5.76 mg/kg. At 2 months, cholinergic agents caused decreased activity during the first interval in mice exposed to ≥5.76 mg/kg, compared with saline-injected mice from the same decaBDE exposure group. This finding is the opposite of the expected increase in activity due to paraoxon or nicotine exposure, which was observed in controls and low-dose decaBDE groups. During the third interval, mice exposed to ≥5.76 mg/kg and cholinergic agent showed impaired habituation. At 4 months, total activity during the first 20 minutes was still significantly decreased at all doses in males, and locomotion and rearing were significantly decreased in males in the mid- and high-dose groups only; all three parameters were significantly decreased in high-dose females (other doses not evaluated). All three parameters were significantly increased in high-dose males and females during the third 20-minute period, indicating decreased habituation; locomotion and rearing were also slightly, but significantly, increased in mid-dose males. In the Morris water maze, initial learning was comparable between exposed and control mice at 5 and 7 months. However, latencies to find the escape platform during the reversal learning phase (learning to find the escape platform in a new location after initial training) were significantly longer in mid- and high-dose males at 5 and 7 months (other exposure groups not assessed). After sacrifice, significant increases in protein levels of CaMKII, Gap-43, and Tau were observed in the cortex and hippocampus in male mice and increased levels of Tau were observed in the cortex and hippocampus of female mice. No changes in synaptophysin were observed.

Dose and end point used for MRL derivation: 1.34 mg/kg

[X] NOAEL [ ] LOAEL

In the first study (Johansson et al. 2008), a NOAEL of 1.34 mg/kg and a LOAEL of 2.22 mg/kg were determined for the nonhabituating profile (i.e., decreased activity early in the test period and increased

activity late in the test period). The singular finding of decreased total activity during the first 20-minute interval at 4 months in the 1.34 mg/kg group was not considered sufficient to establish a LOAEL of 1.34 mg/kg. The nonhabituating profile, which is a common effect observed with developmental PBDE exposure (Eriksson et al. 2002b, 2006; Fischer et al. 2008; Sand et al. 2004; Viberg et al. 2002, 2003a, 2004a, 2004b), was considered to be a stronger basis for a NOAEL/LOAEL determination. BMD modeling was performed on the habituation ratio (activity during the last 20-minute interval/activity during the first 20-minute interval) at 2 and 4 months reported by Johansson et al. (2008) to assess suitability of this approach for determining the POD. However, none of the models provided an adequate fit with constant or nonconstant variance.

In the second study (Buratovic et al. 2014), a NOAEL of 1.34 mg/kg and a LOAEL of 5.76 mg/kg were determined for the nonhabituating profile (i.e., decreased activity early in the test period and increased activity late in the test period). Similar to the Johansson et al. (2008) study, the finding of decreased total activity during the first 20-minute interval at 2 and 4 months in the 1.34 mg/kg group was not considered sufficient to establish a LOAEL of 1.34 mg/kg. The nonhabituating profile was considered to be a stronger basis for a NOAEL/LOAEL determination, and additional neurological effects (impaired learning, altered response to cholinergic agents) support a LOAEL of 5.76 mg/kg. The quantitative habituation ratio was not reported by Buratovic et al. (2014); therefore, BMD modeling was not performed for this study.

Uncertainty factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable (gavage study).

Was a conversion used from intermittent to continuous exposure? Not applicable (single exposure study).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: In a similar study, decreased spontaneous activity and impaired habituation were also observed in 2- and 6-month-old mice exposed to BDE 209 at doses ≥2.22 mg/kg on PND 3 (lowest dose tested) (Viberg et al. 2003b). These effects were not observed if exposure was on PND 10 or 19 at doses up to 20.1 mg/kg (Viberg et al. 2003b). Additionally, decreased spontaneous activity was observed in 2-month-old rats following exposure to BDE 209 doses ≥6.7 mg/kg on PND 3 (lowest dose tested) (Viberg et al. 2007). At 20.1 mg/kg, impaired habituation and decreased nicotine-induced behavior were also observed. This nonhabituating behavior profile (i.e., decreased activity early in the test period and increased activity late in the test period) is consistent with neurobehavioral alterations observed following early postnatal exposure to lower-brominated PBDEs and has been reported in adult mice neonatally exposed to certain PCB congeners (see Acute MRL Worksheet for lower-brominated PBDEs for more details).

Additional neurodevelopmental effects observed in mice following acute exposure to BDE 209 from PND 2 to 15 at 20 mg/kg/day via micropipette include delayed ontogeny of reflexes, increased locomotion in males at PND 70, and learning impairment and impulsivity at 16 months, but not at 3 months (Rice et al. 2007, 2009). In rats, impaired learning was observed in Morris water maze in PND 25 rat offspring of dams exposed to BDE 209 from GD 1 to 14 at doses ≥30 mg/kg/day via gavage (Chen et al. 2014).

Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polybrominated Diphenyl Ethers (PBDEs) [decabromodiphenyl ether (decaBDE)]
CAS Numbers: 1163-19-5
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 29
Species: Rat

Minimal Risk Level: 0.0002 ($2x10^{-4}$) [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Zhang Z, Sun ZZ, Xiao X, et al. 2013a. Mechanism of BDE 209-induced impaired glucose homeostasis based on gene microarray analysis of adult rat liver. Arch Toxicol 87(8):1557-1567.

Experimental design: Adult male rats were administered 2,2′,3,3′,4,4′,5,5′,6,6′-decabromodiphenyl ether (BDE 209) at 0, 0.05, 1, or 20 mg/kg/day daily via gavage in corn oil for 8 weeks. Rats were observed for clinical signs of toxicity and body weights were measured every 3 days. Rats were fasted for 24 hours after the final gavage treatment, and then sacrificed. Body weights and heart, spleen, lung, kidney, and liver weights were recorded. Blood was collected for clinical chemistry analysis (serum total cholesterol, triglycerides, glucose, insulin, and TNF-α) and determination of plasma markers of oxidative stress (MDE, GSH, and SOD). Liver samples from three rats in the control and low-dose (0.05 mg/kg/day) groups were collected for microarray analysis (Affymetrix GeneChip), and gene ontogeny category, pathway, gene-act-network and gene co-expression analyses were conducted. Quantitative real-time-PCR was performed to quantitate gene expression to validate the gene expression data obtained from microarray analysis.

Effects noted in study and corresponding doses: No clinical signs of toxicity or body weight effects were observed. The relative liver weight was significantly decreased at 1 and 20 mg/kg/day by 9% (absolute liver weights were not reported). No changes were observed in relative weights of heart, spleen, lung, or kidney. No exposure-related changes were reported in serum cholesterol or triglyceride levels. Serum glucose levels were significantly increased by 12, 18, and 21% in 0.05, 1, and 20 mg/kg/day groups, compared with controls. Serum insulin was significantly decreased by 50–60% at 1 and 20 mg/kg/day. Subsequent to this finding, the pancreas was evaluated histologically. Consistent with the insulin findings, morphological changes at 1 and 20 mg/kg/day included blurred boundaries among pancreatic islet cells (quantitative data not reported). Plasma SOD activity was significantly decreased in all exposed groups and plasma GSH was significantly decreased at 1 and 20 mg/kg/day. Serum TNF-α was significantly increased at 1 and 20 mg/kg/day.

BDE 209 induced 1,257 liver gene transcript changes, and 18 canonical pathways were significantly enriched. Four of them were involved in immune diseases, including autoimmune thyroid disease, graft-versus-host disease, allograft rejection, and T1DM. Subsequently, gene act network and gene coexpression network found that some major histocompatibility complex molecules and TNF-α were involved in the T1DM pathway.

Dose and end point used for MRL derivation: 0.05 mg/kg/day

[ ] NOAEL [X] LOAEL [ ] $BMDL_{1SD}$

BMD modeling was performed on the serum glucose data to assess suitability of this approach for determining the POD. Modeling was performed using the reference BMR of one standard deviation change from the mean (1SD), as well as an alternate BMR of 20% change from the mean (RD20). The alternate BMR of RD20 was identified by the reference value range for rat glucose levels, which varies ~20% around the mean (reference mean [range] = 118.1 mg/dL [77–141 mg/dL]; Charles River Laboratories 1998). Results are shown in Table A-3 and Figure A-2.

Table A-3. Modeling Results for Increased Serum Glucose Levels Following Exposure to BDE 209 (Zhang et al. 2013a)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (mg/kg)	$BMDL_{1SD}$ (mg/kg)
Constant variance									
Exponential (model 2)[d]	0.0006	0.71	0.0009	2.09	-0.10	-2.66	46.79	18.09	11.79
Exponential (model 3)[d]	0.0006	0.71	0.0009	2.09	-0.10	-2.66	46.79	18.09	11.79
Exponential (model 4)[d]	0.0006	0.71	0.33	0.00	0.00	0.68	35.65	0.04	0.01
Exponential (model 5)[d]	0.0006	0.71	N/A	0.00	0.00	0.68	37.65	0.04	0.01
Hill[d,e]	0.0006	0.71	0.41	-0.01	0.08	-0.61	35.37	0.03	0.006
Linear[f]	0.0006	0.71	0.0009	2.09	-0.11	-2.65	46.75	17.89	11.35
Polynomial (2-degree)[f]	0.0006	0.71	0.0009	2.09	-0.11	-2.65	46.75	17.89	11.35
Polynomial (3-degree)[f]	0.0006	0.71	0.0009	2.09	-0.11	-2.65	46.75	17.89	11.35
Power[d,e]	0.0006	0.71	0.0009	2.09	-0.11	-2.65	46.75	17.89	11.35
								BMD_{RD20} (mg/kg)	$BMDL_{RD20}$ (mg/kg)
Hill[d,f]	0.0006	0.71	0.41	0.54	NA	-0.61	35.37	21.84	0.05

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. With constant variance model applied, the only models that provided adequate fit to the means were the Exponential (model 4) and the Hill models. BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (Hill model).
[f]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BDE = brominated diphenyl ether; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = exposure concentration associated with 10% extra risk); NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); RD = relative deviation; SD = standard deviation

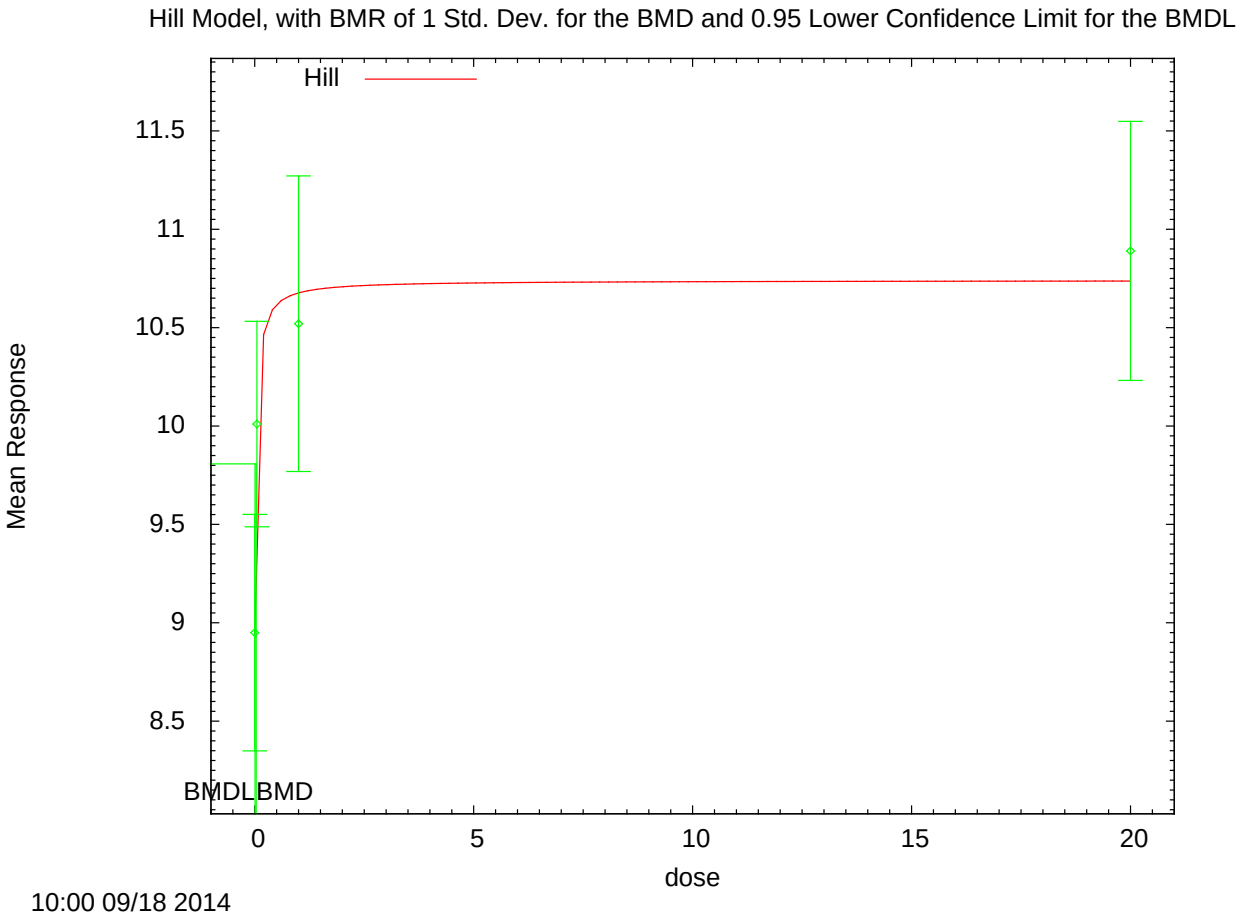

Figure A-2. Fit of Hill Model to Data for Increased Serum Glucose Levels Following Exposure to DecaBDE (Zhang et al. 2013a)

Goodness-of-fit statistics indicate inadequate fit to the data for all models except the Exponential 4 and Hill models, which were considered unsuitable for use in MRL derivation because they did not provide reliable information about the shape of the dose-response curve. For example, using the reference BMR of 1SD change from the mean, the ratio of BMD:BMDL is 5 for the Hill model (0.03/0.006) and 4 for the Exponential Model 4 (0.04/0.01). These values are quite high and suggest that the data do not permit accurate estimation of the BMDL. Using the BMR of RD20 for the Hill model, the ratio was much higher still (21.84/0.05=437). The fact that this ratio changes so much with BMR underscores the instability in the BMDL estimates using this model.

In the absence of a suitable model, the minimal LOAEL of 0.05 mg/kg/day based on a 12% increase in serum glucose was chosen as the POD for MRL derivation. The change in glucose is considered a minimal LOAEL because it is unclear if the magnitude of change represents a biologically adverse effect; however, the increase in serum glucose is considered to be part of a spectrum of effects indicative of altered insulin homeostasis and toxicity to the pancreas, including decreased serum insulin and morphological changes in pancreatic islet cells observed at ≥1 mg/kg/day, following BDE 209 exposure.

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable (gavage study).

Was a conversion used from intermittent to continuous exposure? Not applicable (doses administered daily).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The association between PBDE-exposure and diabetes has been evaluated in a few human studies. An analysis of cross-sectional NHANES data showed a significant increase in risk of diabetes associated with serum levels of BDE 153 (but not BDE 28, BDE 47, BDE 99, or BDE 100; BDE 209 was not assessed), although the risk was higher with exposure to 50–75th percentile BDE 153 levels than >75th percentile BDE 153 levels (Lim et al. 2008). Serum BDE 153 concentrations (but not BDE 28, BDE 47, BDE 85, BDE 99, BDE 100, or BDE 154) were also shown to be significantly associated with increased odds of developing gestational diabetes in a cohort of 258 pregnant women; again, BDE 209 was not assessed (Smarr et al. 2016). However, other cross-sectional and prospective studies found no relationship between serum PBDE concentrations and diabetes in an adult cohort from Wisconsin (Turyk et al. 2015), an elderly cohort in Finland (Airaksinen et al. 2011), or an elderly cohort in Sweden (Lee et al. 2011).

Only one other animal study evaluated the pancreas following decaBDE exposure. In rats exposed to BDE 209 via gavage for 28 days at doses of 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, or 200 mg/kg/day, slight or moderate insulitis was observed in the Langerhan's islets of the "majority of samples," but findings were not exposure-related (Van der ven et al. 2008a). Similarly, no exposure-related effects were observed for serum glucose levels (Van der ven et al. 2008a). The only other study evaluating serum glucose levels after decaBDE exposure instead reported reduced serum glucose levels in male rats exposed to 20 mg/kg/day of a dietary PBDE mixture containing 52.1% pentaBDE (DE-71), 44.2% decaBDE (BDE 209), and 0.4% octaBDE (DE-79) for 70 days (Ernest et al. 2012). The observed decreased glucose levels could be due to the pentaBDE component, as male rats exposed to the commercial pentaBDE mixture DE-71 at doses of 0.27–200 mg/kg/day for 28 days also showed decreased glucose levels; study authors did not report the lowest dose at which glucose levels were significantly lower in male rats, but they reported a BMD_{10RD} of 179.55 mg/kg/day and a $BMDL_{10RD}$ of 66.7 mg/kg/day (Van der ven et al. 2008b). Other effects occurred at doses 4–40-fold higher than the observed pancreatic and related effects:

- A LOAEL of 2 mg/kg/day was identified for transient histopathological effects in the liver of male offspring and kidney of female offspring of rat dams exposed to BDE 209 from GD 10 to PND 21 (no NOAEL identified) (Fujimoto et al. 2011).

- A LOAEL of 10 mg/kg/day was identified for hepatocytic swelling in the liver, vacuolization in the interstitial cells of testes, and sperm damage in PND 71 male offspring of mouse dams exposed to BDE 209 from GD 0 to 17 (no NOAEL identified) (Tseng et al. 2008, 2013).

- A LOAEL of 20 mg/kg/day was identified for decreased anxiety in mice treated with BDE 209 by daily gavage for 15 days (no NOAEL identified) (Heredia et al. 2012).

- A LOAEL of 20.1 mg/kg/day was identified for altered hippocampal electrophysiology in rats exposed to BDE 209 from GD 1 to PND 41, PNDs 1–21, or PNDs 22–41 (no NOAEL identified) (Xing et al. 2009).

Hydroxylated metabolites (OH-PBDEs) may be responsible for the toxic action of PBDEs. There is some evidence that the CYPs involved in metabolism of PBDEs, as well as the OH-PBDEs formed, are different in rats and humans (Erratico et al. 2011, 2012, 2013)—see Section 3.4.3 for more information. However, there is no available evidence indicating that the complement of OH-PBDEs formed in humans is any more or less potent than the complement of OH-PBDEs formed in rats. Therefore, the current use of an animal-to-human uncertainty factor is appropriate for calculating an MRL based on effects observed in rats.

Agency Contact (Chemical Manager): Hana Pohl

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order 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.

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. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology 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 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See 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 exist, 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 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 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

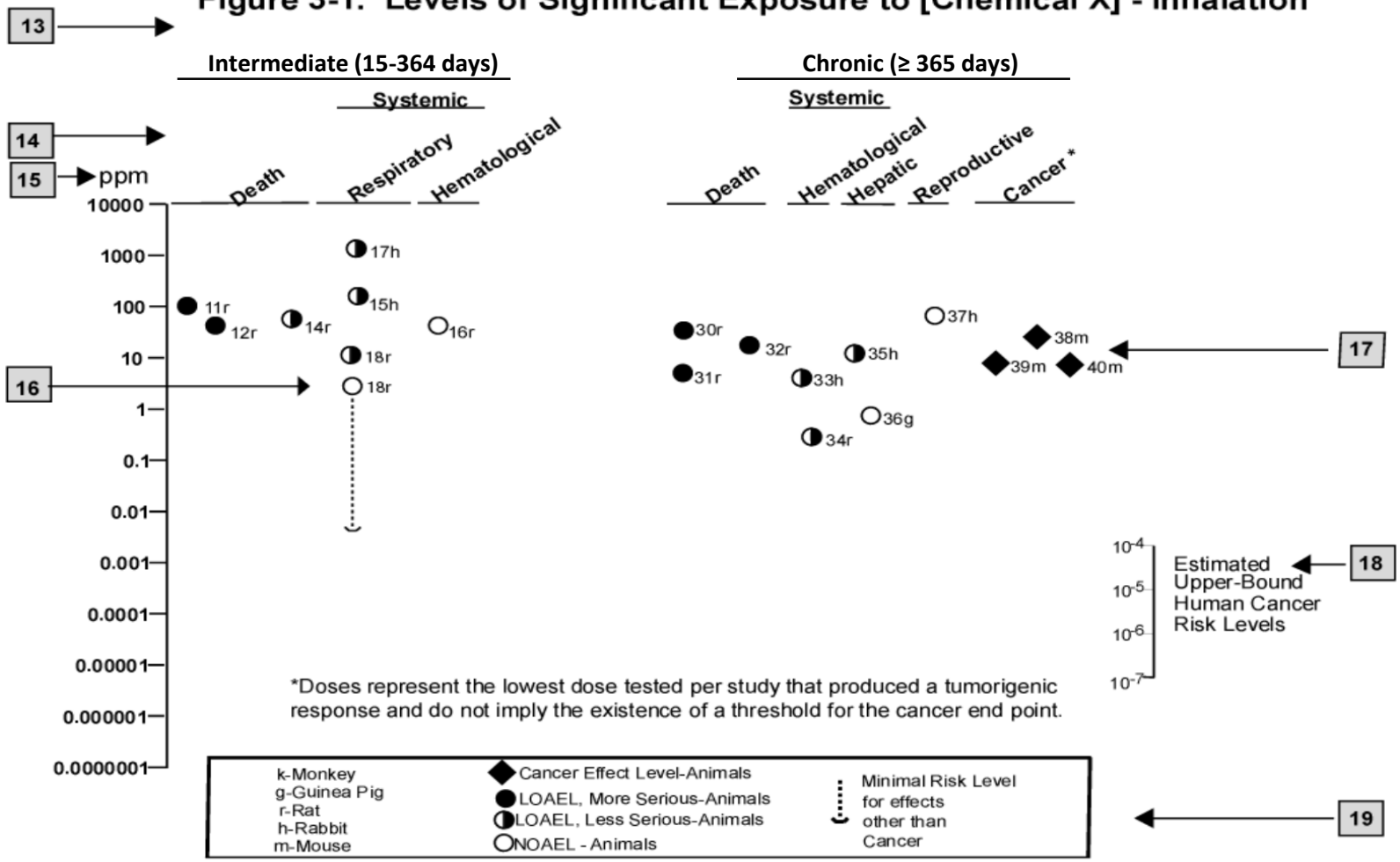
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[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 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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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/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

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