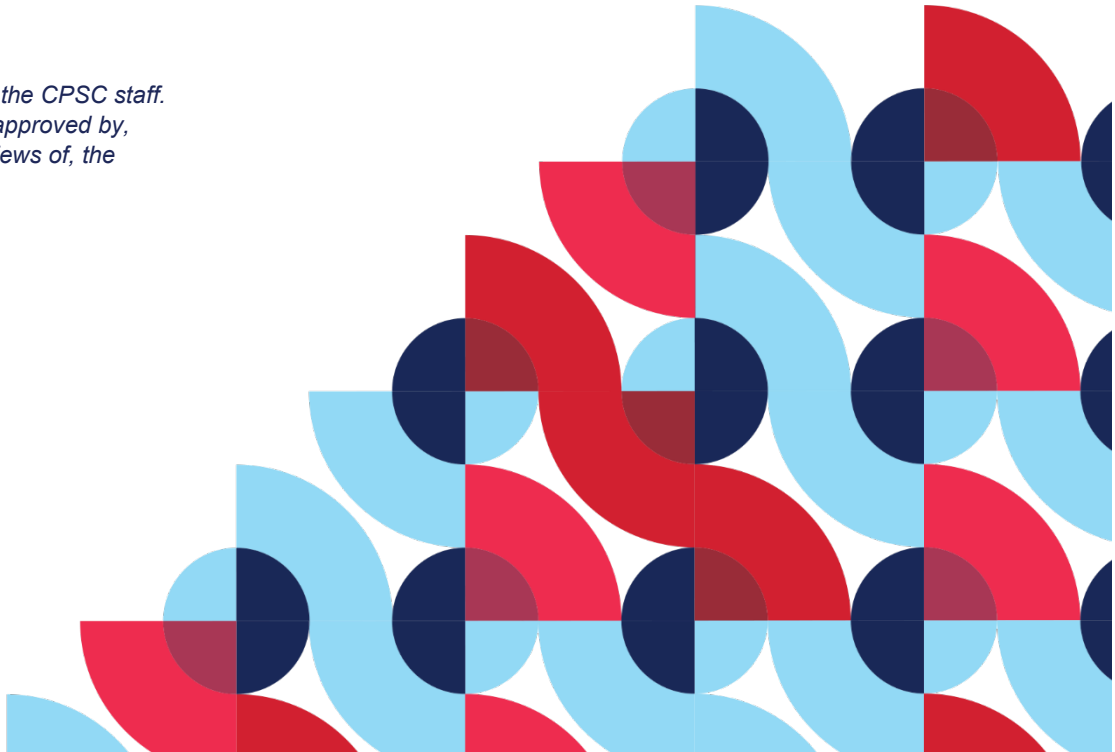
United States
Consumer Product Safety Commission

Organohalogen Flame Retardant Scope Document: Polyhalogenated Phthalate/Benzoate/Imide Subclass

February 2024

This report was prepared by the CPSC staff. It has not been reviewed or approved by, and may not represent the views of, the Commission.



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1. Executive Summary

This scope document addresses the polyhalogenated phthalate/benzoate/imide (PHPBI) 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 PHPBI 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 PHPBI 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 PHPBI 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]

[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).

- 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 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.

[2] CHAP review would occur prior to finalizing any subclass risk assessment if carcinogenicity, mutagenicity, or reproductive/developmental toxicity were chosen as relevant endpoints.

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 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

[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.

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 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

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

[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.

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.

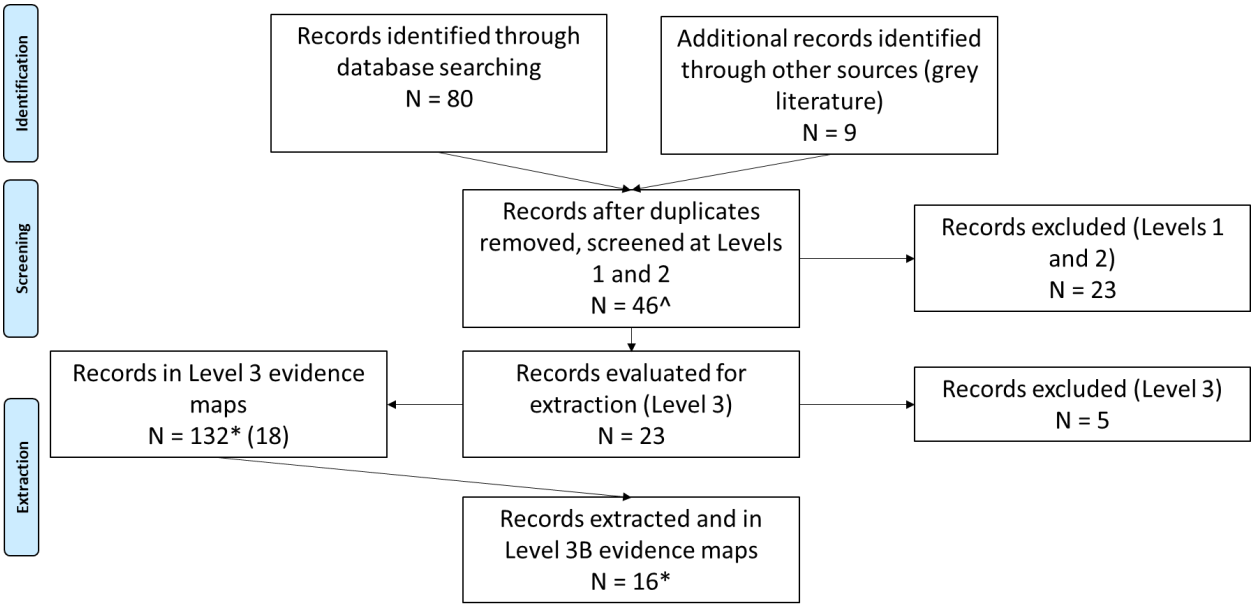
4.4. Literature Survey

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 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.

[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.

Figure 4-1. Literature Flow Diagram



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

5. Scoping for PHPBIs

5.1. PHPBI Subclass Chemistry

The PHPBI subclass generally consists of chemicals containing either an imide, benzoate ester or phthalate ester functional group. The halogenated substituents in this subclass are found on either the alkyl chains or aryl rings of the chemicals. A few acid anhydrides have been included due to their structural similarities with chemicals in this subclass. The presence of the different functional groups in this class may lead to chemistry-based differences throughout this subclass despite structural similarities amongst the members.

Table 5-1 lists 19 individual chemicals in the PHPBI subclass.

Table 5-1. List of Chemicals in PHPBI Subclass

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
1	117-08-8	Tetrachlorophthalic anhydride	BRN 0211560; Niagathal; Tetrathal; TCPA	ClC1=C2C(=O)OC(=O)C2=C(Cl)C(Cl)=C1Cl
2	13810-83-8	Tetrabromophthalic acid	BRN 1885828	OC(=O)C1=C(Br)C(Br)=C(Br)C(Br)=C1C(O)=O

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
3	183658-27-7	2-Ethylhexyl 2,3,4,5-tetrabromobenzoate	Firemaster 550 component; EH-TBB;TBB	CCCCC(CC)COC(=O)C1=C(Br)C(Br)=C(Br)C(Br)=C1
4	20566-35-2	2-(2-Hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate	Saytex RB 79; PHT-4-Diol	CC(O)COC(=O)C1=C(Br)C(Br)=C(Br)C(Br)=C1C(=O)OCCOCCO
5	214216-08-7	bis(2,3-Dibromopropyl) 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate	NA	BrCC(Br)COC(=O)C1=C(C(=O)OCC(Br)CBr)C(Br)=C(Br)C(Br)=C1Br
6	25357-79-3	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, sodium salt (1:2)	NA	[Na+].[Na+].[O-]C(=O)C1=C(Br)C(Br)=C(Br)C(Br)=C1C([O-])=O
7	26040-51-7	Bis(2-ethylhexyl) tetrabromophthalate	TBPH; BEH-TEBP; Firemaster 550 component	CCCCC(CC)COC(=O)C1=C(Br)C(Br)=C(Br)C(Br)=C1C(=O)OCC(CC)CCCC
8	27581-13-1	2,3,4,5-Tetrabromobenzoic Acid	NA	OC(=O)C1=C(Br)C(Br)=C(Br)C(Br)=C1
9	32588-76-4	1,2-Bis(tetrabromophthalimido)ethane	BT 93; BT 93W; BT-93D; Citex BT 93; Saytex BT 93; Saytex BT 93W; Saytex BT93; EBTEBPI	BrC1=C2C(=O)N(CCN3C(=O)C4=C(C3=O)C(Br)=C(Br)C(Br)=C4Br)C(=O)C2=C(Br)C(Br)=C1Br
10	42597-49-9	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-butyl ester	NA	CCCCOC(=O)C1=C(Br)C(Br)=C(Br)C(Br)=C1C(O)=O
11	57011-47-9	Pentabromophenyl benzoate	NA	BrC1=C(Br)C(Br)=C(OC(=O)C2=CC=CC=C2)C(Br)=C1Br
12	55481-60-2	Dimethyl 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate	NA	COC(=O)C1=C(Br)C(Br)=C(Br)C(Br)=C1C(=O)OC
13	632-58-6	Tetrachlorophthalic acid	BRN 1914906	OC(=O)C1=C(C(O)=O)C(Cl)=C(Cl)C(Cl)=C1Cl
14	632-79-1	4,5,6,7-Tetrabromo-1,3-Isobenzofurandione	Bromophthal; Dion 6692 (VAN); Firemaster PHT 4; Firemaster Pht4; PHT-4; Saytex RB 49; TBPA	BrC1=C2C(=O)OC(=O)C2=C(Br)C(Br)=C1Br
15	7415-86-3	1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester	NA	BrCC(Br)COC(=O)C1=CC=CC=C1C(=O)OCC(Br)CBr

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
16	82001-21-6	Bis[(pentabromophenyl)methyl] 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate	NA	BrC1=C(Br)C(Br)=C(COC(=O)C2=C(C(=O)OCC3=C(Br)C(Br)=C(Br)C(Br)=C3Br)C(Br)=C(Br)C(Br)=C2Br)C(Br)=C1Br
17	90075-91-5	Bis[(pentabromophenyl)methyl] benzene-1,4-dicarboxylate	NA	BrC1=C(Br)C(Br)=C(COC(=O)C2=CC=C(C=C2)C(=O)OCC2=C(Br)C(Br)=C(Br)C(Br)=C2Br)C(Br)=C1Br
18	92484-07-6	2-Butenediamide, N1,N4-bis(2,4,6-tribromophenyl)-, (2E)-	NA	BrC1=CC(Br)=C(NC(=O)\C=C\C(=O)NC2=C(Br)C=C(Br)C=C2Br)C(Br)=C1
19	93202-89-2	N-2,3-Dibromopropyl-4,5-dibromohexahydrophthalimide	NA	BrCC(Br)CN1C(=O)C2CC(Br)C(Br)CC2C1=O

SMILES = simplified molecular-input line-entry system; NA = not available or not found.

5.1.1. Physicochemical Property Summaries

The information collected to date led CPSC staff to find that experimental physicochemical data on PHPBI chemicals are limited. Two PHPBI subclass members have experimental data and eighteen PHPBI members have predicted data. Well-studied chemicals in this subclass include Tetrachlorophthalic anhydride (TCPA, CAS RN 117-08-8) and Bis(2-ethylhexyl) tetrabromophthalate (TBPH, CAS RN 26040-51-7). From this data set, studied PHPBIs have predicted boiling points ranging from 171°C to 736 °C, and predicted vapor pressures from 2.81 E^{-12} to $5E^{-1}$ mm Hg. Data show predicted water solubility values ranging from $4.39E^{-8}$ to $4.09E^{1}$ mol/L. The predicted octanol/water partition coefficient (K_{ow}) values, which are commonly expressed as log K_{ow}, range from 3.6 to 10.8.

5.2. Market and Use Summary for PHPBIs

The OFR Market and Use Report, completed in March 2022, includes 19 PHPBI chemicals.

- Eighteen PHPBI chemicals had market and use information and there was one chemical without any market and use information.
- According to EPA data, eight PHPBI chemicals were identified to be on the EPA's TSCA chemical substance (active) inventory, three PHPBI chemicals were identified on the TSCA (inactive) inventory, four were on the CDR, and none were on the TRI program list.
- Two PHPBI chemicals were identified in the Interstate Chemicals Clearinghouse (IC2) HPCDS.
- Nine PHPBI chemicals were identified in the targeted literature search.
- Eighteen PHPBI chemicals had patent data.

5.2.1. PHPBIs 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 18 PHPBIs that are known to be or have been used in commerce, according to data available from these sources.

The one PHPBI chemical that is not known to be used in commerce is Firemaster 550 (CAS RN 860302-33-6). However, Firemaster 550 is actually a mixture of two PHPBI chemicals (2-Ethylhexyl 2,3,4,5-tetrabromobenzoate, CAS 183658-27-7; and Bis(2-ethyl-1-hexyl)tetrabromophthalate, CAS 26040-51-7) and two non-halogenated organophosphates (triphenyl phosphate, and isopropylated triphenyl phosphate). The two PHPBI chemicals used in Firemaster 550 are identified as in commerce.

Among the 18 PHPBI chemicals used in commerce, 11 can be found in the TSCA inventory. Eight chemicals are in the TSCA active inventory and three are in the TSCA inactive inventory. In Table 52, PHPBI 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] Ten PHPBI chemicals appear in one or more of these international inventories. In Table 5-2, the number of international registries for the identified PHPBI chemicals is listed in the ”International Inventories“ column.

Nine PHPBI 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.

All 18 PHPBI chemicals in commerce 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.

Table 5-2. PHPBI Chemicals Used in Commerce

CAS RN	Chemical Name	TSCA	International Inventories	Literature Cites	Patents
117-08-8	Tetrachlorophthalic anhydride	Active	4	0	24,223
13810-83-8	Tetrabromophthalic acid	Not found	1	2	6,173
183658-27-7	2-Ethylhexyl 2,3,4,5-tetrabromobenzoate	Active	1	21	36
20566-35-2	2-(2-Hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate	Active	2	4	43

[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.

CAS RN	Chemical Name	TSCA	International Inventories	Literature Cites	Patents
214216-08-7	Bis(2,3-dibromopropyl) 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate	Not found	Not found	0	16
25357-79-3	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, sodium salt (1:2)	Active	2	0	14
26040-51-7	Bis(2-ethylhexyl) tetrabromophthalate	Active	3	20	190
27581-13-1	2,3,4,5-Tetrabromobenzoic Acid	Not found	1	1	112
32588-76-4	1,2-Bis(tetrabromophthalimido)ethane	Active	4	8	5,683
42597-49-9	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-butyl ester	Inactive	Not found	0	8
55481-60-2	Dimethyl 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate	Not found	Not found	0	42
632-58-6	Tetrachlorophthalic acid	Active	2	1	16,995
632-79-1	4,5,6,7-Tetrabromo-1,3-Isobenzofurandione	Active	4	6	14,941
7415-86-3	1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester	Inactive	Not found	1	58
82001-21-6	Bis[(pentabromophenyl)methyl] 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate	Not found	Not found	0	25
90075-91-5	Bis[(pentabromophenyl)methyl] benzene-1,4-dicarboxylate	Not found	Not found	0	26
92484-07-6	2-Butenediamide, N1,N4-bis(2,4,6-tribromophenyl)-, (2E)-	Inactive	Not found	0	2
93202-89-2	N-2,3-Dibromopropyl-4,5-dibromohexahydrophthalimide	Not found	Not found	0	61

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

5.2.2. PHPBIs Used in Consumer Products

The Market and Use Report identified the use of PHPBIs in consumer products, including children's products. To determine whether individual OFR chemicals are used in consumer and/or children's products, a CPSC-sponsored contractor 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 PHPBI chemicals were also found in the literature.

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

- Gymnastic pit foam (up to 1.37%)
- Baby products (1.85%)
- PU furniture foam (1.97%)
- Kitchen utensils (up to 0.003%)
- Motherboard (0.004807%)
- Flat screen monitor (0.001732%)
- CRT monitor (0.011064%)
- Mattress foam (< 0.00001%)

The following PHPBI 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 183658-27-7: electrical adaptors, heat sealers, powerboards, LCD TVs, TVs, plastic ornaments, furniture and baby foam products, polyurethane foams in upholstered furniture, furnishings, construction and automotive materials, textiles, coatings, adhesives, cable coatings, electrical wires, plastic roofing materials, computer and television connectors, mattresses, electronics, household appliances, foam used in gymnastic pits, polyvinyl chloride (PVC), neoprene, polyurethane foam (PUF), soft foams, wire and cable insulation, carpet backing, coated fabrics, wall coverings, plastic and rubber products, textiles, leather, and fur.

CAS RN 26040-51-7: electrical adaptors, heat sealers, powerboards, LCD TVs, TVs, plastic ornaments, furniture and baby product foams, flexible PUF, textiles, flexible plastic/rubber, PVC, resins, furnishings, wire and cable, electrical and electronic products, construction and automotive materials, coatings, adhesives, couch foam and baby products (mattresses and high-chair foam), PUFs, flexible PVC plastic, neoprene rubber, carpet backing, fabric coatings, films and sheeting, wire and cable insulation, wall coverings, plastic kitchen utensils, PUF for furniture and baby products, neoprene, wall coverings, conveyer belts (e.g., made of plasticized PVC), coated fabrics, thermoplastic olefinics (TPOs) and elastomers, thermoplastic resins, thermoset resins, circuit boards, electronic enclosures, paper, thermal insulation for building applications: polyethylene (PE), PAN, polystyrene (PS), polypropylene (PP; homo- and copolymers); PVC, acrylonitrile butadiene styrene (ABS), polycarbonate (PC)-ABS, high impact polystyrene (HIPS), epoxy resins, phenolics, unsaturated polyester resins, expanded polystyrene (EPS), extruded polystyrene (XPS), and PS/PP.

[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.

CAS RN 32588-76-4: electronics, wire and cable, construction materials, automobiles, "recommended" for HIPS, PE, and PP in electronics, buildings, automotive and engineering plastics; engineering thermoplastics, plastic and rubber products, textiles, leather, fur, polyethylene polypropylene, thermoplastics, rubber, household curtains, and other plastic materials.

CAS RN 632-79-1: unsaturated polyesters, rigid polyurethane foams and paper, rigid PU polyols, wire coatings and wool, polymers and plastic products, and household curtains.

CAS RN 20566-35-2: rigid PU foams for appliances, rigid PUF (unspecified), and plastic products as an intermediate.

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.[15] 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. Approximately two percent, or 25 reports, documented the use of PHPBI chemicals in children's products.

Table 5-3 shows the two PHPBI chemicals reported to be used in children's products. Of the 25 reported uses of PHPBIs in children's products, three were for use as a chemical flame retardant. Of the 25 reported uses of PHPBIs in children's products, all chemicals were reportedly used in trace amounts.[16] There were no reported uses of PHPBIs in concentrations greater than 0.1% that were expressly for use as a chemical flame retardant in a children's product.

Table 5-3. Number of Children's Products with Reported Use as Flame Retardants for Select PHPBI Chemicals

PHPBIs	Total Report Count	Flame Retardant Use	Concentration >0.1%	Concentration >0.1% + FR Use
183658-27-7	15	1	0	0
26040-51-7	10	2	0	0
Total	25	3	0	0

Source: HPCDS, Interstate Chemicals Clearinghouse.

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

[15] 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.

[16] 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.

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.

Table 5-4 shows that one PHPBI chemical was included in the SCIP database. (See Exhibit 3-30 in the Market and Use Report, Volume 1.)

Table 5-4. PHPBI Chemicals Included in SCIP Database

CAS RN	Substance Name	EC No.	Number of Search Results Returned
26040-51-7	Bis(2-ethylhexyl) tetrabromophthalate	247-426-5	227

As of May 2023, there were 227 search results for bis (2-ethylhexyl) tetrabromophthalate (CAS RN 26040-51-7) in the SCIP database. Articles that contain this candidate list substance can be found in 17 article categories that can be used to help identify articles based on function and use. According to SCIP data, bis (2-ethylhexyl) tetrabromophthalate can be found in vinyl chloride polymers, coated textile fabrics, portable data-processing machines, switches and routers,[17] and other machines and mechanical appliances. However, because SCIP data were first released in September 2021, they could not be reviewed in time for publication of the Market and Use Report.

CDR. According to data available from the EPA's CDR, PHPBI chemicals have been used in a variety of product use categories for many years (see Table 5-5.) This table presents both commercial and consumer product uses of PHPBI chemicals because CPSC needs to know the range of product uses for these chemicals during the scoping phase.[18]

EPA changed the names of some product use categories between 2006 and 2012, and again in 2016, and so Table 5-5 presents the names of product use categories of PHPBI chemicals in the three reporting periods.[19] To handle small changes in product use category names over

[17] Machines for the reception, conversion and transmission or regeneration of voice, images or other data, including switching and routing apparatus.
[18] In the global economy, supply chains are complex, and reporters to the CDR do not know (and cannot reasonably ascertain) the end use of a product. Therefore, CPSC is reviewing all product use categories of OFR chemicals reported to the CDR, but may exclude certain categories later, if there is sufficient evidence showing that these chemical substances can be found exclusively in commercial products.
[19] For the 2006, 2012, and 2016 reporting periods, chemical-specific product use reporting was only required for the principal reporting year (PRY), the latest completed calendar year preceding the submission period. Therefore, 2006 data are from PRY 2005, 2012 data are from PRY 2011, and 2016 data from PRY 2015.

these periods, staff used a more generic or general name to be inclusive. The designated general product use category names help maintain consistency over the period displayed in the table below without distorting product use.

According to the CDR, the most common uses of PHPBI chemicals are in building and construction materials, and in electrical and electronic products, although PHPBIs are reported to be used in a variety of other products as well.

Table 5-5. Report Counts of Commercial and Consumer Product Uses of PHPBI Chemicals

Product Use Category	2006	2012	2016	Total
Building/construction materials not covered elsewhere	NR	8	5	**13**
Product description, not identified	3	NR	NR	**3**
Foam seating and bedding products	NR	NR	2	**2**
Rubber and plastic products	3	NR	2	**5**
Adhesives and sealants	NR	2	1	**3**
Electrical and electronic products	2	6	4	**12**
Fabric, textile, and leather products not covered elsewhere	NR	NR	1	**1**
Furniture and furnishing not covered elsewhere	NR	2	NR	**2**
Paints and coatings	NR	NR	2	**2**
Grand Total	**8**	**18**	**17**	**43**

Notes: Data listed as "Product description not identified" may be interpreted as one of any of the other product categories reported for PHPBIs, generally. N.R.=not reported or not available.

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.[20] In 2006, the use of PHPBI chemicals in children's products was considered by reporting firms to be confidential business information (CBI). In 2012, the use of PHPBI chemicals in children's products was considered by reporting firms to be not known or reasonably ascertainable (NKRA) for electrical and electronic products. In 2016, the use of PHPBI chemicals in children's products was considered by reporting firms to be NKRA for paints and coatings.

5.2.3. Regulatory History and Trends for PHPBIs

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.

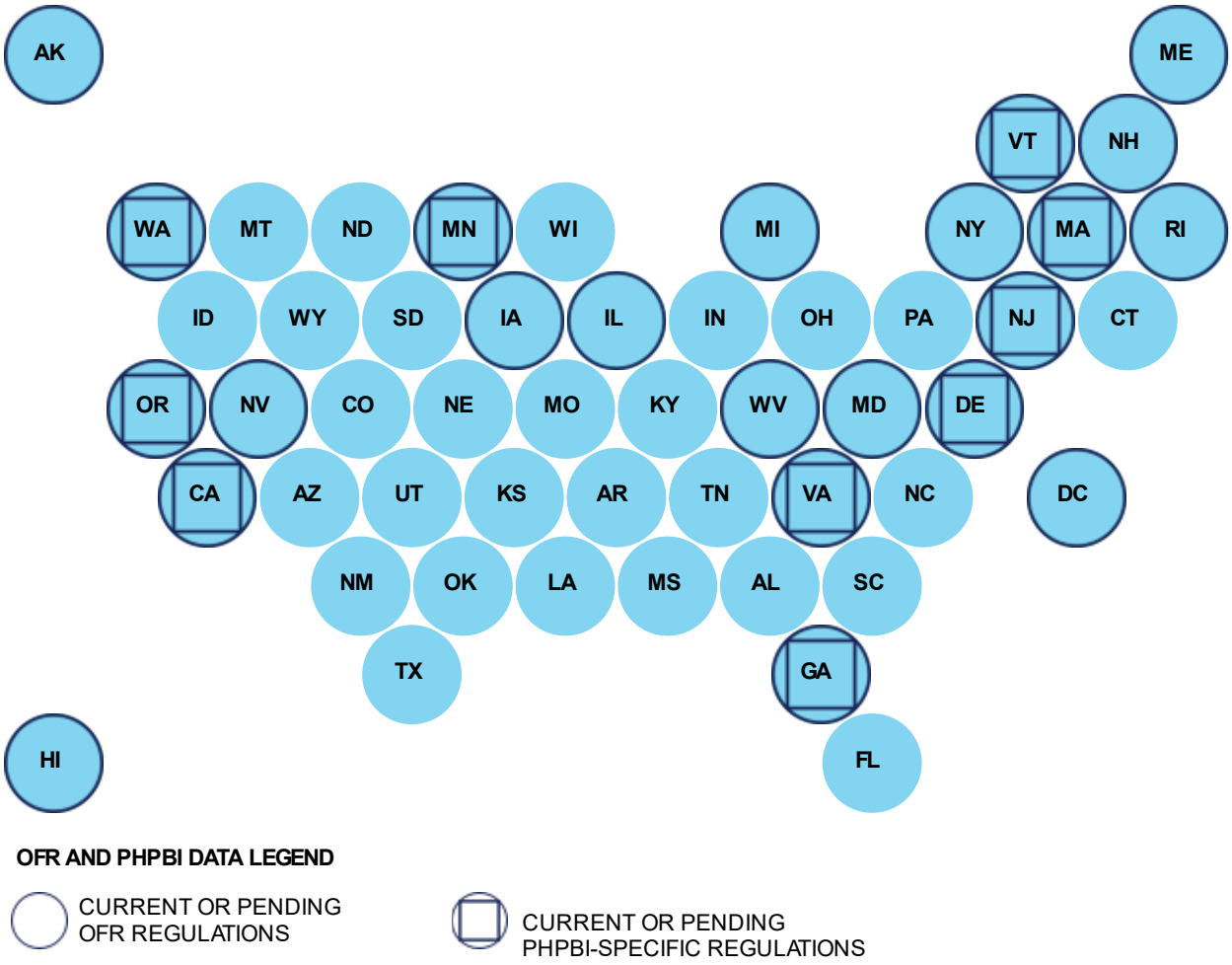
[20] The CDR rule provides reporting exemptions for chemical substances in articles, byproducts, impurities, non-isolated intermediates, certain polymers, research and development, and those produced by small manufacturers and small importers. 40 C.F.R. §§ 704.5 and 711.6. The CDR rule also exempts chemical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

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.[21]

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, 10 states currently regulate the use of PHPBIs specifically or have regulations pending. 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 PHPBIs specifically or have pending PHPBI-specific regulations are shown with a square within the circle. For more information on the state regulation of OFRs and PHPBIs, see Volume 2 of the Market and Use Report, Appendix R.

[21] 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 PHPBI 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.[22] The database counts indicate either

[22] See evidence map files on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

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:

- PHPBI members bis(2-ethylhexyl) tetrabromophthalate and tetrachlorophthalic anhydride had the highest number of toxicity data sources in each category.
- PHPBI members tetrachlorophthalic anhydride; bis(2-ethylhexyl) tetrabromophthalate; 4,5,6,7-tetrabromo-1,3-isobenzofurandione; 1,2-bis(tetrabromophthalimido)ethane; and 2-ethylhexyl 2,3,4,5-tetrabromobenzoate 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 100% of PHPBI members and 100% 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.[23]

The literature survey identified integrated data sources (sum of databases and PDFs) for all 19 PHPBI members and for all 10 analogs. The PHPBI members with the most data sources are bis(2-ethylhexyl) tetrabromophthalate; 2-ethylhexyl 2,3,4,5-tetrabromobenzoate; and tetrachlorophthalic anhydride. Table 5-6 summarizes how many PHPBI members and analogs had different degrees of data source abundance.

Table 5-6. 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	
	PHPBI Chemicals (n = 19)	Analog Chemicals (n = 10)
21+	3	0
6–20	4	1
1–5	12	9
0	0	0

[23] 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 file contain Level 3 and Level 3B toxicity data counts across all toxicity databases and PDFs.[24] 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 5-7 and Table 5-8 summarize how many PHPBI members and analogs had different degrees of Level 3 toxicity data source abundance.

Table 5-7. 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: PHPBI Chemicals (n = 19)						
	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+	5	0	2	4	16	2	5
6–20	1	1	5	0	3	3	1
1–5	3	3	7	4	0	3	2
0	10	15	5	11	0	11	11

Animal Toxicity or Accepted Alternative data sources were available for nine PHPBI members and one analog at Level 3 review and 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:

[24] 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.

- PHPBI members 2-ethylhexyl 2,3,4,5-tetrabromobenzoate and bis(2-ethylhexyl) tetrabromophthalate had data sources in all subcategories.
- PHPBI member tetrachlorophthalic anhydride had data sources for all subcategories except Neurotoxicity and Endocrine Disruption.
- PHPBI member 4,5,6,7-Tetrabromo-1,3-Isobenzofurandione had data sources for all subcategories except Neurotoxicity, Carcinogenicity, and Endocrine Disruption.
- Acute Toxicity and Mutagenicity/Genotoxicity are the subcategories with data sources for the most PHPBI members.

Table 5-8. 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 PHPBI Analogs (n = 10)						
	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+	1	0	0	0	3	1	0
6–20	0	0	0	0	0	0	1
1–5	0	0	3	1	7	0	0
0	9	10	7	9	0	9	9

Human Toxicity data sources were available for four PHPBI members and no analogs at Level 3 review and 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:

- PHPBI member tetrachlorophthalic anhydride had the highest number of hits with data sources in acute toxicity and sensitization.
- PHPBI members 2-ethylhexyl 2,3,4,5-tetrabromobenzoate and bis(2-ethylhexyl) tetrabromophthalate had data sources in carcinogenicity.
- PHPBI member 4,5,6,7-tetrabromo-1,3-isobenzofurandione had data sources in sensitization.

Human, Animal, or Modeled Toxicokinetics (ADME [absorption, distribution, metabolism, and excretion]*)* data sources were available for 14 PHPBI members and three analogs at Level 3 review and 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:

- No data sources were reported for any PHPBI members or analogs under the subcategory Chemical- or Class-Specific PBPK Model.
- PHPBI member bis(2-ethylhexyl) tetrabromophthalate had data sources in all subcategories except Chemical- or Class-Specific PBPK Model.
- 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 12 PHPBI members and three analogs.

Experimental Mechanistic data sources were available for eight PHPBI members and one analog at Level 3 review. Four PHPBI members and one analog had data in the databases and PDFs at Level 3B review.[25] This category has 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.[26] CPSC staff observed the following:

- Three PHPBI members had data sources in both subcategories. These are 2-ethylhexyl 2,3,4,5-tetrabromobenzoate; bis(2-ethylhexyl) tetrabromophthalate; and 4,5,6,7-tetrabromo-1,3-isobenzofurandione. Some of these hit counts were large, with hundreds or thousands of data sources per chemical per subcategory.
- The remaining one PHPBI member, tetrachlorophthalic anhydride had hundreds of data sources for the subcategory, Study Makes Connection to MOA and Potential Health Effect.

QSAR, Read-Across, Analog data sources were available for all PHPBI members and all analogs at Level 3 review and in the databases and PDFs at Level 3B review. Level 3B reviews provided additional detail across the same nine subcategories used for *Animal Toxicity or Accepted Alternative* above. CPSC staff observed the following:

- No data sources for PHPBI members or analogs were identified for Neurotoxicity. 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.
- Of the remaining subcategories, at least one data source was available for the majority of PHPBI members and analogs per subcategory.
- Mutagenicity/Genotoxicity and Endocrine Disruption are subcategories that contain the richest data sources for PHPBI members and analogs.

Qualitative Hazard Characterization data sources were available for eight PHPBI members and one analog at Level 3 review and 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

[25] 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.
[26] Many database sources could not be tagged for Level 3B because it was not clear whether a connection was made to MOA.

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:

- PHPBI member bis(2-ethylhexyl) tetrabromophthalate had data sources for all nine subcategories.
- PHPBI member tetrachlorophthalic anhydride had data sources in all subcategories except Endocrine Disruption.
- PHPBI member 2-ethylhexyl 2,3,4,5-tetrabromobenzoate had data sources in all subcategories except Irritation.

Quantitative Hazard Characterization data sources were available for eight PHPBI members and one analog 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:

- PHPBI members 2-ethylhexyl 2,3,4,5-tetrabromobenzoate and bis(2-ethylhexyl) tetrabromophthalate had data sources in all subcategories except Carcinogenicity, Sensitization, and Endocrine Disruption.
- PHPBI members tetrachlorophthalic anhydride; 1,2-bis(tetrabromophthalimido)ethane; and 4,5,6,7-tetrabromo-1,3-isobenzofurandione had data sources available in Acute toxicity, Systemic or Repeated Dose Toxicity, and Reproductive Toxicity/Developmental Toxicity subcategories.
- PHPBI member 2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate had data sources available in Acute toxicity, Systemic or Repeated Dose Toxicity, and Carcinogenicity subcategories.

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.[27] 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 the individual PDF file. PHPBI 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:

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

- PHPBI members 2,3,4,5-tetrabromobenzoic acid; bis(2-ethylhexyl) tetrabromophthalate; and 2-ethylhexyl 2,3,4,5-tetrabromobenzoate had the highest number of data sources in each category.
- PHPBI members 2,3,4,5-tetrabromobenzoic acid; bis(2-ethylhexyl) tetrabromophthalate; 2-ethylhexyl 2,3,4,5-tetrabromobenzoate; and 1,2-bis(tetrabromophthalimido)ethane 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 13 of 19 PHPBI members.[28] The PHPBI members with the most data sources were bis(2-ethylhexyl) tetrabromophthalate and 2-ethylhexyl 2,3,4,5-tetrabromobenzoate. Table 5-9 summarizes how many PHPBI members have different degrees of data source abundance. The PDFs provided more total data sources and covered more PHPBI members than the database.

Table 5-9. 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
	PHPBI Chemicals (n = 19)
21+	2
6–20	5
1–5	6
0	6

5.4.2. Summary of Levels 3 and 3B

The "EXP_Integrated" tabs from each file contains Level 3 and 3B exposure data counts.[29] The Level 3 integrated counts indicate the number of data sources per chemical from the MMDB database and identified PDFs. Level 3 counts are 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 5-10 summarizes how many PHPBI members had different degrees of Level 3 exposure data source abundance.

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

Table 5-10. 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					
	PHPBI Chemicals (n = 19)					
	Environmental Monitoring	Biomonitoring/ Personal Monitoring	Source Characterization	Epidemiology – Population Group	Modeled Concentrations	Modeled Human Dose
21+	2	3	2	0	0	2
6–20	0	0	4	0	0	0
1–5	4	0	7	3	3	1
0	13	16	6	16	16	16

Environmental Monitoring data sources were available for six PHPBI members at Level 3 review. Three PHPBI 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.

- PHPBI members 2-ethylhexyl 2,3,4,5-tetrabromobenzoate and bis(2-ethylhexyl) tetrabromophthalate had sources in all subcategories and the highest numbers of hits for Indoor Dust, followed by Outdoor Air subcategory.
- PHPBI member 1,2-bis(tetrabromophthalimido)ethane had data only in the Indoor Dust subcategory.

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

- PHPBI members 2-ethylhexyl 2,3,4,5-tetrabromobenzoate and bis(2-ethylhexyl) tetrabromophthalate had data sources in all subcategories except Human (other) subcategory.
- PHPBI member 2,3,4,5-tetrabromobenzoic acid had data sources for Urine subcategory.

Source Characterization data sources were available for 13 PHPBI members at Level 3 review and in the databases 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.

- Twelve PHPBI members had at least one data source for the subcategory Other Qualitative or Quantitative Description of Product Use or Class/Chemical.
- PHPBI member 2-ethylhexyl 2,3,4,5-tetrabromobenzoate had the largest number (30) of data sources for the Product Testing: Content Only subcategory.

Environmental Epidemiology[30] data sources were available for three PHPBI members at Level 3 review. No data under this category were identified for any of the PHPBI members in the Level 3B review. The subcategories were Children; Adult, Non-Occupational; and Other, Specify (with Suggestions).

Modeled Concentrations data sources were available for three PHPBI members at Level 3 review and in the databases and PDFs at Level 3B review. The subcategories were Indoor Concentration, Outdoor Concentration, and Dietary/Food.

- PHPBI members 2-ethylhexyl 2,3,4,5-tetrabromobenzoate; bis(2-ethylhexyl) tetrabromophthalate; and 1,2-bis(tetrabromophthalimido)ethane had data sources for the subcategory Outdoor Concentration.

Modeled Human Dose data sources were available for three PHPBI members at Level 3 review and in the databases and PDFs at Level 3B review. The subcategories were Children; Adult, Non-occupational; and Other, Specify (with Suggestions).

- PHPBI members 2-ethylhexyl 2,3,4,5-tetrabromobenzoate; bis(2-ethylhexyl) tetrabromophthalate; and 1,2-bis(tetrabromophthalimido)ethane had data sources for the subcategories Children and Adult, Non-occupational.

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 contains summed Level 2 risk data counts from PDF sources.[31] No risk data were found in the databases. Four PHPBI members and no analogs had PDF data sources for risk at Level 2 review. Table 5-11 summarizes how many PHPBI members had different degrees of data source abundance. PHPBI member 2-ethylhexyl 2,3,4,5-tetrabromobenzoate has the highest numbers of human health risk assessments available.

[30] 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.
[31] Risk evidence map files are available on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022

Table 5-11. 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
	PHPBI Chemicals (n = 19)
21+	0
6–20	2
1–5	2
0	15

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.[32] 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 5-12 summarizes how many PHPBI members and analogs had different degrees of Level 3 human health risk data source abundance.

Human Health Risk Assessment data sources were available for four PHPBI members and no analogs at Level 3 review and in the databases and PDFs at Level 3B review. The subcategories used were Noncancer Risk and Cancer Risk, with four Noncancer Risk and no Cancer Risk assessments identified. Staff noted the following observations:

- PHPBI members, 2-ethylhexyl 2,3,4,5-tetrabromobenzoate; bis(2-ethylhexyl) tetrabromophthalate; 2,3,4,5-tetrabromobenzoic acid; and 1,2-bis(tetrabromophthalimido)ethane had one Noncancer Risk data source each.
- None of the 10 analogs had risk assessment data sources.

Table 5-12. 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
	PHPBI Chemicals (n = 19)
21+	0
6–20	2
1–5	2
0	15

5.6. Literature Survey Results: Key References

Among the literature survey results are several references from authoritative sources. These references include European Chemicals Agency (ECHA) reports, National Toxicology Program

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

(NTP) technical reports, and U.S. Environmental Protection Agency (EPA) reviews and assessments. Each of these references addressed one or more PHPBIs. These reports included nine specific PHPBIs.[33] These nine chemicals are among the PHPBIs most frequently noted in the market use report as found in consumer products, as well as in the literature survey results generally. 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 PHPBIs.

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 PHPBI 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 PHPBI 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 a minority of chemicals that are "no data" substances.

CPSC staff concludes that the PHPBI subclass includes four data-rich chemicals and that a majority of PHPBI chemicals and some analogs have some data. The evidence maps show that many PHPBI 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 PHPBI 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 four data-rich chemicals and that a majority of chemicals have some data. In addition, according to available data sources, 18 of the 19 chemicals have market information for use in commerce.

Following the determination that the PHPBI 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-

[33] The 9 PHPBIs included in one or more key references are (by CAS RN): 32588-76-4; 26040-51-7; 117-08-8; 632-79-1; 32588-76-4; 26040-51-7; 183658-27-7; 20566-35-2; 7415-86-3.

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 PHPBI 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 PHPBIs, data-rich PHPBI analogs, PHPBIs with some toxicity information, and PHPBIs 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][34]) from the comprehensive literature search.
3. CPSC staff will refine the NAS analog list and characterize analog substances for the PHPBI 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 PHPBI class members to be associated with them, will be deprioritized. CPSC staff's initial survey shows that empirical toxicity data are available for one analog and empirical toxicokinetic data are available for three analogs.
4. CPSC staff will estimate major metabolites of PHPBI 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 PHPBI class members and analogs with available toxicity data can be used to read-across to PHPBI 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 PHPBI class are acute toxicity, systemic repeat dose toxicity, reproductive toxicity/developmental toxicity, and irritation.

[34] 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.

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 PHPBI 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 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 PHPBI class members.
8. CPSC staff will explore the variability and uncertainty associated with dose response values for PHPBI 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 PHPBIs.

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

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 consider 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.

Acute oral toxicity is low (LD50 > 5000 mg/kg) for PHBPI subclass members BEH-TEBP (U.S. EPA, 2015), FM BZ-54[35] (U.S. EPA, 2015), FM-550 (Hsu et al., 2018), TEBP-Anh (U.S. EPA HPVIS), TCPA (NTP, 1993), TBPA (Dong et al., 2021), and EBTEBPI (EFSA, 2012). It is also relatively low for TBPA-Diol (LD50 > 2000 mg/kg; U.S. EPA, 2015; EFSA, 2012). Acute inhalation toxicity is reported as > 8 mg/m^3 for TBPA-Diol (U.S. EPA, 2015) and >10,920 mg/m^3 for TEBP-Anh (U.S. EPA HPVIS). Acute dermal toxicity also appears low for PHPBI subclass members, with LD50 values > 2000 mg/kg for BEH-TEBP (U.S. EPA, 2015), Firemaster BZ-54 (U.S. EPA, 2015), TBPA-Diol (LU.S. EPA, 2015), TEBP-Anh (U.S. EPA HPVIS), and TCPA (NTP, 1993).

Kidneys were affected in rats exposed orally for 28 days to FM BZ-54 (regeneration of kidney tubule epithelium; Hays and Kirman, 2017; U.S. EPA, 2015; ECCC and HC, 2019a). Rats orally exposed to TCPA for 28 days also had kidney effects (increased kidney weight, tubular dilation, necrosis; NTP, 1993), but no kidney effects were seen in mice; some of the rats at mid- and high doses of TCPA died (NTP, 1993). The liver was affected in rats exposed via inhalation and rabbits exposed dermally to TEBP-Anh (decreased liver weight and macroscopic changes, respectively; U.S. EPA HPVIS), and for rats exposed via inhalation to TCPA (hepatocellular hypertrophy; NTP, 1993). The rats exposed to TEBP-Anh via inhalation also had increased adrenal and thyroid weights (U.S. EPA HPVIS). Rats exposed orally to EBTEBPI up to ~1000

[35] Firemaster® BZ-54 is a flame retardant additive and consists of a brominated benzoate (2-ethylhexyl 2,3,4,5-tetrabromobenzoate; TBB) and a brominated phthalate (bis (2-ethylhexyl) 2,3,4,5-tetrabromophthalate; TBPH).

mg/kg-day for 28 or 90 days experienced no adverse effects (EFSA, 2012; ECCC and HC, 2019b).

In rat developmental studies, both FM BZ-54 (with mild maternal toxicity; Hays and Kirman, 2017; U.S. EPA, 2015; ECCC and HC, 2019a) and TCPA (without maternal toxicity; NTP, 1993) caused skeletal malformations, although with TCPA the change was slight and only at the highest dose. Exposure to FM BZ-54 decreased body weights in all generations of a 2-generation reproductive toxicity study (Hays and Kirman, 2017; U.S. EPA, 2015; ECCC and HC, 2019a), but FM-550 increased body weights of rat pups, an effect that persisted into adulthood (Hsu et al., 2018; ECHA, 2020). In oral reproductive/developmental toxicity studies, neither TEBP-Anh (U.S. EPA HPVIS) nor EBTEBPI (EFSA, 2012; ECCC and HC, 2019b) caused developmental effects.

EH-TBB and BEH-TEBP (separately or as a commercial mixture) affected developmental neurobehavior, neurotransmitters, and neuroendocrine systems (Dong et al., 2021). Effects in rats included increased levels of 5-hydroxytryptamine (5-HT), increased expression of estrogen receptor 1 (ER1), estrogen receptor 2 (ER2), and T3, and decreased levels of norepinephrine (Dong et al., 2021). BEH-TEBP and EH-TBB also increased estrogen levels and BEH-TEBP increased testosterone levels in pig primary testicular cells, and estrogen increased in adrenal sebaceous carcinoma cells (Dong et al., 2021). Furthermore, FM-550 disrupted 5-HT and retinoid X receptor (RXR)/retinoic acid receptor (RAR) signaling between the placenta and the developing rat brain (Dong et al., 2021).

BEH-TEBP and EH-TBB are both potential endocrine disruptors (Zuiderveen et al., 2020). Exposure of pregnant and lactating rats to FM-550 increased T4 in dams (without evidence of effects on T3 levels or deiodinase activity) and decreased T4 levels in offspring (Dong et al., 2021; Hsu et al., 2018; ECHA, 2020). Pregnant rats exposed to TBMEHP had lower serum T3 and no change in T4 levels, findings that were interpreted as inhibition of deiodinase (Hsu et al., 2018). In vitro, EH-TBB and BEH-TEBP (and their respective metabolites TBBA and TBMEPH) were thyroid receptor antagonists and anti-androgenic, and directly competed for the glucocorticoid receptor (ECHA, 2020; Dong et al., 2021; Hsu et al., 2018). In addition, BEH-TEBP could inhibit deiodinase and sulfotransferases (Dong et al., 2021). EH-TBB had mixed effects on estrogen synthesis (either increasing or no effect; Hsu et al., 2018; ECHA, 2020), though it can act as an antagonist of both estrogen and androgen receptors and can upregulate CYP21A2 and associated aldosterone and cortisol synthesis (Hsu et al., 2018). QSAR models predicted high activity for EBTEBPI for T4-TTR competition and estradiol sulfotransferase inhibition, and moderate activity for progesterone receptor antagonism, though the reliability of these models for EBTEBPI is uncertain (EFSA, 2012).

Although a full complement of genotoxicity assays is not available for all of the subclass members, the available test data indicate that this subclass is not genotoxic, although one chemical was positive for chromosome aberrations. Similar results were obtained in QSAR analyses. BEH-TEBP was not mutagenic in bacterial or mammalian cells and was negative in the micronucleus test, though it did cause chromosomal aberrations in vitro at the highest tested dose (ECHA, 2020; ECCC and HC, 2019a; U.S. EPA, 2015). An unspecified commercial EH-TBB/BEH-TEBP mixture was negative in vitro for mutagenicity and clastogenicity (ECCC and HC, 2019a). TBPA-diol was negative for in vitro gene mutation (U.S. EPA, 2015). TEBP-Anh and TCPA were negative in bacterial mutagenicity assays (U.S. EPA HPVIS; NTP, 1993), and

TCPA was negative in chromosomal aberration assays (NTP, 1993). EBTEBPI (ECCC and HC, 2019b; EFSA, 2012) and TBPA-Diol (EFSA, 2012) were not mutagenic in bacterial mutagenicity assays. EBTEBPI was also negative for chromosomal aberration in vitro (ECCC and HC, 2019b). Various QSAR predictions categorized TBPA-diol and bis(methyl)tetrabromophthalate as weak genotoxicants (ECHA, 2020), and BEH-TEBP and EH-TBB as either weak genotoxicants or nongenotoxic (ECCC and HC, 2019a; ECHA, 2020).

No chronic/carcinogenicity studies were located for any subclass member, although some QSAR predictions are available. QSAR predictions categorized BEH-TEBP, EH-TBB, TBPA-diol, and bis(methyl)tetrabromophthalate as carcinogens (ECHA, 2020; ECCC and HC, 2019a). However, these QSAR models may not be appropriate, since they consider DEHP an analog for BEH-TEBP and the literature does not support similar carcinogenic modes of action for DEHP and BEH-TEBP (ECCC and HC, 2019a). Given the absence of chronic or carcinogenicity studies for EBTEBPI, and inconclusive QSAR results, Health Canada (2019b) determined that EBTEBPI is unlikely to be carcinogenic based on negative genotoxicity results, lack of adverse effects in animal studies, and likely limited uptake. NTP (1993) identified no chronic/carcinogenicity studies of TCPA.

Overall, it appears that a class-based assessment may be possible for this subclass. PHPBI subclass members may share some targets, including kidney (BEH-TEBP, EH-TBB, and TCPA), liver (TEBP-Anh and TCPA), endocrine (BEH-TEBP, EH-TBB, and EBTEBPI), and developmental (including neurodevelopmental toxicity; BEH-TEBP, EH-TBB, and TCPA). Interpretation of the data is complicated by the fact that many of the studies on EH-TBB and BEH-TEBP were conducted on commercial mixtures containing these chemicals, and the mixture used (or even that a mixture was used) may not always have been accurately reported. FM BZ-54 is a mixture that contains only EH-TBB and BEH-TEBP, but the FM-550 also includes triphenyl phosphate and isopropylated triphenyl phosphate (U.S. EPA, 2015).

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:

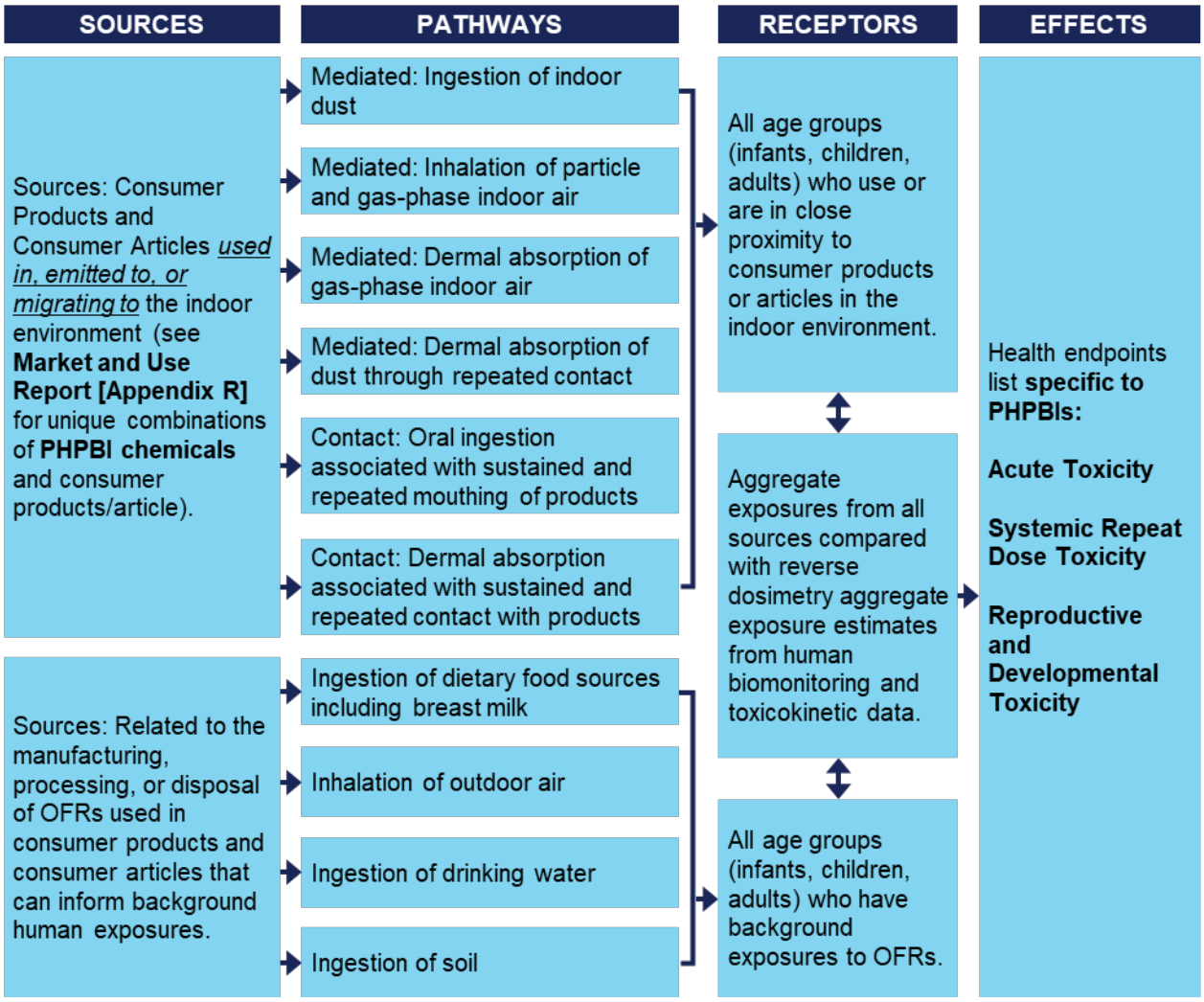
1. CPSC staff, in coordination with DTT staff, is working on a comprehensive literature search. Available exposure information from PHPBI class members will be further summarized and integrated after this search is complete. After the search, staff will refine the list of data-rich PHPBIs, PHPBIs with some exposure and use information, and PHPBIs with no exposure and use information.
2. Using the market and use research, CPSC staff expects to compile a list of PHPBI chemicals that have been or could be used in consumer products. While 18 of the 19 chemicals had some market-use information, eight PHPBI chemicals had more market and use information that could be used to inform analyses for PHPBI chemicals with less information. CPSC staff will characterize uses for PHPBIs 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 eight and 18 PHPBI subclass members.
4. Exposure pathways with likely higher potential for PHPBI 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 PHPBI 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 13 chemicals in the class with source characterization data, six chemicals in the class with environmental monitoring data, and six 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 PHPBI 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 three PHPBI 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 PHPBIs.

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 PHPBI 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 nonconsumer 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 PHPBIs are listed.

Figure 6-1. PHPBI Conceptual Exposure Model



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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

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