United States
Consumer Product Safety Commission

Organohalogen Flame Retardant Scope Document: Polyhalogenated Benzene Subclass

February 2024

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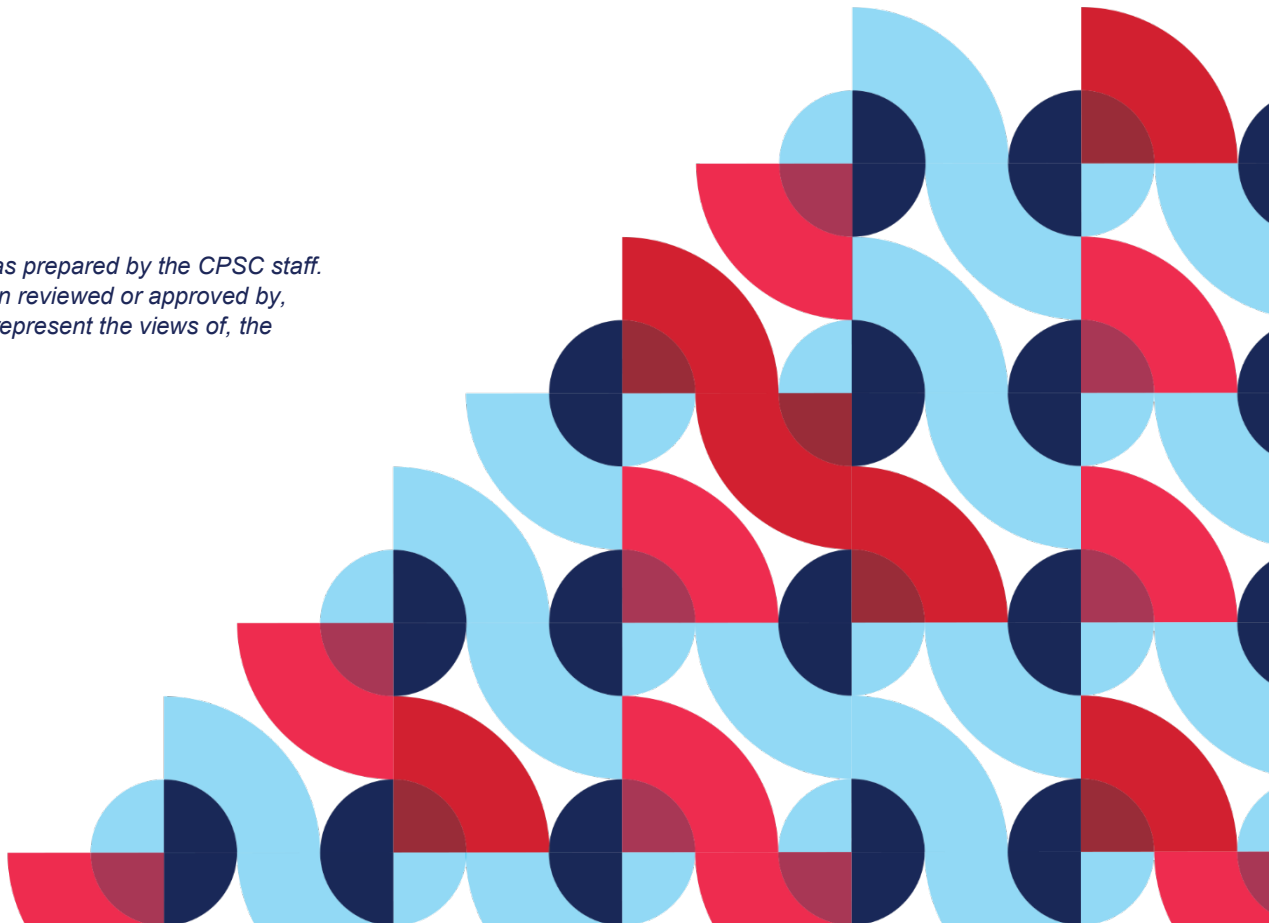

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1. Executive Summary

This scope document addresses the polyhalogenated benzene (PHB) subclass, one of 14 subclasses of organohalogen flame retardants (OFR). OFRs contain a carbon-halogen bond and are one of the main categories of flame retardants (FRs). FRs are substances that alter the normal degradation or combustion processes of materials. They are incorporated into materials or used on surfaces to reduce or eliminate the tendency to ignite when exposed to heat or flame for a short period of time.

Informed by initial review of the market and use research, evidence maps, and availability of physicochemical data for the PHB subclass and its analogs, as well as the Criteria for Scoping Determination described in this document, Consumer Product Safety Commission (CPSC or Commission) staff concludes, at the time of writing, that the PHB subclass has sufficient data to proceed with risk assessment. Next steps, as resources are available, involve completing the hazard, dose-response, and exposure assessments before drafting the class-based risk assessment.

2. Introduction

This document contains the results of scoping efforts by CPSC staff to characterize readily available information on the chemistry, uses, human toxicity, exposure, and human health risk of members of the PHB subclass of OFRs. This document is one of the scope documents that CPSC staff is producing to address each of 14 OFR chemical subclasses.

The primary question answered by the scope documents is:

> *Can a risk assessment for this subclass be completed based on a combination of existing data and estimation (modeling) approaches?*

To answer this question, the scope document developed for each subclass outlines the criteria for determining sufficiency for hazard assessments and exposure assessments, describes the data available, and provides the scoping determination. If the answer to the question above is yes for that subclass, the scope document describes (i) CPSC staff's interpretation of available data through evidence maps and estimation approaches and (ii) the analysis plan and conceptual model that CPSC staff plans to follow to complete this assessment. These subclasses will then be prioritized for risk assessments.

If the answer is no, then the scope document for that particular subclass describes (i) CPSC staff's interpretation of available data through evidence maps and estimation approaches and (ii) key data gaps. These subclasses will be temporarily deprioritized for risk assessments.

For additional details on how the information contained in all scope documents was compiled, refer to the following CPSC companion documents:[1]

- Development of a Flame Retardant and an Organohalogen Flame Retardant Chemical Inventory
- Market and Use Report: Characterizing OFR Chemistries, Sources, and Uses in the U.S. and International Markets, Volumes 1 and 2 (Appendices)
- Literature Survey Guide: Approaches Taken to Develop Evidence Maps from Readily Available Databases, Completed Assessments, and Literature Reviews

3. Background

In 2015, several organizations and individuals petitioned CPSC (Petition HP 15-1) to ban the use of additive OFRs, as a class, in durable infant or toddler products, children's toys, childcare articles, or other children's products (other than car seats), residential upholstered furniture, mattresses and mattress pads, and the plastic casings of electronic devices. In 2017, the Commission voted to grant the petition to direct staff to convene a Chronic Hazard Advisory Panel,[2] and to complete a scoping and feasibility study in cooperation with the National Academy of Sciences, Engineering, and Medicine (NASEM).

NASEM established a committee of experts to address the charge and published the Committee's report, "A Class Approach to Hazard Assessment of Organohalogen Flame Retardants," in May 2019 (NASEM, 2019). The Committee first decided to determine whether the chemicals of interest can be defined as a single class or as subclasses, based on structure, physicochemical properties, biology, or a combination of characteristics. The Committee stated that if a class approach is viable, then the hazard assessment approach would be to survey the literature to determine availability of all types of toxicity data (human, animal, in vitro, other relevant studies) for all relevant toxicity end points. Then, if relevant data are available on any chemical of interest for a given end point, the plan would be to extract, evaluate, and integrate the data to reach a decision about potential hazards that can be applied to the entire class or subclass. A key conclusion of the Committee is that OFRs cannot be treated as a single class. Rather, the Committee identified 14 subclasses of OFRs, based on chemical structure, physicochemical properties of the chemicals, and predicted biological activity.

In fiscal year 2020 (FY 2020), CPSC staff developed a process for assessing the risks of OFRs in consumer products. A staff report to the Commission (Staff Plan) (CPSC, 2020) builds on the recommendations from the NASEM committee and outlines options and recommendations for proceeding with the project in FY 2021 and beyond (subject to availability of resources). In brief, the Staff Plan outlined work that initially would establish procedures for class-based risk

[1] Project documents, including CPSC staff reports, contractor reports, and key references may be found on the CPSC Organohalogen Flame Retardant Chemicals Assessment website (https://www.cpsc.gov/Business--Manufacturing/Organohalogen-Flame-Retardant-Chemicals-Assessment) or Docket No. CPSC-2015-0022 (https://www.regulations.gov/docket/CPSC-2015-0022).
[2] CHAP review would occur prior to finalizing any subclass risk assessment if carcinogenicity, mutagenicity, or reproductive/developmental toxicity were chosen as relevant endpoints.

assessment of each OFR subclass, refine the chemicals and analogs for multiple OFR subclasses, identify data sources, and determine available toxicity, chemical use, and exposure information. Staff subsequently initiated several activities, largely through contractors and interagency collaborations, to begin work on the project.

4. Approach

4.1. Criteria for Scoping Determination

CPSC staff will determine whether a subclass has sufficient data to proceed, at this time, with risk assessment based on data availability. In this context, data availability among subclass members and among identified analog chemicals is characterized as "no data," "some data," or "data rich" for both hazard information and exposure information, with definitions of each category provided below.

4.1.1. Hazard

The criteria for sufficiency for hazard assessment for the subclass are:

- At least one data rich chemical among the subclass chemicals or analog chemicals and
- Multiple chemicals with some data among subclass chemicals or analog chemicals with empirical short-term toxicity and other data (availability of modeled physicochemical and toxicity data can contribute to the determination).
- Only a minority of the substances in the subclass are "no data" substances.

The data availability categories are defined using the literature survey results as follows:

- Chemicals with no data:
    - No empirical data for physicochemical characteristics, and
    - No empirical data for toxicity, and
    - No or limited predicted/modeled physicochemical or toxicity data.
- Chemicals with some data (i.e., chemicals that are neither data rich nor have no data):
    - Some physicochemical data (may include empirical or modeled), and
    - No to limited traditional chronic/subchronic animal toxicity studies, and
    - Some short-term toxicity, in vitro, high-throughput, or other nonanimal data.

- Chemicals that are data rich:
    - Near complete empirical physicochemical data, and
    - Multiple traditional animal toxicity studies (i.e., acute, systemic repeated dose toxicity, or reproductive/developmental), and
    - Multiple short-term in vivo toxicity studies, and in vitro, high-throughput, or other nonanimal data, and
    - Available empirical data likely support derivation of a quantitative toxicity reference value(s).
    - Modeled toxicity data, if such data demonstrate close agreement with available empirical data, are acceptable to support this category, but such data are not required.
    - Availability of human data supports this category but is not required.

In addition to evaluating the amount and breadth of available data for each chemical in a subclass, CPSC staff plans to consider the availability of similar types of data for multiple subclass members (e.g., similar subchronic/chronic studies, similar endpoints evaluated, and similar short-term toxicity studies, in vitro assays, or mechanistic data). That is, CPSC staff plans to consider consistency in data availability across members of a subclass.

4.1.2. Exposure

The criteria for sufficiency for exposure assessment for the subclass are:

- At least one data rich chemical among the subclass chemicals for which average daily doses for human populations have been reported or can be estimated, and
- Multiple subclass chemicals with some data from environmental monitoring, biomonitoring, product-testing, or any toxicokinetic studies (availability of modeled physicochemical, emissions, migration, occurrence, or disposition data can contribute to the determination).
- Note that subclass members classified as “no data” chemicals do not have sufficient information for exposure assessment.

The data availability categories are defined using the literature survey and market and use research results as follows:

- Chemicals with no data:
    - No market and use information indicating use as a flame retardant.
- Chemicals with some data (i.e., chemicals that are neither data rich nor have no data):
    - Some evidence (per market and use information) that it has been, currently is, or could be used as a flame retardant, and
    - Some physicochemical data (may include empirical or modeled), or
    - At least one experimental environmental monitoring, biomonitoring, product-testing, or toxicokinetic study, or comparable modeling studies that provide information on estimated occurrence, emissions, or disposition, or
    - Existing or de novo modeled estimates of physicochemical properties, emissions, migration, occurrence, or disposition.

- Chemicals that are data rich:
    - Evidence (per market and use information) that it has been, currently is, or could be used as a flame retardant, and
    - Near complete empirical physicochemical data, and
    - Multiple environmental monitoring, biomonitoring, product-testing, or toxicokinetic studies, and
    - Available empirical data support estimates of quantitative average daily dose(s) for human exposure, and
    - Modeled exposure data (emissions, occurrence, disposition), if such data demonstrate close agreement with empirical data, are acceptable to support this category, but such data are not required.

4.2. Inventory

The NASEM committee, as part of its consideration of class approaches to hazard assessment, created an inventory of 161 OFRs and identified more than 1,000 analog chemicals (i.e., chemicals with similar functional, structural, and predicted biological activity) across 14 chemical subclasses. Subsequently, CPSC staff, in collaboration with the U.S. Environmental Protection Agency (EPA), refined a Quantitative-Structure-Use-Relationship (QSUR) model to predict the probability of whether a chemical is a flame retardant or an OFR. These efforts, in combination with market and use research, led to a manuscript, "Development of a Flame Retardant and an Organohalogen Flame Retardant Chemical Inventory," published in *Nature Scientific Data* (Bevington et al., 2022). This work identified additional OFR chemicals, resulting in an expanded inventory of 488 OFRs in 14 subclasses.

The OFR inventory completed by CPSC staff should not be considered a fixed and final list of all possible OFR chemicals. This project, including the market and use research and literature survey work, has used established identifiers for each chemical, such as CAS RN®,[3] DTXSID,[4] INCHIKEY,[5] PUBCHEM ID,[6] and SMILES,[7] as well as chemical names and common synonyms. However, even with identifiers that should uniquely describe chemicals, there are a few cases in the inventory of the same chemical identified in different ways. CPSC staff also acknowledges that some identifiers correspond to mixtures.[8] To the extent that information on chemicals would be located using different identifiers, CPSC staff will maintain separate listings; however, once

[3] CAS RN®, or CAS Registry Number®, is a unique identification number for individual chemical substances assigned by CAS, a division of the American Chemical Society.
[4] DTXSID, or DSSTox substance identifier, is an alphanumeric identifier for individual chemical substances used in the U.S. Environmental Protection Agency's CompTox Chemicals Dashboard.
[5] INCHIKEY, stands for International Chemical Identifier and is a unique 27-character identifier.
[6] PUBCHEM ID is a unique identifier specific to the National Library of Medicine's PUBCHEM database.
[7] Simplified molecular-input line-entry system (SMILES) describes the structure of a chemical in a way that can be used by a computer.
[8] See, for example, CAS RN 85535-84-8, which refers to a group of halogenated aliphatic chain chemicals with chain length from 10 to 13 carbons. Chemical names associated with this CAS RN include short chain chlorinated paraffins; alkanes, C10-13, chloro; and chlorinated paraffins, C10-13.

staff confirms that multiple records apply to a single chemical (or mixture), analyses of the chemical will consider the combined data for that chemical regardless of the identifiers.

CPSC staff also notes that the inventory may be modified through the course of the project as staff continues analyses of chemicals in each subclass and considers additional information. The result of additional analyses could be the removal or addition of chemicals to the inventory.

4.3. Market and Use Research

The OFR market and use research was intended to collect relevant information and data to (1) characterize each OFR subclass, (2) identify uses of chemicals in each OFR subclass, and (3) identify trends associated with each OFR subclass. CPSC staff sought information about production or consumption of OFR chemicals and identified uses in consumer products and other market information. CPSC staff also sought information on regulatory actions, including current and proposed laws, policies, and regulations related to OFR chemicals at international, federal, state, and local levels of government. Detailed descriptions of the approach and process are found in Volume 1 of the Market and Use Profile (see Appendix: Supporting Files) completed under a CPSC-sponsored contract. Briefly, the market and use research captured information from targeted scientific literature and gray literature, and from readily available data sources in other formats. Data sources included national chemical inventories, other government data, such as from required reporting of production and waste information for specified chemicals or other types of curated databases, and certain commercial sources.

4.3.1. Targeted Literature Search

Section 3.2.6 of the Market and Use Report explains the methodology used for the targeted literature search completed for the OFR market and use research. The targeted searches for literature related to the flame-retardant market identified sources of relevant material from databases, websites, or other online information repositories, and broader searches of internet-based sources using standard search tools such as Google Scholar and selected searches of commercial online literature databases (e.g., Dialog/ProQuest). Specifically, the contractor executed searches of 140 literature databases using the Dialog/ProQuest platform.[9]

Following a review of the source title and abstract, the contractor rated each identified source for relevance on a scale of 1 to 5, 5 being the most relevant, and obtained PDF copies of as many of the sources identified as possible, with priority given to those sources rated higher for relevance. Among all 255 sources obtained, the contractor prioritized the review of 187 complete sources.

For each PDF reviewed, the contractor highlighted information on topics of interest for the study, such as manufacturing or import activity, use of chemicals in products, lifecycle considerations, and regulatory or other trends. The report further identified all OFR chemicals discussed in the source, and where available, captured the CAS RN for each chemical and any synonyms, abbreviations, and trade names. From the 187 sources extracted and reviewed, the contractor made over 2,200 OFR identifications (for 488 unique OFRs). The summary of sources reviewed

[9] For a list of data sources searched using Dialog/ProQuest, see Exhibit 3-32 of the Market and Use Report Volume 1.

is provided in the Data Source Synthesis Excel workbook of the supplemental Market and Use Profile Supporting Files, referenced by OFR subclass.

4.3.2. Other Data Sources

The OFR Market and Use Report contains information collected from inventories and registries from the United States, Canada, Mexico, the EU, Japan, and China. In the United States, the Toxic Substances Control Act (TSCA) inventory was used to identify if an OFR substance was designated as active or inactive.[10] In addition to determining whether OFR substances appear as active substances on the TSCA chemical inventory, the contractor conducted a detailed analysis of U.S. production and import activity using data available from the EPA Chemical Data Reporting (CDR) program, and the manufacturing, processing, and waste management trends of OFR substances from the Toxic Release Inventory (TRI), as reported by industrial and federal facilities.

To determine whether individual OFR chemicals are used in consumer and/or children's products the contractor reviewed information available from the EPA's CDR and the Interstate Chemicals Clearinghouse High Priority Chemicals Data System (HPCDS). European data on OFR substances in products could not be reviewed in their entirety in time for the publication of the report.

In addition, the contractor made efforts to identify OFR chemicals on several chemical business to business (B2B) or e-Commerce sites, using automated techniques to "scrape" data on OFRs from these sites. From Buyersguide.com and Chemnet.com, the contractor obtained the identity, country, and website of OFR suppliers. From Alibaba.com, they obtained the name and website of the OFR suppliers, as well as some data on quantities available and pricing.

4.4. Literature Survey

The OFR literature survey was intended to gather readily available toxicity, exposure, and risk information to characterize the types and amounts of data available for chemicals (and analogs) within a class. CPSC staff defined data sources for the literature survey effort as toxicity, exposure, and chemistry databases; completed toxicity, exposure, or risk assessments; and completed literature reviews. Sources identified in the literature survey were screened to confirm utility and identify the type of data, but the actual data were not evaluated or extracted.

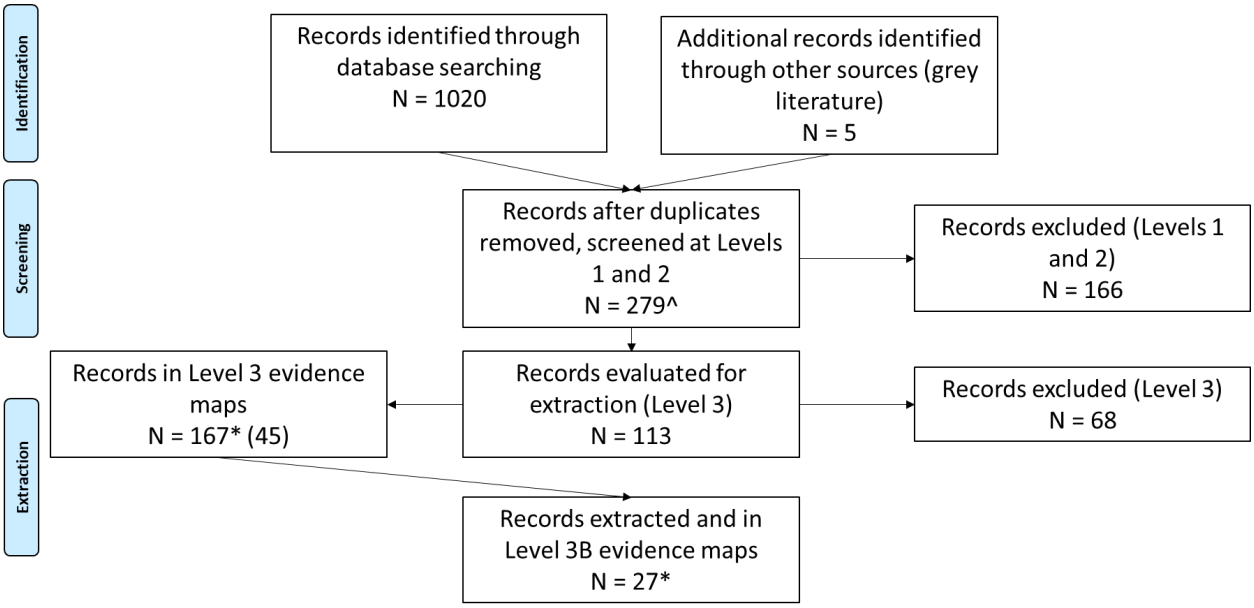
Detailed descriptions of the literature survey approach and process are found in the Literature Survey Guide and accompanying documentation. These documents were developed by University of Cincinnati (UC) Risk Science Center staff as part of work performed under a CPSC-sponsored contract (UC, 2022a; UC, 2022b). Development of the evidence maps followed a multilevel process to screen data sources initially identified in a defined search.

Briefly, for peer-reviewed and gray literature, **Level 1** screening was used to confirm that the reference might contain information about at least one OFR chemical and that the reference

[10] Active chemicals are those that have been reported to EPA for manufacture or processing in the U.S., including those reported within a 10-year time period ending on June 21, 2016. Inactive chemicals are those that have not been reported and are, therefore, not considered to be in commercial use.

was relevant to the PECO statement.[11] **Level 2** screening identified the OFR subclasses included in each reference and tagged the references for the types of data (hazard, exposure, risk). **Level 3** identified the specific OFR or analog chemicals in each reference and extracted more specific information about the types of hazard data, exposure data, or risk assessment information presented for each chemical. Finally, **Level 3B** tagging was performed on a subset of toxicity assessments, toxicity literature reviews, risk assessments, and exposure literature reviews selected from Level 3 to identify even more specific information for the chemicals in these references. Similarly, data from databases were tagged for type of data using a database logic developed to provide consistency across different data sources. Finally, the tagged information was organized into evidence maps by OFR subclass and specific chemicals. Figure 4-1 shows the numbers of records initially identified and the number of records screened or extracted at each level.

Figure 4-1. Literature Flow Diagram



Notes:
^Removal of duplicates within the subclass, and between this subclass and previous subclasses.
*PHB evidence maps contain additional references uploaded with other subclasses. Number in parentheses is the number of references identified by searching for the PHB subclass only, excluding the references identified by searching for subclasses.

5. Scoping for PHBs

5.1. PHB Subclass Chemistry

The PHB subclass generally consists of chemicals containing one or more benzene groups with halogenated substituents on the ring. In particular, members of this subclass all have an aryl

[11] PECO refers to population (P), exposure (E), comparator (C), and outcomes (O) of interest, and generally describes the scope of a literature search and subsequent analyses.

carbon–halogen chemical bonds. The presence of additional functional groups such as ethers and pyrroles, may lead to chemistry-based differences throughout this subclass despite structural similarities amongst the members. Table 5-1 lists 50 individual chemicals in the PHB subclass.

Table 5-1. List of Chemicals in PHB Subclass

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
1	115245-07-3	1,1'-Biphenyl, 2,4,5-tribromo-	PBB-29	C1=CC=C(C=C1)C2=CC(=C(C=C2Br)Br)Br
2	119264-59-4	1,1'-Biphenyl, 2,2',3,3',4,4',6,6'-octabromo-	PBB-197	C1=C(C(=C(C(=C1Br)Br)Br)C2=C(C(=C(C=C2Br)Br)Br)Br)Br
3	119264-60-7	2,2',3,3',4,5',6,6'-Octabromobiphenyl	NA	C1=C(C(=C(C(=C1Br)Br)Br)C2=C(C(=CC(=C2Br)Br)Br)Br)Br
4	119264-61-8	2,2',3,4,4',5,6,6'-Octabromobiphenyl	NA	C1=C(C=C(C(=C1Br)C2=C(C(=C(C(=C2Br)Br)Br)Br)Br)Br)Br
5	119264-62-9	2,2',3,3',4,4',5,6,6'-Nonabromo-1,1'-biphenyl	PBB 207; Bromkal 80-9D	C1=C(C(=C(C(=C1Br)Br)Br)C2=C(C(=C(C(=C2Br)Br)Br)Br)Br)Br
6	119264-63-0	2,2',3,3',4,5,5',6,6'-Nonobromobiphenyl	PBB 208	C1=C(C(=C(C(=C1Br)Br)C2=C(C(=C(C(=C2Br)Br)Br)Br)Br)Br)Br
7	13654-09-6	1,1'-Biphenyl, 2,2',3,3',4,4',5,5',6,6'-decabromo-	PBB 209	C1(=C(C(=C(C(=C1Br)Br)Br)Br)Br)C2=C(C(=C(C(=C2Br)Br)Br)Br)Br
8	14957-65-4	4,4',6,6'Tetrabromo2,2'biphenyldiol	NA	C1=C(C=C(C(=C1O)C2=C(C=C(C=C2Br)Br)O)Br)Br
9	16400-50-3	1,1'-Biphenyl, 3,3',5,5'-tetrabromo-	PBB 80	C1=C(C=C(C=C1Br)Br)C2=CC(=CC(=C2)Br)Br
10	198126-86-2	Tetrabromo trichloromethyl benzene	NA	NA
11	2113-57-7	3-Bromobiphenyl	NA	C1=CC=C(C=C1)C2=CC(=CC=C2)Br
12	27858-07-7	Octabromobiphenyl	PBB 8	C1=CC(=C(C(=C1C2=C(C(=C(C(=C2Br)Br)Br)Br)Br)Br)Br)Br
13	31710-32-4	p-Tetradecachloroterphenyl	NA	C1(=C(C(=C(C(=C1Cl)Cl)C2=C(C(=C(C(=C2Cl)Cl)Cl)Cl)Cl)Cl)C3=C(C(=C(C(=C3Cl)Cl)Cl)Cl)Cl
14	36355-01-8	Hexabromobiphenyl	NA	NA
15	42429-88-9	1,1':2',1''-Terphenyl, 2,2'',3,3',3'',4,4',4'',5,5',5'',6,6',6''-tetradecachloro-	NA	C1(=C(C(=C(C(=C1Cl)Cl)Cl)Cl)Cl)C2=C(C(=C(C(=C2Cl)Cl)Cl)Cl)Cl)C3=C(C(=C(C(=C3Cl)Cl)Cl)Cl)Cl

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
16	42429-89-0	1,1':3',1"-Terphenyl, 2,2',2",3,3",4,4',4",5,5',5",6,6',6"-tetradecachloro-	NA	C1(=C(C(=C(C(=C1Cl)Cl)Cl)C2=C(C(=C(C(=C2Cl)Cl)Cl)Cl)Cl)C3=C(C(=C(C(=C3Cl)Cl)Cl)Cl)Cl
17	56890-89-2	1,2,3,4,7,7-Hexachloro-5-(2,4,6-tribromophenyl)bicyclo[2.2.1]hept-2-ene	NA	C1C(C2(C(=C(C1(C2(Cl)Cl)Cl)Cl)Cl)Cl)C3=C(C=C(C=C3Br)Br)Br
18	59080-37-4	2,2',5,5'-Tetrabromobiphenyl	NA	C1=CC(=C(C=C1Br)C2=C(C=CC(=C2)Br)Br)Br
19	59080-39-6	2,2',4,5',6-Pentabromobiphenyl	PBB 103	C1=CC(=C(C=C1Br)C2=C(C=C(C=C2Br)Br)Br)Br
20	59080-40-9	2,2',4,4',5,5'-Hexabromobiphenyl	PBB 153	C1=C(C(=CC(=C1Br)Br)Br)C2=CC(=C(C=C2Br)Br)Br
21	59080-41-0	2,3,5,6,2',3',5',6'-Octabromobiphenyl	PBB 202	C1=C(C(=C(C(=C1Br)Br)C2=C(C(=CC(=C2Br)Br)Br)Br)Br)Br
22	59447-57-3	Poly(pentabromobenzyl acrylate)	NA	C=CC(=O)OCC1=C(C(=C(C(=C1Br)Br)Br)Br)Br
23	59536-65-1	2,3,3',4,4',5'-Hexabromobiphenyl	Firemaster BP-6	C1=CC(=C(C(=C1C2=CC(=C(C(=C2)Br)Br)Br)Br)Br)Br
24	59789-51-4	1H-Pyrrole-2,5-dione, 1-(2,4,6-tribromophenyl)-	NA	C1=CC(=O)N(C1=O)C2=C(C=C(C=C2Br)Br)Br
25	60044-24-8	2,2',4,5-Tetrabromo-1,1'-biphenyl	PBB 49	C1=CC(=C(C(=C1Br)Br)C2=C(C=CC(=C2)Br)Br
26	60044-25-9	2,2',5,6'-Tetrabromobiphenyl	PBB 053	C1=CC(=C(C(=C1)Br)C2=C(C=CC(=C2)Br)Br)Br
27	60044-26-0	3,3',4,4',5,5'-Hexabromobiphenyl	PBB-169	C1=C(C=C(C(=C1Br)Br)Br)C2=CC(=C(C(=C2)Br)Br)Br
28	608-90-2	Benzene, pentabromo-	NA	C1=C(C(=C(C(=C1Br)Br)Br)Br)Br
29	626-39-1	1,3,5-Tribromobenzene	PARAGOS 530416	C1=C(C=C(C=C1Br)Br)Br
30	636-28-2	1,2,4,5-Tetrabromobenzene	NA	C1=C(C(=CC(=C1Br)Br)Br)Br
31	67733-52-2	1,1'-Biphenyl, 2,2',3,4,4',5,5'-heptabromo-	PBB-180	C1=C(C(=CC(=C1Br)Br)Br)C2=CC(=C(C(=C2Br)Br)Br)Br
32	67888-96-4	1,1'-Biphenyl, 2,2',4,5,5'-pentabromo-	PBB 101	C1=CC(=C(C(=C1Br)C2=CC(=C(C=C2Br)Br)Br)Br
33	67888-97-5	2,4,5,3',4'-Pentabromobiphenyl	PBB 118	C1=CC(=C(C=C1C2=CC(=C(C=C2Br)Br)Br)Br)Br
34	67888-98-6	2,2',3,4,4',5-Hexabromobiphenyl	PBB 138	C1=CC(=C(C(=C1C2=CC(=C(C=C2Br)Br)Br)Br)Br)Br
35	67888-99-7	2,3',4,4'5,5'-Hexabromobiphenyl	PBB 167	C1=C(C=C(C(=C1Br)Br)Br)C2=CC(=C(C=C2Br)Br)Br
36	67889-00-3	2,3,4,5,2',3',4',5'-Octabromobiphenyl	PBB 194	C1=C(C(=C(C(=C1Br)Br)Br)Br)C2=CC(=C(C(=C2Br)Br)Br)Br

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
37	69278-59-7	1,1'-Biphenyl, 2,2',3,4',5',6-hexabromo-	PBB 149	C1=CC(=C(C(=C1Br)C2=CC(=C(C=C2Br)Br)Br)Br)Br
38	69278-60-0	2,2',3,3',4,4',5-Heptabromobiphenyl	PBB 170	C1=CC(=C(C(=C1C2=CC(=C(C(=C2Br)Br)Br)Br)Br)Br)Br
39	69278-61-1	1,1'-Biphenyl, 2,2',3,3',4,4',5,6'-octabromo-	PBB 196	C1=C(C(=C(C(=C1Br)Br)Br)Br)C2=C(C(=C(C=C2Br)Br)Br)Br
40	69278-62-2	2,2',3,3',4,4',5,5',6-Nonabromo-1,1'-biphenyl	PBB 206	C1=C(C(=C(C(=C1Br)Br)Br)Br)C2=C(C(=C(C(=C2Br)Br)Br)Br)Br
41	69887-11-2	2,2',3,3',4,5,5',6'-Octabromobiphenyl	PBB 201	C1=C(C(=C(C(=C1Br)Br)Br)Br)C2=C(C(=CC(=C2Br)Br)Br)Br
42	77102-82-0	3,3',4,4'-Tetrabromobiphenyl	PBB 077	C1=CC(=C(C=C1C2=CC(=C(C=C2)Br)Br)Br)Br
43	79596-31-9	1~2~,1~3~,1~4~,1~5~,1~6~,2~3~,2~4~,3~2~,3~3~,3~4~,3~5~,3~6~Dodecabromo1~1~,2~1~:2~2~,3~1~terphenyl	NA	C1=CC(=C(C(=C1C2=C(C(=C(C(=C2Br)Br)Br)Br)Br)C3=C(C(=C(C(=C3Br)Br)Br)Br)Br)Br)Br
44	82865-89-2	2,2',3,3',4,4'-Hexabromo-1,1'-biphenyl	PBB 128	C1=CC(=C(C(=C1C2=C(C(=C(C=C2)Br)Br)Br)Br)Br)Br
45	83929-69-5	2,2',3,3',5,5',6,6'Octabromo4phenoxy1,1'biphenyl	NA	C1=CC=C(C=C1)OC2=C(C(=C(C(=C2Br)Br)C3=C(C(=CC(=C3Br)Br)Br)Br)Br)Br
46	84303-46-8	3,3',4,4',5-Pentabromo-1,1'-biphenyl	PBB 126	C1=CC(=C(C=C1C2=CC(=C(C(=C2)Br)Br)Br)Br)Br
47	84303-48-0	1,1'-Biphenyl, 2,3',4,4',5',6-hexabromo-	PBB 168	C1=C(C=C(C(=C1Br)Br)Br)C2=C(C=C(C=C2Br)Br)Br
48	87-82-1	Hexabromobenzene	NA	C1(=C(C(=C(C(=C1Br)Br)Br)Br)Br)Br
49	92-66-0	4-Bromobiphenyl	4-Biphenyl bromide; PBB 3	C1=CC=C(C=C1)C2=CC=C(C=C2)Br
50	92-86-4	1,1'-Biphenyl, 4,4'-dibromo-	PBB 15	C1=CC(=CC=C1C2=CC=C(C=C2)Br)Br

SMILES = simplified molecular-input line-entry system. N.A. = not available or not found.

There are differences between the number of chemicals identified in the inventory, market-use report, and evidence maps. In finalizing the scope document for the PHB class, staff identified that chemical 7436-90-0 (Benzene, dibromoethenyl-), which was initially included in the evidence maps for this class, should be moved to the Polyhalogenated Benzene Aliphatics and Functionalized (PHBAF) Class because this is a chemical with a benzene ring with halogenated aliphatic substituents.

Furthermore, chemicals were flagged in the inventory as uncommonly reported congeners based on data reviewed at that time. Some chemicals were flagged as not being present in commerce, resulting in a total of 12 chemicals that were either flagged as an uncommon congener or not present in commerce. These 12 chemicals were therefore not included in the evidence maps.

5.1.1. Physicochemical Property Summaries

The information collected to date led CPSC staff to find that experimental physicochemical data on PHB chemicals are limited. Eight PHB subclass members have experimental data and 47 PHB members have predicted data. Well-studied chemicals in this subclass include 1,3,5-Tribromobenzene (CAS RN 626-39-1), 4-Bromobiphenyl (PBB 3, CAS RN 92-66-0) and 1,1'-Biphenyl, 4,4'-dibromo- (PBB 15, CAS RN 92-86-4). From this data set, studied PHBs have experimental boiling points ranging from 271°C to 357 °C, and experimental vapor pressures from $3.97E^{-10}$ to $2.35E^{-3}$ mm Hg. Data show experimental water solubility values ranging from $1.87E\ 10^{-10}$ to $2.51E\ 10^{-6}$ mol/L. The experimental octanol/water partition coefficient (K_{ow}) values, which are commonly expressed as log K_{ow}, range from 4.51 to 7.1.

5.2. Market and Use Summary for PHBs

The OFR Market and Use Report, completed in March 2022, includes 50 PHB chemicals.

- Thirty-seven PHB chemicals had market and use information and there were 13 chemicals without any market and use information.
- According to EPA data, seven PHB chemicals were identified to be on the EPA's Chemical Substance (active) Inventory, five PHB chemicals were identified on the TSCA (inactive) inventory, none were on the CDR, and one was on the TRI program list.
- No PHB chemicals were identified in the Interstate Chemicals Clearinghouse (IC2) HPCDS.
- Fifteen PHB chemicals were identified in the targeted literature search.
- Twenty-four PHB chemicals had patent data.

5.2.1. PHBs Used in Commerce

The Market and Use Report summarizes data from a variety of sources, including U.S. and international chemical registries, scientific literature, patents, and chemical databases. To determine whether individual OFRs are currently in commerce, have been used in the past, or may be used in the future, these registries, patent data, and literature were reviewed in detail under a CPSC-sponsored contract and data were compiled from four main types of sources. Chemicals that have been in commerce appear on the (1) TSCA inventory, (2) international inventories, (3) in literature, or (4) in patent data. Table 5-2 lists the 37 PHBs that are known to be or have been used in commerce, according to data available from these sources.

The 13 PHB chemicals that are not known to be used in commerce are:

- 1,1'-Biphenyl, 2,2',3,3',4,4',6,6'-octabromo- (CAS RN 119264-59-4)
- 2,2',3,3',4,5',6,6'-Octabromobiphenyl (CAS RN 119264-60-7)
- 2,2',3,4,4',5,6,6'-Octabromobiphenyl (CAS RN 119264-61-8)
- p-Tetradecachloroterphenyl (CAS RN 31710-32-4)
- 1,1':2',1"-Terphenyl, 2,2",3,3',3",4,4',4",5,5',5",6,6',6"-tetradecachloro- (CAS RN 42429-88-9)
- 1,1':3',1"-Terphenyl, 2,2',2",3,3",4,4',4",5,5',5",6,6',6"-tetradecachloro- (CAS RN 42429-89-0)
- 2,3,5,6,2',3',5',6'-Octabromobiphenyl (CAS RN 59080-41-0)
- PBB 053 (CAS RN 60044-25-9)
- 1,1'-Biphenyl, 2,2',3,4,4',5,5'-heptabromo- (CAS RN 67733-52-2)
- 1,1'-Biphenyl, 2,2',3,3',4,4',5,6'-octabromo- (CAS RN 69278-61-1)
- 2,2',3,3',4,5,5',6'-Octabromobiphenyl (CAS RN 69887-11-2)
- 1~2~,1~3~,1~4~,1~5~,1~6~,2~3~,2~4~,3~2~,3~3~,3~4~,3~5~,3~6~-Dodecabromo-1~1~,2~1~:2~2~,3~1~-terphenyl (CAS RN 79596-31-9)
- 2,2',3,3',5,5',6,6'-Octabromo-4-phenoxy-1,1'-biphenyl (CAS RN 83929-69-5)

Among the 37 PHB chemicals used in commerce, 12 can be found in the TSCA inventory. Seven chemicals are in the TSCA active inventory and five PHBs are in the TSCA inactive inventory. In Table 5-2, PHB chemicals found in the TSCA inventory are identified as "Active" or "Inactive," accordingly.

Five other international registries were reviewed: EU REACH (2021), CANADA DSL (2021), MEXICO INSQ (2009), JAPAN CSCL (2021), AND CHINA IECSC (2013).[12] Twenty-five PHB chemicals appear in one or more of these international inventories. In Table 5-2, the number of international registries in which the PHB chemical was identified is listed in the "International Inventories" column.

Fifteen PHB chemicals were identified in the literature through a targeted literature search.[13] In Table 5-2, the numeric value listed in the "Literature Cites" column is the number of sources from the targeted literature search that referenced the chemical.

Twenty-four PHB chemicals were mentioned in patents. The total count of patents is provided for each chemical in Table 5-2, returned from a search of the associated Compound Identifier (CID) in PubChem. For those chemicals that were not associated with a CID, "No CID" is reported in the "Patents" column.

[12] EU REACH = European Union Registration, Evaluation, Authorisation, and Restriction of Chemicals; INSQ = Inventario Nacional de Sustancias Químicas; CSCL = Chemical Substances Control Law; IECSC = Inventory of Existing Chemical Substances Produced or Imported in China.
[13] For additional detail on the methodology used for the targeted literature search, see Section 4.3.1, Targeted Literature Search, in this scope document.

Table 5-2. PHB Chemicals Used in Commerce

CAS RN	Chemical Name	TSCA	International Inventories	Literature Cites	Patents
115245-07-3	1,1'-Biphenyl, 2,4,5-tribromo-	Not found	1	1	0
119264-62-9	2,2',3,3',4,4',5,6,6'-Nonabromo-1,1'-biphenyl	Not found	Not found	1	0
119264-63-0	2,2',3,3',4,5,5',6,6'-Nonobromobiphenyl	Not found	Not found	0	50
13654-09-6	1,1'-Biphenyl, 2,2',3,3',4,4',5,5',6,6'-decabromo-	Inactive	3	5	2,516
14957-65-4	4,4',6,6'-Tetrabromo-2,2'-biphenyldiol	Not found	Not found	0	1
16400-50-3	1,1'-Biphenyl, 3,3',5,5'-tetrabromo-	Not found	1	1	154
198126-86-2	Tetrabromo trichloromethyl benzene	Not found	Not found	1	No CID
2113-57-7	3-Bromobiphenyl	Active	1	1	2,611
27858-07-7	Octabromobiphenyl	Inactive	1	1	1,502
36355-01-8	Hexabromobiphenyl	Inactive	2	2	No CID
56890-89-2	1,2,3,4,7,7-Hexachloro-5-(2,4,6-tribromophenyl)bicyclo[2.2.1]hept-2-ene	Inactive	Not found	0	0
59080-37-4	2,2',5,5'-Tetrabromobiphenyl	Not found	1	0	2
59080-39-6	PBB 103	Not found	1	0	0
59080-40-9	2,2',4,4',5,5'-Hexabromobiphenyl	Not found	1	2	649
59447-57-3	Poly(pentabromobenzyl acrylate)	Active	3	4	4,024
59536-65-1	Polybrominated biphenyls (PBB)	Not found	Not found	3	124
59789-51-4	1H-Pyrrole-2,5-dione, 1-(2,4,6-tribromophenyl)-	Inactive	Not found	1	391
60044-24-8	2,2',4,5-Tetrabromo-1,1'-biphenyl	Not found	1	0	1
60044-26-0	3,3',4,4',5,5'-Hexabromobiphenyl	Not found	1	0	14
608-90-2	Benzene, pentabromo-	Not found	Not found	3	889
626-39-1	1,3,5-Tribromobenzene	Active	1	0	3,936
636-28-2	1,2,4,5-Tetrabromobenzene	Active	Not found	0	455
67888-96-4	1,1'-Biphenyl, 2,2',4,5,5'-pentabromo-	Not found	1	0	0
67888-97-5	2,4,5,3',4'-Pentabromobiphenyl	Not found	1	0	0

CAS RN	Chemical Name	TSCA	International Inventories	Literature Cites	Patents
67888-98-6	2,2',3,4,4',5-Hexabromobiphenyl	Not found	1	0	0
67888-99-7	2,3',4,4'5,5'-Hexabromobiphenyl	Not found	1	0	0
67889-00-3	2,3,4,5,2',3',4',5'-Octabromobiphenyl	Not found	Not found	0	227
69278-59-7	1,1'-Biphenyl, 2,2',3,4',5',6-hexabromo-	Not found	1	0	0
69278-60-0	2,2',3,3',4,4',5-Heptabromobiphenyl	Not found	Not found	0	1
69278-62-2	2,2',3,3',4,4',5,5',6-Nonabromo-1,1'-biphenyl	Not found	Not found	0	18
77102-82-0	PBB 077	Not found	1	0	10
82865-89-2	2,2',3,3',4,4'-Hexabromo-1,1'-biphenyl	Not found	1	0	291
84303-46-8	3,3',4,4',5-Pentabromo-1,1'-biphenyl	Not found	1	0	0
84303-48-0	1,1'-Biphenyl, 2,3',4,4',5',6-hexabromo-	Not found	1	0	0
87-82-1	Hexabromobenzene	Active	2	10	10,670
92-66-0	4-Bromobiphenyl	Active	3	0	7,113
92-86-4	1,1'-Biphenyl, 4,4'-dibromo-	Active	2	1	4,482

Table 5-2 shows that information on commercially used PHB chemicals is available from thousands of patents, numerous literature sources, and multiple chemical inventories.

5.2.2. PHBs Used in Consumer Products

The Market and Use Report identified the use of PHBs in consumer products, including children's products. To determine whether individual OFR chemicals are used in consumer and/or children's products, work performed under a CPSC-sponsored contract reviewed the information available from the EPA's CDR,[14] the European Chemicals Agency's (ECHA) Substances of Concern in articles as such or in complex objects (Products) (SCIP) database, and the IC2's HPCDS. Data on the uses and applications of PHB chemicals were also found in the literature.

Targeted Literature Search. In the literature, several sources report the results of product testing, and these indicate PHBs have been found in a variety of consumer and/or children's products (product reported concentrations are in parentheses), such as:

[14] Data from the review of EPA's CDR for consumer products was generally incomplete, especially for children's products, and therefore are not summarized below however they are available in Section 3.2.5.1 in Volume I of the Market and Use Report.

- Children's toys (mean concentrations between 0.000004% and 0.000016%)
- Construction materials and textiles (maximum concentration 0.0001%)
- Computer casings (0.018%)
- Sound insulation cotton (0.0468%)
- Decorative laminates (0.0165%)
- Foam from car seats (0.000076%)
- Fabric from car seats (0.000013%)
- Composites from car seats (0.000023%)

Of the uses of PHBs in products, chemicals were found in trace contaminant amounts (to date); levels below 0.1% are considered contaminant levels by CPSC staff.[15] The following PHB chemicals were identified from the targeted literature search to have been used in consumer and children's products, and example uses are provided below:

CAS RN 119264-62-9: typewriters, calculator and microfilm-reader housings, business machine housings, radio and TV parts, thermostats, shaver and hand tool housings, projector housings, movie equipment cases, miscellaneous small automotive parts, electrical-wire connectors, switch connectors, speaker grills, small parts for electrical applications, motor housings, and components for industrial equipment.

CAS RN 13654-09-6: insulation, assembly foams, IT devices, upholstered furniture, upholstery foams, mattresses and circuit boards, typewriters, calculator and microfilm-reader housings, business machine housings, radio and TV parts, thermostats, shaver and hand tool housings, projector housings, movie equipment cases, miscellaneous small automotive parts, electrical-wire connectors, switch connectors, speaker grills, small parts for electrical applications, motor housings, and components for industrial equipment.

CAS RN 27858-07-7: typewriters, calculator and microfilm-reader housings, business machine housings, radio and TV parts, thermostats, shaver and hand tool housings, projector housings, movie equipment cases, miscellaneous small automotive parts, electrical-wire connectors, switch connectors, speaker grills, small parts for electrical applications, motor housings, and components for industrial equipment.

CAS RN 36355-01-8: typewriters, calculator and microfilm-reader housings, business machine housings, radio and TV parts, thermostats, shaver and hand tool housings, projector housings, movie equipment cases, miscellaneous small automotive parts, electrical-wire connectors, switch connectors, speaker grills, small parts for electrical applications, motor housings, and components for industrial equipment.

[15] This amount corresponds with information on candidate list substances in articles for which importers and producers have to submit a SCIP notification to the European Chemicals Agency (ECHA) if a substance is present in a concentration above 0.1% weight by weight (Introduction to Information on Candidate List substances in articles ECHA [echa.europa.eu]). CPSC staff rationale is that it should consider 0.1% or below to represent a contamination level given that concentrations of these chemicals when used intentionally as flame retardants are typically much higher.

CAS RN 59080-40-9: insulation, assembly foams, IT devices, upholstered furniture, upholstery foams, mattresses, and circuit boards.

CAS RN 59447-57-3: automotive and electronics.

CAS RN 59536-65-1: polystyrene foam, baby textiles, soft non-PVC toys, baby mattresses, diaper-changing mats, feeding chairs, baths, and aprons.

CAS RN 608-90-2: upholstered furniture, electrical and electronic equipment (EEE), and children's toys.

CAS RN 87-82-1: curtains, upholstered furniture, electrical and electronic equipment (EEE), paper, wood textiles, electronics, plastic, polymers, and children's toys.

HPCDS. Using the HPCDS reporting tool, private industry reports the use of chemicals of concern in products intended for use by children that are sold in select states.[16] From 2012 to 2020, 1,093 reports were submitted to HPCDS identifying the use of OFR chemicals from seven subclasses in children's products sold in two U.S. states, Washington and Oregon. No reports to HPCDS documented the use of PHB chemicals in children's products.

SCIP. ECHA maintains a database of information through the REACH regulation, which was enacted in 2007 to improve the protection of human health from risks posed by chemicals. REACH applies to consumer products as well as to the chemicals industry. The REACH regulation requires suppliers of articles (products) containing potentially hazardous chemicals, including OFRs, to communicate down the supply chain and to consumers sufficient information to allow for the safe use of those products that contain them. Any supplier of an article containing a substance of very high concern (SVHC) in a concentration above 0.1% weight by weight (w/w) on the EU market is required to submit information on that article to ECHA. This information is commonly referred to as a "SCIP notification." From data available from the European Union, SCIP notifications have supported the development of the SCIP database.

The SCIP database is an important tool of the REACH framework and helps ensure that information regarding the use of hazardous substances in products is more readily and efficiently shared within the supply chain, and that certain information regarding the use of hazardous substances in products is also available to the public.

No PHB chemicals were included in the SCIP database. (See Exhibit 3-30 in the Market and Use Report, Volume 1.)

CDR. According to data available from the EPA's CDR, zero PHB chemicals have been reported to be used in commercial or consumer products between 2006 and 2016. However, several sources from the targeted literature search reported the results of product testing indicating PHBs have been found in a variety of consumer and/or children's products.

[16] At this time, CPSC staff is unable to determine if information reported to the HPCDS for Washington and Oregon is representative. Presumably, the number of reports would go up if information for all 50 states were available; however, it is not known whether the chemicals identified and types of children's products would also change.

In addition, the CDR provides an opportunity for firms that report the use of a chemical substance to identify if the substance could be used in children's products. However, the CDR should not be considered a complete source for identifying the use of OFR chemical substances in children's products.[17] In 2006, 2012 and 2016, the use of PHB chemicals in children's products was not reported in the CDR.

5.2.3. Regulatory History and Trends for PHBs

OFRs have received considerable regulatory attention from governmental jurisdictions in the United States and around the world; however, the scope and applicability of these regulatory actions varies significantly. This section describes legislative actions taken in the United States at the state level.

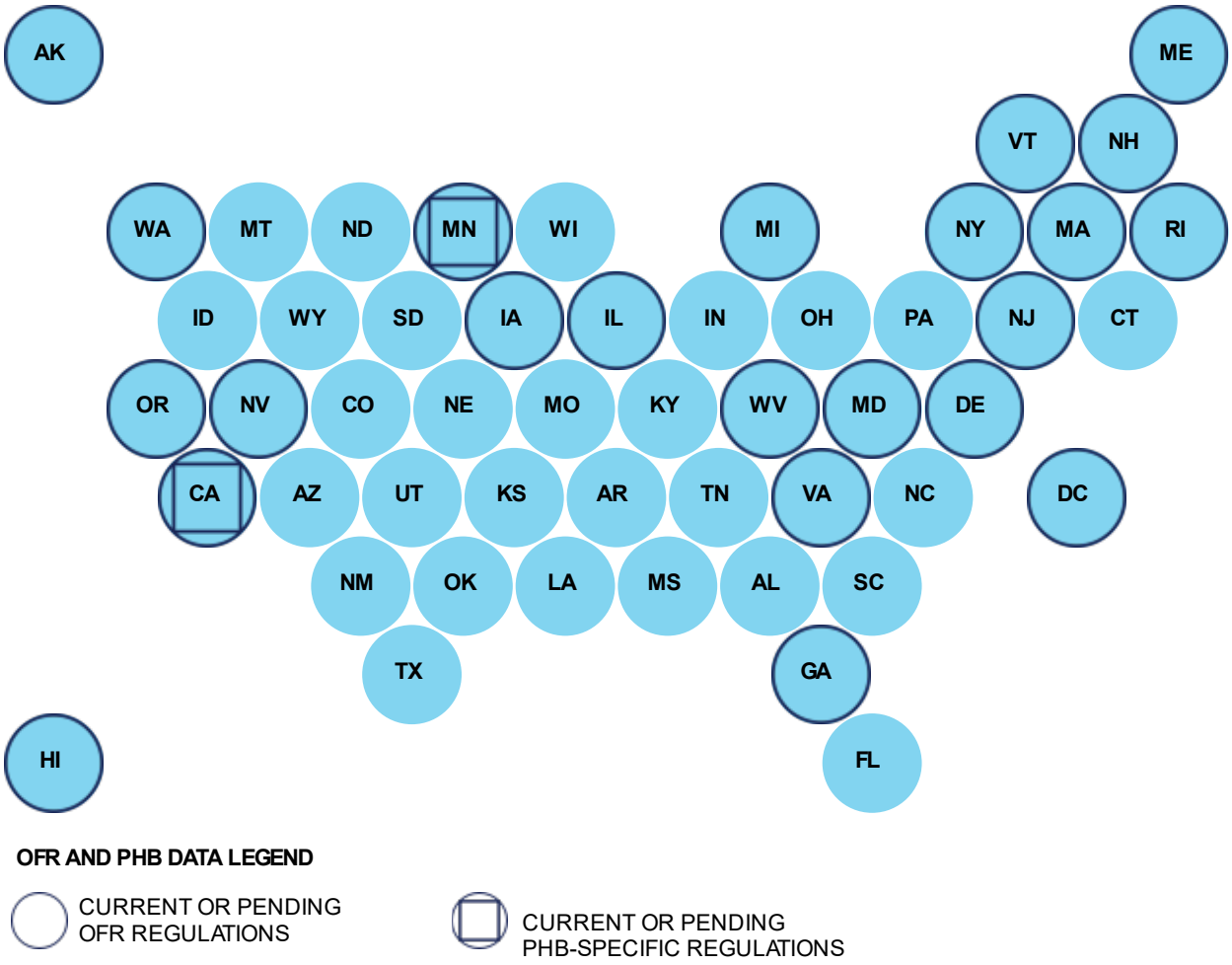
The Market and Use Report provides greater detail of legislative action taken in the United States, as well as by other nations. Volume 2, Appendix R of the Market and Use Report provides detailed fact sheets describing specific pieces of legislation enacted or under consideration since 1986 in 21 U.S. states and the District of Columbia, at the U.S. federal level, and by Canada, the EU, and Japan.[18]

According to the Market and Use Report, 22 states and the District of Columbia have current or pending OFR chemicals regulations. State regulation of OFRs has tended to focus primarily on the use of these chemicals in children's products, upholstered furniture, and mattresses. (See Market and Use Report Volume 1, section 4.1.2.4 Summary of U.S. Regulatory Trends.) Among areas that have regulated the use of OFRs, two states have proposed or enacted regulation of PHBs specifically. In the map below (Figure 5-1), states that regulate OFRs or have pending regulations are shown with a circle border, and states that regulate PHBs specifically or have pending PHB-specific regulations are shown with a square within the circle. For more information on the state regulation of OFRs and PHBs, see Volume 2 of the Market and Use Report, Appendix R.

[17] The CDR rule provides reporting exemptions for chemical substances in articles, byproducts, impurities, non-isolated intermediates, certain polymers, research and development, and those produced by small manufacturers and small importers. 40 C.F.R. §§ 704.5 and 711.6. The CDR rule also exempts chemical substances manufactured in quantities of less than 2,500 pounds. *Id.* at § 711.15.

[18] As part of work performed under the CPSC-sponsored contract, CPSC staff also sought to identify legislation developed in China related to OFRs. The literature review suggests China imposes some restrictions on OFRs, which is discussed more generally in Section 4.1.3 of Volume 1 of the Market and Use Report.

Figure 5-1. U.S. States That Regulate the Use of OFR and PHB Chemical Flame Retardants



The sharing of data reported to states helps to improve the effectiveness of enacted legislation on potentially hazardous OFR chemicals and to address information asymmetries in the market. Increasingly, state legislation compels reporting and allows for reciprocal data-sharing agreements with trade associations, the IC2, or other independent third parties. Reported data are also shared with the public. According to data compiled in the Market and Use Report (see Appendix R of Volume 2), eight states and the District of Columbia have reporting or data-sharing requirements for OFR chemicals.

5.3. Literature Survey Results: Evidence Maps of Toxicity Data

The toxicity evidence map descriptions below are high-level observations of the Level 2, 3, and 3B literature surveys in the designated spreadsheet files.[19] The database counts indicate either the number of sources within the database (if available) or the number of entries in the database (if no information on source is available) after attempts were made to remove duplicates. The unit for PDF counts is the individual PDF file. Level 3B tagging was performed on a subset of toxicity assessments, toxicity literature reviews, and risk assessments selected from Level 3 to identify even more specific information for the chemicals in these references. Note that most of the Level 3B data are from database data, and only a subset of the PDF data sources is tagged at Level 3B.

The general observations from the Level 2, 3, and 3B reviews are:

- PHB members PBB, hexabromobenzene, and hexabromobiphenyl had the highest number of toxicity data sources in many categories.
- PHB member 2,2',4,4',5,5'-hexabromobiphenyl had the most representation across toxicity categories for database and PDF reviews.
- The *QSAR, Read-across, Analog* category (QSAR = quantitative structure activity relationships) had broad representation with 92.3% of PHB members and 94.6% of analogs having at least one data source at Level 3 review and similar representation at Level 3B.

5.3.1. Summary of Level 2

The "Integrated" tab contains summed Level 2 toxicity data counts across PDF and database data.[20]

The literature survey identified integrated data sources (sum of databases and PDFs) for 37 of 39 PHB members and for 105 of 111 analogs. The PHB members with the most data sources were polybrominated biphenyls, hexabromobenzene, and 2,2',4,4',5,5'-Hexabromobiphenyl. Table 5-3 summarizes how many PHB members and analogs had different degrees of data source abundance.

Table 5-3. Distribution of Toxicity Data Source Abundance Levels at Level 2

Distribution of Number of Data Sources Available for Each Chemical	Number of Chemicals with Level 2 Toxicity Data Sources	
	PHB Chemicals (n = 39)	Analog Chemicals (n = 111)
21+	3	0
6–20	14	3
1–5	20	102
0	2	6

[19] See evidence map files on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.
[20] See evidence map file "PHACH Level 2 Evidence Maps 12.2.22, Tab: Integrated" on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

5.3.2. Summary of Levels 3 and 3B

The "TOX_Integrated" tabs from each evidence map file contain Level 3 and Level 3B toxicity data counts across all toxicity databases and PDFs.[21] The Level 3B tabs were divided into A, B, and C to keep the spreadsheets manageable. Integrated Level 3B counts report the sum of data sources from databases and selected PDFs (i.e., not all PDFs identified at Level 3 were reviewed at Level 3B). The integrated counts indicate the number of data sources per chemical from databases and PDFs identified and classified into seven toxicity data type categories. At Level 3B, reviewers tagged the data sources from each category with subcategories to provide additional details of specific data types. Table 5-4 and Table 5-5 summarize how many PHB members and analogs had different degrees of Level 3 toxicity data source abundance.

Table 5-4. Distribution of Toxicity Data Source Abundance Levels at Level 3 – Chemicals

Distribution of Number of Data Sources Available for Each Chemical	Number of Chemicals with Level 3 Toxicity Data Sources PHB Chemicals (n = 39)						
	Animal Toxicity or Accepted Alternative	Human Toxicity	Human, Animal, or Modeled Toxicokinetics (ADME)	Experimental Mechanistic	QSAR, Read-Across, Analog	Qualitative Hazard Characterization	Quantitative Hazard Characterization
21+	3	0	2	6	29	2	2
6–20	4	2	13	3	6	2	2
1–5	17	3	13	9	1	10	17
0	15	34	11	21	3	25	18

[21] See evidence map file "PHACH Level 3 Evidence Maps 12.2.22, Tab: TOX Integrated" and "PHACH Level 3B Evidence Maps 12.2.22, Tab: TOX Integrated" on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

Table 5-5. Distribution of Toxicity Data Source Abundance Levels at Level 3 – Analogs

Distribution of Number of Data Sources Available for Each Chemical	Number of Chemicals with Level 3 Toxicity Data Sources						
	PHB Analogs (n = 111)						
	Animal Toxicity or Accepted Alternative	Human Toxicity	Human, Animal, or Modeled Toxicokinetics (ADME)	Experimental Mechanistic	QSAR, Read-Across, Analog	Qualitative Hazard Characterization	Quantitative Hazard Characterization
21+	0	0	0	2	37	0	0
6–20	2	0	12	3	13	0	1
1–5	18	0	25	6	55	4	3
0	91	111	74	100	6	107	107

Animal Toxicity or Accepted Alternative data sources were available for 24 PHB members and 20 analogs at Level 3 review. Twenty-two PHB members and five analogs had data in the databases and PDFs at Level 3B review. Level 3B reviews provided additional detail for nine subcategories: Acute Toxicity, Systemic or Repeated Dose Toxicity, Neurotoxicity, Carcinogenicity, Mutagenicity/Genotoxicity, Reproductive Toxicity/Developmental Toxicity, Irritation, Sensitization, and Endocrine Disruption. CPSC staff observed the following:

- PHB member PBB had data sources in all subcategories.
- PHB member Hexabromobiphenyl had data sources for all subcategories except Sensitization.
- PHB member 1,1'-biphenyl, 2,2',3,3',4,4',5,5',6,6'-decabromo- had data sources for all subcategories except Neurotoxicity and Endocrine Disruption.
- Systemic or Repeated Dose Toxicity was the subcategory with data sources for the most PHB members.
- Analog PBB 004 had one or two data sources for the Acute Toxicity, Mutagenicity/Genotoxicity, Irritation and Sensitization subcategories.

Human Toxicity data sources were available for five PHB members and 20 analogs at Level 3 review. Four PHB members and no analogs had data in the databases and PDFs at Level 3B review. Level 3B reviews provided additional detail for the same nine subcategories used for *Animal Toxicity or Accepted Alternative* above. CPSC staff observed the following:

- PHB member PBB had one data source in each of the subcategories Systemic or Repeated Dose Toxicity, Neurotoxicity, Reproductive Toxicity/Developmental Toxicity, and Irritation; and two data sources in each of the Carcinogenicity and Endocrine Disruption subcategories.
- PHB member hexabromobiphenyl had one data source in each of the subcategories Systemic or Repeated Dose Toxicity, Neurotoxicity, Carcinogenicity, and Reproductive Toxicity/Developmental Toxicity.

Human, Animal, or Modeled Toxicokinetics (ADME [absorption, distribution, metabolism, and excretion]*)* data sources were available for 28 PHB members and 37 analogs at Level 3 review. Twenty-nine PHB members and 39 analogs had data in the databases and PDFs at Level 3B review. Level 3B reviews provided additional detail on seven subcategories: Human Absorption, Distribution, Excretion; Animal Absorption, Distribution, Excretion; Human Metabolism; Animal Metabolism; In Vitro; Chemical- or Class-Specific physiologically based pharmacokinetic (PBPK) Model; and Chemical- or Class-Specific QSAR for an ADME Parameter. CPSC staff observed the following:

- PHB member 2,2',4,4',5,5'-hexabromobiphenyl had data sources in all subcategories. This was the only chemical in the PHB subclass that had data in the Chemical- or Class-Specific PBPK Model subcategory.
- The subcategory with the most data sources and for the most chemicals was Chemical- or Class-Specific QSAR for an ADME Parameter, with data sources identified for 24 PHB members and 34 analogs.
- The subcategory with the second most data sources and for the most chemicals was Human Absorption, Distribution, Excretion, with data sources identified for 19 PHB members and 13 analogs.

Experimental Mechanistic data sources were available for 18 PHB members and 11 analogs at Level 3 review. Fifteen PHB members and nine analogs had data in the databases and PDFs at Level 3B review.[22] This category had two subcategories at Level 3B review separating those data sources that make a connection to a mode of action (MOA) and a potential health effect from those that do not.[23] CPSC staff observed the following:

- Eight PHB members and two analogs had data sources in both subcategories.
- Seven PHB members had 93 to 279 data sources in the Study Makes Connection to MOA and Potential Health Effect subcategories.

QSAR, Read-Across, Analog data sources were available for 36 PHB members and 105 analogs at Level 3 review. Thirty-seven PHB members and 105 analogs had data in the databases and PDFs at Level 3B review. Level 3B reviews provided additional detail across the

[22] See "TOX_DB" and "TOX_PDF" tabs of evidence map file on the CPSC Organohalogen Flame Retardant Chemicals Assessment website. The 3B data counts for Experimental Mechanistic data are presented only in the "TOX_DB" and "TOX_PDF" tabs and not in the "TOX_Integrated" tab, because PubChem Bioassay data did not contain enough information to distinguish between the Level 3B tags for mechanistic data.
[23] Many database sources could not be tagged for Level 3B because it was not clear whether a connection was made to MOA.

same nine subcategories used for *Animal Toxicity or Accepted Alternative* above. CPSC staff observed the following:

- Sixteen PHB members and 31 analogs had data sources in all subcategories except Neurotoxicity.
- One PHB member, poly(pentabromobenzyl acrylate), had data sources in all subcategories except Endocrine Disruption. This was the only PHB member with a data source in the Neurotoxicity subcategory. The vast majority of data with the *QSAR, Read-across, Analog* tag are from the Danish QSAR Database, which does not include any data that are taggable as Neurotoxicity.

Qualitative Hazard Characterization data sources were available for 14 PHB members and four analogs at Level 3 review. Twelve PHB members and four analogs had data in the databases and PDFs at Level 3B review. In contrast with all other data types, a tag for Qualitative Hazard Characterization indicates that a review/assessment was attempted, not necessarily that data were found (e.g., if a review/assessment clearly stated that authors looked for data for endpoint X for chemical Y but found none, chemical Y was tagged for Qualitative Hazard Characterization for endpoint X, but not as any other data type.) This category was separated into the same nine subcategories used for *Animal Toxicity or Accepted Alternative* above for Level 3B review. CPSC staff observed the following:

- PHB member PBB had data sources for all nine subcategories.
- PHB members hexabromobiphenyl; 1,1'-biphenyl, 2,2',3,3',4,4',5,5',6,6'-decabromo-; and poly(pentabromobenzyl acrylate) had data sources in all subcategories except Endocrine Disruption.

Quantitative Hazard Characterization data sources were available for 21 PHB members and four analogs at Level 3 review and in the databases and PDFs at Level 3B review. At Level 3B review, this category was further divided into seven subcategories: Acute Toxicity, Systemic or Repeated Dose Toxicity, Neurotoxicity, Carcinogenicity, Reproductive Toxicity/Developmental Toxicity, Sensitization, and Endocrine Disruption. CPSC staff observed the following:

- PHB member hexabromobiphenyl had data sources available in all subcategories except Sensitization. This was the only PHB member with a Neurotoxicity data source.
- Subcategories Acute Toxicity and Systemic or Repeated Dose Toxicity had the most data sources for PHB members and analogs.
- No PHB members or analogs had data in the Sensitization subcategory.

5.4. Literature Survey Results: Evidence Maps of Exposure Data

The exposure evidence maps below describe high-level observations of the Level 2, 3, and 3B literature surveys in the indicated spreadsheet files.[24] Level 3B tagging was performed on a subset of 25 toxicity exposure literature reviews selected from Level 3 to identify even more specific information for the chemicals in these references. The database counts indicate the number of entries in the Multimedia Monitoring Database (MMDB). The unit for PDF counts is

[24] Exposure evidence map files are available on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

the individual PDF file. PHB analogs were not included in the exposure evidence map analyses because exposure to the analogs is outside the scope of the current project.

The general observations from the Level 2, 3, and 3B reviews are:

- PHB members PBB; 2,2',4,4',5,5'-hexabromobiphenyl; and hexabromobenzene had the highest number of data sources in at least half of the categories.
- PHB members PBB and hexabromobenzene had the most representation across exposure categories for database and PDF reviews.

5.4.1. Summary of Level 2

The MMDB database and PDF searches identified exposure data sources for 28 of 39 PHB members.[25] The PHB members with the most data sources were polybrominated biphenyls, hexabromobenzene, and 2,2',4,4',5,5'-hexabromobiphenyl. Table 5-6 summarizes how many PHB members had different degrees of data source abundance. The PDFs provided more total data sources and covered more PHB members than the database.

Table 5-6. Distribution of Exposure Data Source Abundance Levels at Level 2

Distribution of Number of Data Sources Available for Each Chemical	Number of Chemicals with Level 2 Exposure Data Sources PHB Chemicals (n = 39)
21+	3
6–20	7
1–5	18
0	11

5.4.2. Summary of Levels 3 and 3B

The "EXP_Integrated" tabs from each exposure evidence map file contains Level 3 and 3B exposure data counts.[26] The Level 3 integrated counts indicate the number of data sources per chemical from the MMDB database and identified PDFs. Level 3 counts were classified into six exposure data type categories. Integrated Level 3B counts report the sum of data sources from MMDB and selected PDFs. At Level 3B, reviewers tagged the data sources to subcategories to provide additional details of specific data types. Table 5-7 summarizes how many PHB members had different degrees of Level 3 exposure data source abundance.

[25] Exposure evidence map files are available on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.
[26] Exposure evidence map files are available on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

Table 5-7. Distribution of Exposure Data Source Abundance Levels at Level 3

Distribution of Number of Data Sources Available for Each Chemical	Number of Chemicals with Level 3 Exposure Data Sources					
	PHB Chemicals (n = 39)					
	Environmental Monitoring	Biomonitoring/ Personal Monitoring	Source Characterization	Epidemiology – Population Group	Modeled Concentrations	Modeled Human Dose
21+	3	3	2	0	0	1
6–20	4	0	4	1	0	0
1–5	14	14	20	7	3	7
0	18	22	13	31	36	31

Environmental Monitoring data sources were available for 21 PHB members at Level 3 review. Nineteen PHB members had data in the database and PDFs at Level 3B review. This category was separated into six subcategories for Level 3B review: Indoor/Personal Air, Indoor Dust, Outdoor Air, Food/Dietary, Soil, and Drinking Water.

- PHB member PBB had data sources in all of the subcategories except Drinking Water; and had a high number of hits for the Indoor Dust and Food/Dietary subcategories.
- The Food/Dietary subcategory had data sources for the most PHB members (n = 17).

Biomonitoring/Personal Monitoring data sources were available for 17 PHB members at the Level 3 and Level 3B reviews. This category was separated into five subcategories for Level 3B review: Blood/Serum, Urine, Breast Milk/Lipids, Skin/Dermal, and Human (Other).

- PHB member PBB had data sources in all of the subcategories except Urine; and had a high number of hits for the Blood/Serum, Breast Milk/Lipids, and Human (Other) subcategories.
- PHB member 2,2',4,4',5,5'-hexabromobiphenyl had a high number of hits for the Blood/Serum and Breast Milk/Lipids subcategories.
- The Blood/Serum subcategory had data sources for the most PHB members (n = 16).

Source Characterization data sources were available for 26 PHB members at Level 3 review. Twenty-one PHB members had data in the database and PDFs at Level 3B review. This category was separated into four subcategories for Level 3B review: Product Testing: Content Only, Product Testing: Emission/Migration Data, Nonexperimental Product- or Chemical-Specific Modeling Inputs, and Other Qualitative or Quantitative Description of Product Use or Class/Chemical.

- PHB member hexabromobenzene had data sources in all of the subcategories except Emission/Migration Data; and had a high number of hits for the Product Testing: Content Only subcategory. This was the only PHB member with a Product Testing: Content Only data source.
- The Other Qualitative or Quantitative Description of Product Use or Class/Chemical subcategory had data sources for the most PHB members (n = 21).

Environmental Epidemiology[27] data sources were available for eight PHB members at Level 3 review. Five PHB members had data in the database and PDFs at Level 3B review. The subcategories were Children; Adult, Non-Occupational; and Other, Specify (with Suggestions).

- PHB member hexabromobenzene had data sources in the Children and Adult, Non-Occupational subcategories. This was the only PHB member with a Children data source.
- The Adult, Non-Occupational subcategory had data sources for five PHB members.

Modeled Concentrations data sources were available for three PHB members at Level 3 review. Level 3B reviews of the database and PDFs found no sources in any of three subcategories (Indoor Concentration, Outdoor Concentration, and Dietary/Food).

Modeled Human Dose data sources were available for eight PHB members at Level 3 review. Five PHB members had data in the database and PDFs at Level 3B review. The subcategories were Children; Adult, Non-occupational; and Other, Specify (with Suggestions). PHB members hexabromobenzene and PBB 103 had data sources in the Children and Adult, Non-Occupational subcategories.

5.5. Literature Survey Results: Summary of Existing Human Health Risk Assessments

None of the "Database" (DB) tabs at Levels 2, 3, or 3B reported risk assessment data sources. Therefore, the Integrated and PDF data counts for Human Health Risk Assessments are identical at all levels. In the files that reported PDF data sources, human health risk assessments were included in the tabs for spreadsheets displaying toxicity data sources.

5.5.1. Summary of Level 2

The "Integrated" tab of the risk evidence map file contains summed Level 2 risk data counts from PDF sources.[28] No risk data were found in the databases. Six PHB members and no analogs had PDF data sources for risk at Level 2 review. Table 5-8 summarizes how many PHB members had different degrees of data source abundance. Hexabromobenzene had the highest numbers of human health risk assessments available.

[27] The category *Environmental Epidemiology* here was identified as "*Epidemiology – POP Group*" in the "EXP_Integrated_C" tab of the Excel file, which can be found on the CPSC Organohalogen Flame Retardant Chemicals Assessment website). The change was made in this document for clarity.
[28] Risk evidence map files are available on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022

Table 5-8. Distribution of Human Health Risk Data Sources Abundance Levels at Level 2

Distribution of Number of Data Sources Available for Each Chemical	Number of Chemicals with Level 2 Risk Data Sources
	PHB Chemicals (n = 39)
21+	0
6–20	1
1–5	5
0	33

5.5.2. Summary of Levels 3 and 3B

The ”Integrated” tab for the Level 3 file contains the *Human Health Risk Assessment* counts from PDF data sources.[29] The “TOX_PDF” tab for Level 3B contains the *Human Health Risk Assessment* counts from 25 PDFs that were selected for 3B extraction. The counts indicate the number of PDFs identified per chemical for each Noncancer and Cancer risk assessment. Table 5-9 summarizes how many PHB members and analogs had different degrees of Level 3 human health risk data source abundance.

Human Health Risk Assessment data were available for six PHB members and no analogs at Level 3 review. Three PHB members and no analogs had data in the selected PDFs at Level 3B review. The subcategories used were Noncancer Risk and Cancer Risk, with 25 Noncancer Risk and nine Cancer Risk assessments identified. Staff noted the following observations:

- PHB member PBB had one Noncancer Risk and one Cancer Risk data source.
- PHB members 1,1'-Biphenyl, 2,2',3,3',4,4',5,5',6,6'-decabromo- and 1,1'-Biphenyl, 2,2',4,5,5'-pentabromo- each had one Noncancer Risk data source.

Table 5-9. Distribution of Human Health Risk Data Sources Abundance Levels at Level 3

Distribution of Number of Data Sources Available for Each Chemical	Number of Chemicals with Level 3 Risk Data Sources
	PHB Chemicals (n = 39)
21+	0
6–20	1
1–5	5
0	33

5.6. Literature Survey Results: Key References

Among the literature survey results are several references from authoritative sources. These references include a carcinogenicity profile by the National Toxicology Program (NTP) and a U.S. Environmental Protection Agency (EPA) review. These reports included two PHBs (CAS

[29] Risk evidence map files are available on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

RN 36355-01-8; CAS RN 87-82-1) and one PHB analog (CAS RN 615-54-3). None of these PHBs appear in the PHBs market use report. These reports demonstrate the existence of data about these chemicals, including hazard and potential exposures, that are sufficient to support hazard, exposure, and risk assessment, and are likely to be useful references for CPSC staff evaluations of these and other PHBs.

6. Scoping Determination and Next Steps

6.1. Scoping Determination

Informed by initial review of the market and use research, evidence maps, and availability of physicochemical data for the PHB subclass and its analogs, and the criteria described in Section 4.1, Criteria for Scoping Determination, CPSC staff concludes, at the time of writing, that the PHB subclass has sufficient data to proceed with risk assessment.

The criteria for sufficiency for hazard assessment for the subclass require that the subclass and analogs must have at least one data rich chemical, multiple chemicals with some data, and two chemicals are “no data” substances.

CPSC staff concludes that the PHB subclass includes six data rich chemicals and that a majority of PHB chemicals and some analogs have some data. The evidence maps show that many PHB chemicals have data in the Animal Toxicity or Accepted Alternative category, including among acute, systemic or repeated dose toxicity, or reproductive/developmental studies. In addition, a majority of PHB chemicals and some analogs have data in the experimental, mechanistic, and QSAR categories, all of which may be used to support further analyses, including performing read-across analyses for predictions among class members with less available data.

The criteria for sufficiency for exposure assessment for the subclass require that the subclass must have at least one data rich chemical and multiple chemicals with some data.

CPSC staff concludes that the subclass includes up to 10 data rich chemicals and that a majority of chemicals have some data. In addition, according to available data sources, 37 of the 50 chemicals have market information for use in commerce.

Following the determination that the PHB subclass has sufficient data to proceed with risk assessment, the sections below outline the next steps that CPSC staff plans to take, resources permitting. Below, CPSC staff provides plans for analysis to complete a class-based risk assessment. The first analysis plan describes how CPSC staff will consider data in the development of a class-based hazard identification and dose response assessment for select endpoints. The second analysis plan describes how CPSC staff will consider data in a class-based human exposure assessment. The last step of both analysis plans is identical in that CPSC staff will consider how to combine class-based human exposure estimates with class-based toxicity reference values in a class-based risk assessment.

6.2. Next Steps for Class-Based Hazard Assessment

6.2.1. Analysis Plan

CPSC staff plans to actively work on the remaining list of activities outlined below. Many of these activities can be undertaken concurrently, as resources are available. Before completing a hazard analysis, CPSC staff expects to consider and analyze data that could inform hazard identification and dose-response as follows, if resources are available:

1. CPSC staff, in coordination with the Division of Translational Toxicology (DTT) at the National Institute of Environmental Health Sciences, is working on a comprehensive literature search. Available toxicity information from PHB class members and analogs will be further summarized and integrated after this search is complete. After the search, staff will refine the list of data rich PHBs, data rich PHB analogs, PHBs with some toxicity information, and PHBs with no toxicity information.
2. CPSC staff plans to complete a systematic evidence map that will be based on a scoping review in coordination with DTT. This evidence map will include a wide range of toxicity data (e.g., animal, human, mechanistic, QSAR, read-across, new approach methodologies [NAMs][30]) from the comprehensive literature search.
3. CPSC staff will refine the NAS analog list and characterize analog substances for the PHB class that are both chemically and toxicologically similar and have any amount of empirical toxicity information. Analog substances that are data poor, and not sufficiently similar to PHB class members to be associated with them, will be deprioritized. CPSC staff's initial survey shows that empirical toxicity data are available for 20 analogs and empirical toxicokinetic data are available for 37 analogs.
4. CPSC staff will estimate major metabolites of PHB class members by interpreting results from the major metabolite prediction tools, such as GLORYx and the OECD QSAR toolbox, and comparing these results with data presented in the literature. CPSC staff will consider predicted and measured metabolites to inform class-based approaches for hazard identification.
5. CPSC staff plans to use a read-across approach that incorporates multiple types of data (i.e., animal, human, mechanistic, QSAR, read-across). Data rich PHB class members and analogs with available toxicity data can be used to read-across to PHB class members with insufficient data to estimate toxicity reference values for one or more endpoints of concern. The initial CPSC literature survey suggests that toxicity endpoints that are likely higher priority for the PHB class are acute toxicity, systemic repeat dose toxicity, carcinogenicity, and mutagenicity/genotoxicity.
6. CPSC staff will identify a smaller number of endpoint(s) and studies that are candidates for identifying points of departure (POD) and generating toxicity reference values for multiple PHB class members. PODs may be developed using a wide range of toxicity studies (e.g., animal, human, NAM, QSAR, read-across). CPSC staff will identify studies

[30] NAMs include any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals. NAM studies may include studies using human or animal cells and tissues (i.e., in vitro assays, ex vivo studies), toxicity testing using alternative animal species, such as zebrafish and nematodes, and a variety of computational modeling approaches.

with a range of reported doses and associated contextual information when developing dose-response information. Benchmark dose modeling will be used as appropriate.
7. CPSC staff will compare these values with toxicity reference values developed by other organizations for PHB class members.
8. CPSC staff will explore the variability and uncertainty associated with dose response values for PHB chemicals within the class.
9. CPSC staff will use information developed in a class-based hazard assessment and dose-response assessment to support a class-based risk assessment for PHBs.

6.2.2. Initial Human Health Hazard Observations for Class-Based Assessment of PHBs

The primary objective of completing a literature survey for a subclass of OFRs is to array available information and determine whether a class-based assessment is possible. CPSC staff considers class-based exposure assessment possible for any class if data on consumer uses and physicochemical properties are available. However, CPSC staff considers class-based hazard assessment as highly data dependent. Thus, whether a class-based risk assessment is possible depends on the availability of different types of human hazard data. When sufficient human health hazard data were identified from the literature survey, this section of the scope document includes initial observations informed by review of select data sources.

Polybrominated biphenyls (PBBs) are insoluble in water and those with three or more bromine atoms are solids with low volatility. Increasing the number of bromine atoms decreases the volatility. Much of the available data on PBBs derive from two commercial mixtures, FireMaster FF-1 and FireMaster BP-6. Hexabromobiphenyl (HBBP) is the main component of FireMaster FF-1, but the mixture also includes pentabromobiphenyls and heptabromobiphenyls (NTP, 2021). The major components of FireMaster BP-6 are pentabromobiphenyls (4%), hexabromobiphenyls (62.6%), and heptabromobiphenyls (33.4%) (NTP, 2021).

The primary targets of PBBs in experimental animals are the liver, kidney, and thyroid. Body weight loss, skin disorders, and nervous system effects are also reported in animal studies. Based on an exposure registry on people who ate food contaminated with PBBs, PBBs did not cause definite liver or immune system effects, but skin disorders were observed, including acne and hair loss (ATSDR, 2004).

The thyroid is a clear target of PBBs in rodents, causing decreased serum levels of T4 and T3 and follicular hyperplasia (ATSDR, 2004). Most of the available studies were conducted with FireMaster FF-1 or FireMaster BP-6. There is some support from human data of the thyroid as a target. Workers exposed to unspecified PBBs and/or decabromobiphenyl (congener not identified) had decreased serum T4 (ATSDR, 2004). ATSDR (2004) did not address the mechanism of the effect on the thyroid.

Several studies suggest an effect on female reproduction, but ATSDR (2004) did not report on estrogen receptor binding. Monkeys fed FireMaster FF-1 had increased menstrual cycle duration and decreased serum progesterone. Delayed vaginal opening was observed in the offspring of rats fed FireMaster FF-1 from GD8 through weaning (ATSDR, 2004). Workers exposed to unspecified PBBs and/or decabromobiphenyl (congener not identified) had increased serum follicle stimulating hormone (ATSDR, 2004).

Several of the effects of PBBs resemble those of dioxin and are consistent with aryl hydrocarbon receptor (AhR)-mediated mode of action. These effects include altered vitamin A homeostasis, thymic atrophy, dermal and ocular effects (including chloracne and inflammation of eyelids), and wasting syndrome. To a large degree, mechanistic data on these chemicals comes from in vitro studies of binding to AhR (tetrabromobiphenyl bound with a higher affinity than hexabromobiphenyl). Binding affinity is stereospecific, with congeners substituted in both para and two or more meta positions binding with higher affinity (ATSDR, 2004). PBB mixtures also induced CYP1A1 and CYP1A2, consistent with the effect of other AhR agonists. Structure-toxicity analyses found that AhR induction correlated with immunological and hepatic effects, with the most toxic congeners being structurally related to 2,3,7,8-TCDD. Ortho-substituted congeners act via an AhR-independent MOA, and have a different spectrum of effects, including neurotoxicity (ATSDR, 2004).

PBBs are not genotoxic, based on negative results in bacterial and mammalian gene mutation assays and chromosome aberration assays (ATSDR, 2004). A full suite of assays does not appear to be available for any specific congener or group of congeners, but the results were consistently negative for PBBs containing 5, 6, or 10 bromines.

The Report on Carcinogens labeled polybrominated biphenyls (PBBs) as reasonably anticipated to be human carcinogens, based on sufficient evidence of carcinogenicity in experimental animal studies (NTP, 2021). This conclusion was based on multiple studies in rats and mice with FireMaster FF-1. Oral exposure to FireMaster FF-1 resulted in hepatocellular carcinoma in mice and rats of both sexes and cholangiocarcinoma (bile duct cancer) in rats of both sexes. Informative human data are limited, but a PBB-exposure registry found a significant exposure-response based on serum HBB concentration with lymphoma and digestive system cancer.

The polyhalogenated benzenes (PHBs) are a very data rich class, and include the PBBs, as well as derivatives with a single benzene ring (e.g., HBB) and chemicals with three benzene rings (terphenyls). Overall, there is substantial support for treating PBBs as a class, and much of the literature addresses the PBBs as such (e.g., ATSDR, 2004). However, even among the PBBs, it appears that there are substantial differences among congeners, depending on the position of substitution and similarity to 2,3,7,8-TCDD, and that it may be necessary to categorize the PBBs based on structure.

6.3. Next Steps for Class-Based Exposure Assessment

6.3.1. Analysis Plan

CPSC staff plans to actively work on the remaining list of activities outlined below. Many of these activities can be undertaken concurrently, as resources are available. Before completing a hazard analysis, CPSC staff expects to consider and analyze data that could inform hazard identification and dose-response as follows, as resources permit:

1. CPSC staff, in coordination with DTT staff, is working on a comprehensive literature search. Available exposure information from PHB class members will be further summarized and integrated after this search is complete. After the search, staff will refine the list of data rich PHBs, PHBs with some exposure and use information, and PHBs with no exposure and use information.

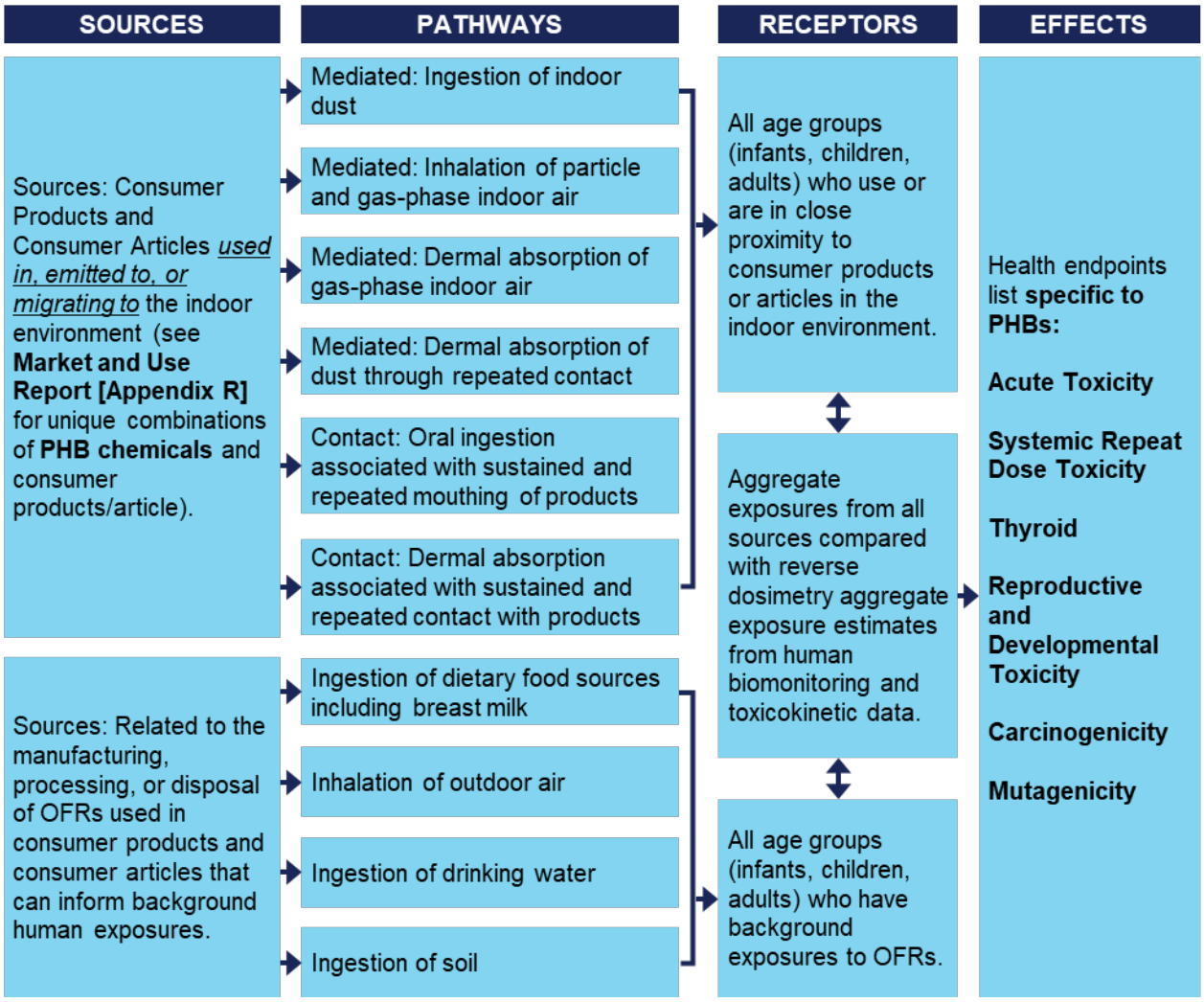
2. Using the market and use research, CPSC staff expects to compile a list of PHB chemicals that have been or could be used in consumer products. While 37 of the 50 chemicals had some market-use information, 10 PHB chemicals had more market and use information that could be used to inform analyses of PHB chemicals with less information. CPSC staff will characterize uses for PHBs according to available information and consider temporal trends when developing exposure scenarios.
3. CPSC staff will characterize the uses identified in the market and use research and combine this information with likely exposure pathways and populations exposed to define unique combinations of exposure scenarios for chemical substances within the class. Depending on available information, CPSC may be able to quantify exposure scenarios for between 10 and 37 PHB subclass members.
4. Exposure pathways with likely higher potential for PHB class members include dietary ingestion, drinking water ingestion, contact exposures with consumer products and articles, indoor dust ingestion, and inhalation of indoor air. Exposure pathways with likely lower potential for PHB class members include inhalation of ambient air and soil ingestion. CPSC staff will review available environmental monitoring data to determine a range of potential concentrations to which people could be exposed. There are 28 chemicals in the class with source characterization data, 21 chemicals in the class with environmental monitoring data, and 19 chemicals in the class with both types of data.
5. CPSC staff plans to review measurement techniques and analytical methods and assess how they have changed over time with regard to identification and quantification of PHB chemicals. Lack of detection in older studies may be due to older analytical methods with higher detection limits, whereas presence in newer studies may be due to newer analytical methods with lower detection limits. CPSC staff plans to evaluate reported methods and how they influence likely distributions of OFRs in different environmental media or biological matrices.
6. CPSC staff will explore the connection between consumer product sources and reported levels in environmental media by estimating environmental concentrations for a range of uses and determining whether these estimates fall within the range of reported environmental monitoring data. CPSC staff plans to consider indoor exposure modeling, modeling approaches specific to semi-volatile organic compounds (SVOCs), and product-testing measurement techniques that characterize emissions or migration of OFRs from products into the indoor environment. When environmental monitoring is not available for comparison, CPSC staff will estimate environmental concentrations for the range of reported uses. There are seven chemicals in the class with source characterization data and no corresponding environmental monitoring data.
7. CPSC staff will explore the connection between reported or estimated environmental concentrations and reported exposures from human biomonitoring data. First, doses will be estimated using reported or estimated environmental concentrations and population specific exposure factors and activity patterns. Second, doses will be estimated using reported human biomonitoring data and reported or estimated toxicokinetic data. There are 14 PHB class members with both environmental monitoring data and human biomonitoring data.

8. CPSC staff plans to use multiple approaches to estimate exposures and doses for multiple age groups and populations. CPSC staff plans to develop both deterministic and probabilistic estimates of dose, as data allow. CPSC staff will explore the variability and uncertainty associated with exposure and dose estimates for the population groups included in the human exposure assessment.
9. CPSC staff will use information developed in a class-based exposure assessment to support a class-based risk assessment for PHBs.

6.3.2. Conceptual Exposure Model

A conceptual exposure model visually represents connections between sources, pathways, receptors, and health effects. Figure 6-1 shows the conceptual exposure model for the PHB subclass. Sources are grouped into (i) those that can be related back to consumer products and (ii) all other sources that can inform background exposures. These sources will be part of a generic background exposure scenario. Each product/source will be part of an exposure scenario and quantified. Exposure pathways similarly are grouped into pathways related to emission or migration from consumer products and pathways related to occurrence in non-consumer product-related media. Receptors include human populations of all age groups for which human biomonitoring data will be used to inform ranges of aggregate exposures from all sources. Finally, human health effects most likely to be considered for PHBs are listed.

Figure 6-1. PHB Conceptual Exposure Model



7. References

Agency for Toxic Substances and Disease Registry (ATSDR). (2004). *Toxicological profile for polybrominated biphenyls*. U.S. Department of Health and Human Services, Public Health Service. https://www.atsdr.cdc.gov/ToxProfiles/tp68.pdf

Bevington, C., Williams, A.J., Guider, C., Baker, N.C., Meyer, B., Babich, M.A., Robinson, S., Jones, A., & Phillips, K.A. (2022). Development of a flame retardant and an organohalogen flame retardant chemical inventory. *Scientific Data, 9*, Article 295. https://doi.org/10.1038/s41597-022-01351-0

Consumer Product Safety Commission (CPSC). (2020). *Staff briefing package: Project plan: Organohalogen flame retardant chemicals assessment: July 1, 2020*. https://www.cpsc.gov/s3fs-public/OFR-plan-report-package-final.pdf

National Academies of Sciences, Engineering, and Medicine (NASEM). (2019). *A class approach to hazard assessment of organohalogen flame retardants*. The National Academies Press. https://doi.org/10.17226/25412

National Toxicology Program (NTP). (2021). *15th report on carcinogens*. U.S. Department of Health and Human Services, Public Health Service. https://doi.org/10.22427/NTP-OTHER-1003

University of Cincinnati (UC). (2022a). *Literature survey guide: Draft 6: October 17, 2022.* Prepared by Risk Science Center, Department of Environmental and Public Health Science, University of Cincinnati under contract with the U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022b). *Screener guide for class-based OFR literature surveys: April 5, 2022*. Prepared by Risk Science Center, Department of Environmental and Public Health Science, University of Cincinnati under contract with the U.S. Consumer Product Safety Commission.

8. Appendix: Supporting Files

The following supporting files are available on the CPSC Organohalogen Flame Retardant Chemicals Assessment website. They can also be found on Docket No. CPSC-2015-0022.

Literature Survey Guide: Approaches Taken to Develop Evidence Maps from Readily Available Databases, Completed Assessments, and Literature Reviews

University of Cincinnati (UC). (2022). *Literature survey guide: Draft 6* [Literature Survey Guide Draft 6_10.17.22_final.docx]. U.S. Consumer Product Safety Commission.

Market and Use Report: Characterizing OFR Chemistries, Sources, and Uses in the U.S. and International Markets, Volumes 1 and 2 (Appendices)

Industrial Economics Incorporated (IEc). (2022). *Characterizing organohalogen flame retardant (OFR) chemistries, sources, and uses in United States and international markets: Vol. 1 – Main report* [Vol 1 Main Report 03.24.2022_Final.pdf]. U.S. Consumer Product Safety Commission.

Industrial Economics Incorporated (IEc). (2022). *Characterizing organohalogen flame retardant (OFR) chemistries, sources, and uses in United States and international markets: Vol. 2 – Appendices* [Vol 2 Appendices 03.09.2022_Final.pdf]. U.S. Consumer Product Safety Commission.

Literature Survey Results

University of Cincinnati (UC). (2022). *PHB subclass level 2 literature survey evidence map* [PHB Level 2 Evidence Maps 12.6.22.xlsx]. U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022). *PHB subclass level 3 literature survey evidence map* [PHB Level 3 Evidence Maps 12.6.22.xlsx]. U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022). *PHB subclass level 3B literature survey evidence map* [PHB Level 3B Evidence Maps 12.6.22.xlsx]. U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022). *PHB subclass information downloaded from databases* [PHB Tox Individual Database Evidence Maps - Levels 2, 3, 3B - 12.6.22.xlsx]. U.S. Consumer Product Safety Commission.

Literature Survey Results Supporting Files

University of Cincinnati (UC). (2022). *PHB subclass detailed 3B extraction counts* [PHBs PDF 3B Extraction Final 10.21.22.xlsx]. U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022). *PHB subclass selected studies for 3B extraction* [PHBs 3B Selection Sheets 7.8.22.xlsx]. U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022). *PHB subclass information and heatmaps for level 3B study selection* [PHBs 3B Selection Heatmaps 7.8.22.xlsx]. U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022). *PHB subclass power-query cleaning and visualizing of PDF data sources* [PHBs PQ clean and viz.xlsx]. U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022). *PHB subclass data from Multimedia Monitoring Database* [PHBs MMDB Working.xlsx]. U.S. Consumer Product Safety Commission.

University of Cincinnati (UC). (2022). PHB subclass aggregated toxicity database counts [PHBs DB Tox Totals Working.xlsx]. U.S. Consumer Product Safety Commission.

Market and Use Profile Supporting Files

Industrial Economics Incorporated (IEc). (2022). *Characterizing organohalogen flame retardant (OFR) chemistries, sources, and uses in United States and international markets: Attachment A: Standard operating procedure for producing data source outputs* [Attachment A_Data SOP.pdf]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research CompTox chemical information* [OFR_universe_wCompTox_batch_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research CompTox chemical synonyms* [OFR_universe_wCompTox_syns_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research CompTox experimental data* [OFR_universe_wCompTox_exp_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research CompTox predicted data* [OFR_universe_wCompTox_pred_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research CompTox product use* [OFR_universe_wCompTox_prod_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research data synthesis* [Data Source Synthesis_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research database readme* [00_ReadMe_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research ECHA plastics* [OFR_universe_wECHA_add_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research ECHA sources* [OFR_universe_wECHA_links_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research EPA TRI* [OFR_universe_wTRI_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research field counts* [04_FieldCounts_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research fields list* [03_FieldsList_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research NORMAN database* [OFR_universe_wNorman_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research OFR chemical list* [01_Attachment 1_OFR_universe_cid_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research PubChem chemical data* [OFR_universe_wPCPy_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research PubChem chemical identification* [OFR_universe_wPCBrowser_ID_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research PubChem mass spec* [OFR_universe_wPCBrowser_MS_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research PubChem MassBank spectra* [OFR_universe_wPCBrowser_MoNA_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research PubChem NORMAN* [OFR_universe_wPCBrowser_Norman_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research QSUR* [OFR_universe_wQSUR_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research source list* [02_SourcesList_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Market research TSCA inventory* [OFR_universe_wTSCA_03042022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Organohalogen flame retardant (OFR) market data workbook* [_OFR Market Data Workbook_mod1_01.25.2022.xlsx]. U.S. Consumer Product Safety Commission.

Eastern Research Group Incorporated (ERG). (2022). *Organohalogen flame retardant (OFR) source extraction workbook* [OFR Source Review Workbook_mod1_02.28.2022.xlsx]. U.S. Consumer Product Safety Commission.