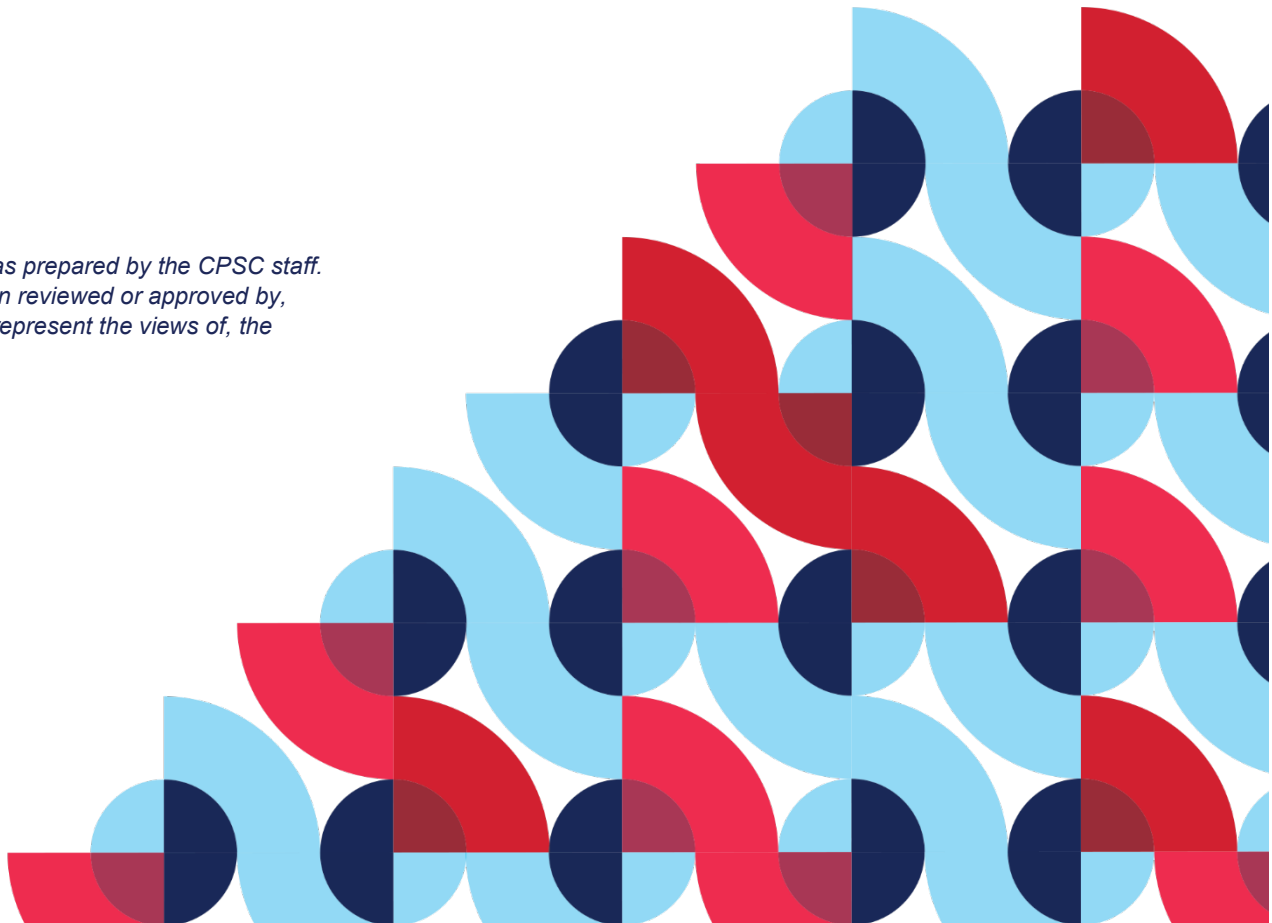
United States
Consumer Product Safety Commission

Organohalogen Flame Retardant Scope Document: Polyhalogenated Alicycle Subclass

January 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 alicycle (PHA) 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 PHA 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 PHA 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 PHA subclass of OFRs. This document is one of the scope documents that CPSC staff is producing to address each of 14 OFR chemical subclasses.

The primary question answered by the scope documents is:

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

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

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

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

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

3. Background

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

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

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

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

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

4. Approach

4.1. Criteria for Scoping Determination

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

4.1.1. Hazard

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

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

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

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

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

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

4.1.2. Exposure

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

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

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

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

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

4.2. Inventory

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

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

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

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

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

4.3. Market and Use Research

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

4.3.1. Targeted Literature Search

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

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

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

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

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

4.3.2. Other Data Sources

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

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

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

4.4. Literature Survey

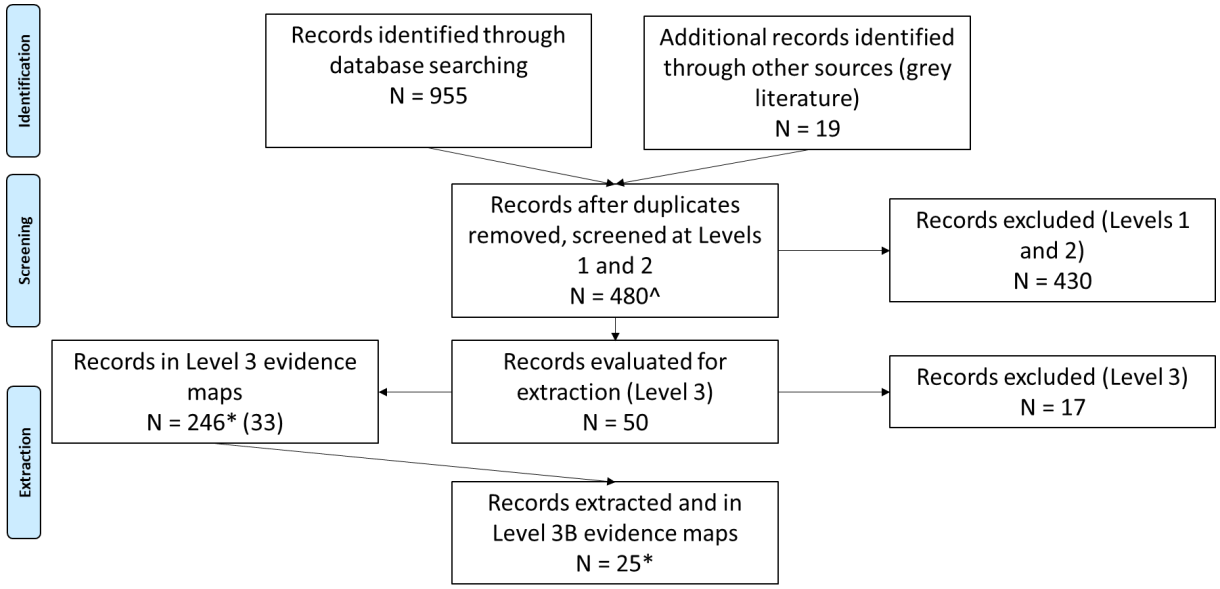
The OFR literature survey was intended to gather readily available toxicity, exposure, and risk information to characterize the types and amounts of data available for chemicals (and analogs) within a class. CPSC staff defined data sources for the literature survey effort as toxicity, exposure, and chemistry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

Detailed descriptions of the literature survey approach and process are found in the Literature Survey Guide and accompanying documentation. These documents were developed by University of Cincinnati (UC) Risk Science Center staff as part of work performed under a CPSC-sponsored contract (UC, 2022a; UC, 2022b). Development of the evidence maps followed a multilevel process to screen data sources initially identified in a defined search. Briefly, for peer-reviewed and gray literature, **Level 1** screening was used to confirm that the reference might contain information about at least one OFR chemical and that the reference

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

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

Figure 4-1. Literature Flow Diagram



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

5. Scoping for PHAs

5.1. PHA Subclass Chemistry

The PHA subclass generally consists of chemicals containing an alicyclic hydrocarbon group with halogenated substituents. In particular, members of this subclass all have a ring of carbon

[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.

with a range of four to six carbon-halogen bonds present. The different sizes in carbon rings as well as the presence of two compounds with aromaticity may lead to chemistry-based differences throughout this subclass despite structural similarities amongst the members.

Table 5-1 lists 22 individual chemicals in the PHA subclass.

Table 5-1. List of Chemicals in PHA Subclass

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
1	1093632-34-8	1,3,5,7,9,11-Hexabromocyclododecane	NA	NA
2	134237-50-6	(+/-)-alpha-Hexabromocyclododecane	alpha-HBCD	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
3	134237-51-7	(+/-)-beta-Hexabromocyclododecane	beta-HBCD	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
4	134237-52-8	(+/-)-gamma-Hexabromocyclododecane	gamma-HBCD	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
5	138257-18-8	(-)-beta-Hexabromocyclododecane	beta-HBCD	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
6	138257-19-9	(+)-alpha-Hexabromocyclododecane	alpha-HBCD	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
7	169102-57-2	(1R,2S,5S,6S,9S,10R)-1,2,5,6,9,10-Hexabromocyclododecane	NA	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
8	1837-91-8	Benzene hexabromide	NA	C1(C(C(C(C(C1Br)Br)Br)Br)Br)Br
9	25495-98-1	Cyclodecane, hexabromo	NA	C1CCCC(C(C(CCC1)(Br)Br)(Br)Br)(Br)Br
10	25637-99-4	1,1,2,2,3,3-Hexabromocyclododecane	HBCD (mixture)	C1CCCCC(C(C(CCCC1)(Br)Br)(Br)Br)(Br)Br
11	26657-83-0	Pentabromocyclododecene	NA	NA
12	30178-92-8	1,1,2,2-Tetrabromocyclododecane	NA	C1CCCCCC(C(CCCC1)(Br)Br)(Br)Br
13	30554-73-5	Tribromotrichlorocyclohexane	NA	C1CC(C(C(C1)(Br)Br)(Cl)Br)(Cl)Cl
14	31454-48-5	1,3,5,7-Tetrabromocyclooctane	NA	NA
15	3194-55-6	1,2,5,6,9,10-Hexabromocyclododecane	HBCD (isomer)	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
16	3194-57-8	1,2,5,6-Tetrabromocyclooctane	TBCO	C1CC(C(CCC(C1Br)Br)Br)Br
17	3322-93-8	1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane	Saytex BCL 462 | DBE-DBCH	C1CC(C(CC1C(CBr)Br)Br)Br
18	678970-15-5	(-)-alpha-Hexabromocyclododecane	alpha-HBCD	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
19	678970-16-6	(+)-beta-Hexabromocyclododecane	beta-HBCD	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
20	678970-17-7	(+)-gamma-Hexabromocyclododecane	gamma-HBCD	C1CC(C(CCC(C(CCC(C1Br)Br)Br)Br)Br)Br
21	77-47-4	Hexachlorocyclopentadiene	Graphlox; perchlorocyclopentadiene; HCCPD	C1(=C(C(C(=C1Cl)Cl)(Cl)Cl)Cl)Cl
22	87-84-3	Pentabromochlorocyclohexane	PBCC	C1(C(C(C(C(C1Br)Br)Br)Br)Br)Cl

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 PHA chemicals were not identified and predicted data is a combination of data on HBCD as a mixture or its component enantiomers (e.g., alpha, beta, and gamma). PHA subclass members have high boiling points, low vapor pressures, low water solubility, and high octanol/water partition coefficient (K_{ow}) values, which are commonly expressed as log K_{ow}.

5.2. Market and Use Summary for PHAs

The OFR Market and Use Report, completed in March 2022, includes 22 PHA chemicals.

- Twenty-one PHA chemicals had market and use information.
- According to EPA data, four PHA chemicals were identified to be on the EPA's TSCA Chemical Substance (active) Inventory, three PHA chemicals were identified on the TSCA (inactive) inventory, three were on the CDR, and two were on the TRI program list.
- One PHA chemical was identified in the Interstate Chemicals Clearinghouse (IC2) HPCDS.
- Thirteen PHA chemicals were identified in the targeted literature search.
- Twenty PHA chemicals had patent data.

5.2.1. PHAs 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 21 PHAs that are known to be or have been used in commerce, according to data available from these sources.

The one PHA chemical that is not known to be used in commerce is pentabromocyclododecene (CAS RN 26657-83-0).

Among the 21 PHA chemicals used in commerce, seven can be found in the TSCA inventory. Four chemicals are in the TSCA active inventory and three PHAs are in the TSCA inactive

inventory. In Table 5-2, PHA 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] Seventeen PHA chemicals appear in one or more of these international inventories. In Table 5-2, the number of international registries for the identified PHA chemical is listed in the “International Inventories” column.

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

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

Table 5-2. PHA Chemicals Used in Commerce

CAS RN	Chemical Name	TSCA	International Inventories	Literature Cites	Patents
1093632-34-8	1,3,5,7,9,11-Hexabromocyclododecane	Not found	Not found	1	20
134237-50-6	(+/-)-α-Hexabromocyclododecane	Not found	1	2	37
134237-51-7	(+/-)-beta-Hexabromocyclododecane	Not found	1	4	37
134237-52-8	(+/-)-gamma-Hexabromocyclododecane	Not found	1	5	34
138257-18-8	(-)-beta-Hexabromocyclododecane	Not found	1	0	34
138257-19-9	(+)-alpha-Hexabromocyclododecane	Not found	1	2	34
169102-57-2	(1R,2S,5S,6S,9S,10R)-1,2,5,6,9,10-Hexabromocyclododecane	Not found	1	0	1
1837-91-8	Benzene hexabromide	Inactive	Not found	0	336
25495-98-1	Cyclodecane, hexabromo	Not found	Not found	2	2,064
25637-99-4	Hexabromocyclododecane	Active	4	6	2,064
30178-92-8	1,1,2,2-Tetrabromocyclododecane	Not found	Not found	0	12

[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
30554-73-5	Tribromotrichlorocyclohexane	Inactive	1	0	12
31454-48-5	1,3,5,7-Tetrabromocyclooctane	Not found	1	1	No CID
3194-55-6	1,2,5,6,9,10-Hexabromocyclododecane	Active	3	22	5,179
3194-57-8	1,2,5,6-Tetrabromocyclooctane	Not found	2	7	5,179
3322-93-8	1,2-Dibromo-4-(1,2-dibromoethyl)cyclohexane	Inactive	2	8	853
678970-15-5	(-)-alpha-Hexabromocyclododecane	Not found	1	0	37
678970-16-6	(+)-beta-Hexabromocyclododecane	Not found	1	0	1
678970-17-7	(+)-gamma-Hexabromocyclododecane	Not found	1	0	2,286
77-47-4	Hexachlorocyclopentadiene	Active	5	2	5,554
87-84-3	Pentabromochlorocyclohexane	Active	2	2	340

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

5.2.2. PHAs Used in Consumer Products

The Market and Use Report identified the use of PHAs 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 PHA chemicals were also found in the literature.

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

- Flexible polyurethane foams (0% to 15%)
- Upholstery fabric (6% to 15%)
- Expanded polystyrene (0% to 2%)
- Textile backing (10% to 25%)
- High-impact polystyrene (1% to 7%)
- Child car seat foam (no concentration indicated)

[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.

The following PHA 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 1093632-34-8: polystyrene foam in building insulation.

CAS RN 25637-99-4: insulation boards for buildings and construction, high-impact polystyrene in electronics and appliances, EPS and XPS resins for building and construction materials, floormats, roof interior coverings, and other interior fabrics of motor vehicles. In Europe EPS may be used in child car seats or for insulation for transport vehicles.

CAS RN 3194-55-6: curtains, insulation boards for construction, HIPS resin in electronics, appliances, EXP/XPS for building industry rigid insulation panels or boards, textile coatings in upholstered furniture, expanded (EPS) and extruded (XPS) polystyrene foams for thermal insulation materials, binders, paints, HIPS plastic, and electronic housing.

CAS RN 3194-57-8: curtains.

CAS RN 3322-93-8: curtains, high-impact plastic parts of appliances, thermal insulation in houses, polystyrene foam, adhesives in fabric/vinyl, electric cable coating, and textiles.

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. Twelve percent, or 126 reports, documented the use of PHA chemicals in children's products.

Table 5-3 shows the PHA chemical reported to be used in children's products. Of the 126 reported uses of PHAs in children's products, half (63) were for use as a chemical flame retardant. Of the 126 reported uses of PHAs in children's products, most chemicals were reportedly used in trace amounts, although three reports identified the use of PHAs in children's products in concentrations greater than 1,000 ppm (0.1%); levels below 0.1% are considered contaminant by CPSC staff.[16] There were three reported uses of PHAs in concentrations greater than 0.1% that were expressly for use as a chemical flame retardant in a children's product.

[15] At this time, CPSC staff is unable to determine if information reported to the HPCDS for Washington and Oregon are representative. Presumably, the number of reports would go up substantially 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 SCIP notification to 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.

Table 5-3. Number of Children's Products with Reported Use as Flame Retardants for a Select PHA Chemical

PHAs	Total Report Count	Flame Retardant Use	Concentration >0.1%	Concentration >0.1% + FR Use
25637-99-4	126	63	3	3

Source: HPCDS, Interstate Chemicals Clearinghouse.

As shown in Figure 5-1, the three reported applications for which PHAs are used as chemical FRs (in concentrations greater than 0.1%) were fancy dress accessories, non-ride toy vehicles (non-powered), and baby car/booster seats. (See Exhibit 3-28 in the Market and Use Report, Volume 1.)

Figure 5-1. Children's Products That Contain PHA Chemical Flame Retardants

Source: HPCDS, Interstate Chemicals Clearinghouse.

Among children's products identified to contain PHA chemical FRs in a concentration greater than 0.1%, these high priority chemicals are reportedly found in synthetic polymers (such as synthetic rubber, plastics, foams) and in surface coatings (such as paints, plating, and waterproofing), in concentrations greater than 1,000 ppm. (See Table 5-4.)

Table 5-4. Component Parts That Contain PHA Chemicals, at a Concentration Equal to or Greater Than 1,000 ppm, When Used as Flame Retardant in a Children's Product (2012–2020)

Chemical (CAS RN)	Chemical Name	Synthetic Polymers (Synthetic Rubber, Plastics, Foams, Etc.)	Surface Coatings (Paints, Plating, Waterproofing Etc.)
25637-99-4	Hexabromocyclododecane	X	X

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

information is commonly referred to as a "SCIP notification." From data available from the European Union, SCIP notifications have supported the development of the SCIP database.

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

Table 5-5 shows that at least five PHA chemicals are included in the SCIP database. (See Exhibit 3-30 in the Market and Use Report, Volume 1.)

Table 5-5. PHA Chemicals Included in SCIP Database

CAS RN	Substance Name	EC No.	Number of Search Results Returned
134237-50-6	(+/-)-alpha-Hexabromocyclododecane	–	8
134237-51-7	(+/-)-beta-Hexabromocyclododecane	–	0
134237-52-8	(+/-)-gamma-Hexabromocyclododecane	–	1
25637-99-4	Hexabromocyclododecane	247-148-4	1,559
3194-55-6	1,2,5,6,9,10-Hexabromocyclododecane	221-695-9	692

As of May 2023, there were over 2,000 search results for PHA chemicals in the SCIP database. Articles that contain PHA candidate list substances can be found in over 60 article categories that can be used to help identify articles based on function and use. According to SCIP data, PHA chemicals can be found in polystyrene, cellular polymers, rubber-to-metal bonded parts, piston and displacement pumps, air conditioners, dishwashers, elevators and other machinery instruments and apparatus. 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, PHA chemicals have been used in a variety of product use categories for many years. (See Table 5-6.) This table presents the commercial and consumer product uses of PHA chemicals because CPSC needs to know the range of the product uses for these chemicals during the scoping phase.[17]

EPA changed the names of some product use categories between 2006 and 2012, and again in 2016, and so Table 5-6 presents the names of product use categories of PHA chemicals in the three reporting periods.[18] To handle small changes in product use category names over the period, 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.

[17] 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.
[18] 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.

According to the CDR, the most common uses of PHA chemicals are in building and construction materials, and rubber and plastic products, although PHAs are reported to be used in a variety of other products as well.

Table 5-6. Report Counts of Commercial and Consumer Product Uses of PHA Chemicals

Product Use Category	2006	2012	2016	Total
Building/construction materials not covered elsewhere	NR	4	6	**10**
Product description, not identified	1	1	NR	**2**
Rubber and plastic products	2	2	1	**5**
Electrical and electronic products	NR	NR	1	**1**
Fabric, textile, and leather products not covered elsewhere	1	NR	NR	**1**
Pesticides and fungicides (intermediate for agricultural)	NR	NR	1	**1**
Grand Total	**4**	**7**	**9**	**20**

Notes: Data listed as "Product description not identified" may be interpreted as one of any of the other product categories reported for PHAs, generally. NR = 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.[19] Over the period 2006 to 2016, the use of PHA chemicals in children's products was considered by reporting firms to be confidential business information (CBI) or not known or reasonably ascertainable (NKRA).

5.2.3. Regulatory History and Trends for PHAs

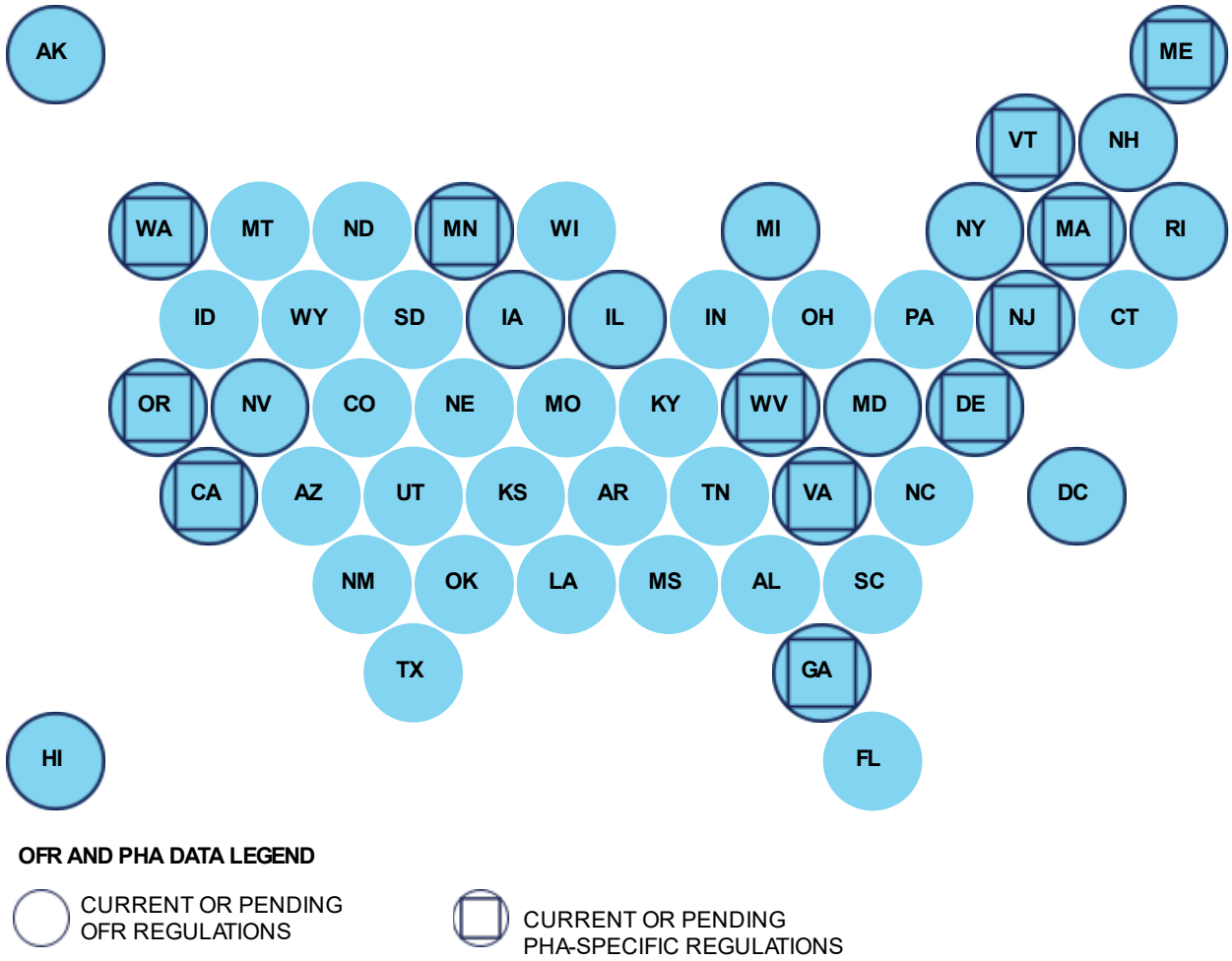
OFRs have received considerable regulatory attention from governmental jurisdictions in the United States and around the world; however, the scope and applicability of these regulatory actions varies significantly. This section discusses legislative action taken in the United States at the state level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

The Market and Use Report provides greater detail of legislative action taken in the United States, as well as action taken 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.[20]

[19] 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.
[20] 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.

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, 12 states have proposed or enacted regulation of PHAs specifically. In the map below (Figure 5-2), states that regulate OFRs are shown with a circle border and states that regulate PHDEs specifically are shown with a square within the circle. For more information on the state regulation of OFRs and PHAs, see Volume 2 of the Market and Use Report, Appendix R.

Figure 5-2. U.S. States That Regulate the Use of OFR and PHA 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.[21] The database counts indicate either the number of sources within the database (if available) or the number of entries in the database (if no information on source is available) after attempts were made to remove duplicates. The unit for PDF counts is the individual PDF file. Level 3B tagging was performed on a subset of toxicity assessments, toxicity literature reviews, and risk assessments selected from Level 3 to identify even more specific information for the chemicals in these references. Note that most of the Level 3B data are from database data, and only a subset of the PDF data sources is tagged at Level 3B.

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

- PHA members 1,2,5,6,9,10-hexabromocyclododecane; hexabromocyclododecane; hexachlorocyclopentadiene; and pentabromochlorocyclohexane had the highest number of toxicity data sources in each category.
- PHA members hexabromocyclododecane; hexachlorocyclopentadiene; and 1,2,5,6,9,10-hexabromocyclododecane 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 95% of PHA members and 97% 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 of the evidence map contains summed Level 2 toxicity data counts across both PDF and database data.[22]

The literature survey identified integrated data sources (sum of databases and PDFs) for all 22 PHA members and for 308 of 318 analogs. The PHA members with the most data sources were hexabromocyclododecane; (+/-)-alpha-hexabromocyclododecane; 1,2,5,6,9,10-hexabromocyclododecane; (+/-)-gamma-hexabromocyclododecane; and (+/-)-beta-hexabromocyclododecane. Table 5-7 summarizes how many PHA members and analogs had different degrees of data source abundance.

[21] See evidence map files on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.
[22] See evidence map file “PHA Level 2 Evidence Maps 12.6.22, Tab: Integrated” on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

Table 5-7. 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	
	PHA Chemicals (n = 22)	Analog Chemicals (n = 318)
21+	7	0
6–20	2	7
1–5	13	301
0	0	10

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.[23] 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 5-8 and Table 5-9 summarize how many PHA members and analogs had different degrees of Level 3 toxicity data source abundance.

Table 5-8. 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						
	PHA Chemicals (n = 22)						
	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	5	5	11	2	4
6–20	3	2	4	5	10	3	4
1–5	3	5	6	6	0	6	1
0	11	15	7	6	1	11	13

[23] See evidence map file "PHA Level 3 Evidence Maps 12.6.22, Tab: TOX Integrated" and "PHA Level 3B Evidence Maps 12.6.22, Tab: TOX Integrated" on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

Table 5-9. 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						
	PHA Analogs (n = 318)						
	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+	2	0	0	12	83	0	0
6–20	5	0	0	25	17	5	6
1–5	12	1	71	17	207	4	4
0	299	317	247	264	11	309	308

Animal Toxicity or Accepted Alternative data sources were available for 11 PHA members and 19 analogs 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:

- PHA member hexabromocyclododecane had data sources in all subcategories.
- PHA member hexachlorocyclopentadiene had data sources for all subcategories except Endocrine Disruption.
- PHA member 1,2,5,6,9,10-hexabromocyclododecane had data sources for all subcategories except Sensitization.
- Systemic Repeated Dose Toxicity and Irritation were the subcategories with data sources for the most PHA members.
- Sensitization and Acute Toxicity were the subcategories with data sources for the most analogs.

Human Toxicity data sources were available for seven PHA 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 the same nine subcategories used for *Animal Toxicity or Accepted Alternative* above. CPSC staff observed the following:

- PHA member hexabromocyclododecane had the highest number of hits with data sources in the subcategories Neurotoxicity, Mutagenicity/Genotoxicity, Reproductive Toxicity/Developmental Toxicity, and Sensitization.
- Systemic Repeated Dose Toxicity and Endocrine Disruption were the subcategories with data sources for the most PHA members.

- Analog 1-Bromohexane had one data source for Irritation.

Human, Animal, or Modeled Toxicokinetics (ADME [absorption, distribution, metabolism, and excretion]*)* data sources were available for 15 PHA members and 71 analogs at Level 3 review and in the databases and PDFs at Level 3B review. Level 3B reviews provided additional detail 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:

- PHA member 1,2,5,6,9,10-hexabromocyclododecane had data sources in all subcategories.
- PHA member (+/-)-alpha-hexabromocyclododecane had data sources in all subcategories except Human Metabolism and Chemical- or Class-Specific QSAR for an ADME Parameter.
- PHA member hexabromocyclododecane had data sources in all subcategories except Human Metabolism and 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 nine PHA members and 71 analogs.

Experimental Mechanistic data sources were available for 16 PHA members and 54 analogs at Level 3 review. Fourteen PHA members and 10 analogs had data in the databases and PDFs at Level 3B review.[24] This category had two subcategories at Level 3B review separating those data sources that make a connection to a mode of action (MOA) and a potential health effect from those that do not.[25] CPSC staff observed the following:

- Six PHA members had data sources in both subcategories. These were (+/-)-alpha-hexabromocyclododecane; (+/-)-beta-hexabromocyclododecane; (+/-)-gamma-hexabromocyclododecane; 1,2,5,6,9,10-hexabromocyclododecane; 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane; and hexachlorocyclopentadiene. Some of these hit counts were large, with hundreds or thousands of data sources per chemical per subcategory.
- Analog 1-Bromohexane had data sources in both subcategories.
- Nine Analogs had data only in the subcategory Study Makes Connection to MOA and Potential Health Effect.

QSAR, Read-Across, Analog data sources were available for 21 PHA members and 307 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:

[24] 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.
[25] Many database sources could not be tagged for Level 3B because it was not clear whether a connection was made to MOA.

- One data source for PHA member hexabromocyclododecane was identified for Neurotoxicity.
- Subcategories Acute Toxicity, Mutagenicity/Genotoxicity, and Endocrine Disruption had data for all PHA members except pentabromocyclododecene.
- Subcategory Reproductive Toxicity/Developmental Toxicity had data for all PHA members except hexabromocyclododecane and pentabromocyclododecene.
- PHA members benzene hexabromide; 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane; and pentabromochlorocyclohexane had data in all subcategories except Neurotoxicity.
- Three hundred seven analogs had at least one data source for the Acute Toxicity, Mutagenicity/Genotoxicity, and Endocrine Disruption subcategories.

Qualitative Hazard Characterization data sources were available for 11 PHA members and nine analogs 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 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:

- PHA member hexabromocyclododecane had data in all subcategories.
- PHA member hexachlorocyclopentadiene had data sources in all subcategories except Endocrine Disruption.
- The subcategory Acute Toxicity had data for six PHA members and eight analogs.
- The subcategories Endocrine Disruption and Reproductive Toxicity/Developmental Toxicity had data for six PHA members and no analogs.
- The subcategory Mutagenicity/Genotoxicity had data for five PHA members and eight analogs.

Quantitative Hazard Characterization data sources were available for nine PHA members and 10 analogs at Level 3 review and in the databases and PDFs at Level 3B review. At Level 3B review, this category was further divided into seven subcategories: Acute Toxicity, Systemic or Repeated Dose Toxicity, Neurotoxicity, Carcinogenicity, Reproductive Toxicity/Developmental Toxicity, Sensitization, and Endocrine Disruption. CPSC staff observed the following:

- PHA members hexabromocyclododecane; (+/-)-alpha-hexabromocyclododecane; (+/-)-beta-hexabromocyclododecane; 1,2,5,6,9,10-hexabromocyclododecane; and (+/-)-gamma-hexabromocyclododecane had data sources in all subcategories except Carcinogenicity and Sensitization.
- The subcategory Systemic and Repeated Dose Toxicity had data sources for nine PHA members and one analog.
- The subcategory Acute Toxicity had data sources in eight PHA members and nine analogs.

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.[26] 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. PHA 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:

- PHA members hexabromocyclododecane; (+/-)-alpha-hexabromocyclododecane; (+/-)-gamma-hexabromocyclododecane; and hexachlorocyclopentadiene had the highest number of data sources in each category.
- PHA members hexabromocyclododecane; (+/-)-alpha-hexabromocyclododecane; and (+/-)-gamma-hexabromocyclododecane 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 19 of 22 PHA members.[27] The PHA members with the most data sources were hexabromocyclododecane; (+/-)-alpha-hexabromocyclododecane; (+/-)-gamma-hexabromocyclododecane; and (+/-)-beta-hexabromocyclododecane. Table 5-10 summarizes how many PHA members had different degrees of data source abundance.

Table 5-10. 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
	PHA Chemicals (n = 22)
21+	7
6–20	1
1–5	11
0	3

5.4.2. Summary of Levels 3 and 3B

The "EXP_Integrated" tabs from each file contains Level 3 and 3B exposure data counts.[28] The Level 3 integrated counts indicate the number of data sources per chemical from the MMDB database and identified PDFs. Level 3 counts were classified into six exposure data type

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

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 5-11 summarizes how many PHA members had different degrees of Level 3 exposure data source abundance.

Table 5-11. 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					
	PHA Chemicals (n = 22)					
	Environmental Monitoring	Biomonitoring/ Personal Monitoring	Source Characterization	Epidemiology – Population Group	Modeled Concentrations	Modeled Human Dose
21+	7	3	6	0	0	1
6–20	1	3	2	1	1	5
1–5	4	5	10	5	7	2
0	10	11	4	16	14	14

Environmental Monitoring data sources were available for 12 PHA members at Level 3 review and 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.

- PHA member 1,2,5,6,9,10-hexabromocyclododecane had sources in all of the subcategories.
- PHA members (+/-)-alpha-hexabromocyclododecane and (+/-)-gamma-hexabromocyclododecane each had sources in all subcategories except Soil.
- Subcategories Indoor Dust and Food/Dietary each had data sources for nine PHA members.
- PHA member hexachlorocyclopentadiene had a relatively high number of data sources (N = 250) in the subcategory Drinking Water.

Biomonitoring/Personal Monitoring data sources were available for 11 PHA members at Level 3 review and in the database 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).

- PHA members hexabromocyclododecane; (+/-)-alpha-hexabromocyclododecane; and 1,2,5,6,9,10-hexabromocyclododecane had data sources in all of the subcategories except urine.
- PHA members (+/-)-gamma-hexabromocyclododecane and (+/-)-beta-hexabromocyclododecane each had data sources in all subcategories except Urine and Skin/Dermal.
- PHA member hexachlorocyclopentadiene had one data source in the Urine subcategory.
- The subcategories Blood/Serum and Breast Milk/Lipids had data sources for eight and 10 PHA members, respectively.

Source Characterization data sources were available for 18 PHA members at Level 3 review. Twelve PHA members had data in the database and PDFs at Level 3B review. This category was separated into four subcategories for Level 3B review: Product Testing: Content Only, Product Testing: Emission/Migration Data, Nonexperimental Product or Chemical-Specific Modeling Inputs, and Other Qualitative or Quantitative Description of Product Use or Class/Chemical.

- PHA member hexabromocyclododecane had data sources for all subcategories except Product Testing: Content Only.
- Nine PHA members had at least one data source for the subcategories Nonexperimental Product or Chemical-Specific Modeling Inputs and Other Qualitative or Quantitative Description of Product Use or Class/Chemical.
- The subcategory Other Qualitative or Quantitative Description of Product Use or Class/Chemical had data sources for 12 PHA members.
- The subcategory Nonexperimental Product or Chemical-Specific Modeling Inputs had data sources for 10 PHA members.

Environmental Epidemiology[29] data sources were available for six PHA members at Level 3 review. Four PHA members had data in the database and PDFs at Level 3B review. The subcategories were Children; Adult, Non-Occupational; and Other, Specify (with Suggestions). The subcategory Adult, Non-Occupational had one data source for the PHA members (+/-) -alpha-hexabromocyclododecane; (+/-)-gamma-hexabromocyclododecane; (+/-)-beta-hexabromocyclododecane; and 1,2,5,6,9,10-hexabromocyclododecane.

Modeled Concentrations data sources for eight PHA members were identified at Level 3 review. Three PHA members had data in the database and PDFs at Level 3B review. The subcategories were Indoor Concentration, Outdoor Concentration, and Dietary/Food.

- PHA members 1,2,5,6,9,10-hexabromocyclododecane; hexachlorocyclopentadiene; and hexabromocyclododecane had data sources for the subcategory Outdoor Concentration.
- PHA member hexachlorocyclopentadiene had one data source for the subcategory Dietary/Food.
- The subcategory Indoor Concentration had no data sources for PHA members.

[29] 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.

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

- PHA members (+/-)-alpha-hexabromocyclododecane and (+/-)-gamma-hexabromocyclododecane had data sources for all three subcategories.
- Six PHA members had data sources for the subcategory Adult, Non-occupational.
- Five PHA members had data sources for the subcategory Children.
- Four PHA members had data sources for the subcategory Other, Specify (with Suggestions).

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.[30] No risk data were found in the databases. Seven PHA members and no analogs had PDF data sources for risk at Level 2 review. Table 5-12 summarizes how many PHA members had different degrees of data source abundance. Hexabromocyclododecane and 1,2,5,6,9,10-hexabromocyclododecane had the highest numbers of human health risk assessments available.

Table 5-12. 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
	PHA Chemicals (n = 22)
21+	1
6–20	1
1–5	5
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.[31] 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

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

number of PDFs identified per chemical for each Noncancer and Cancer risk assessment. Table 5-13 summarizes how many PHA members and analogs had different degrees of Level 3 human health risk data source abundance.

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

- PHA members hexachlorocyclopentadiene; hexabromocyclododecane; and 1,2,5,6,9,10-hexabromocyclododecane respectively had one, three, and five Noncancer Risk data sources.
- None of the analogs had risk assessment data sources.

Table 5-13. 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
	PHA Chemicals (n = 22)
21+	0
6–20	0
1–5	3
0	19

5.6. Literature Survey Results: Key References

Among the literature survey results are several references from authoritative sources. These references include a toxicological profile by the Agency for Toxic Substances and Disease Registry toxicological profiles, technical reports from the National Toxicology Program, EPA assessments and evaluations, Health Canada assessments, European Union risk assessment reports, International Agency for Research on Cancer evaluations, and Organisation for Economic Co-operation and Development assessments. Each of these references addressed one or more PHAs. These reports included seven specific PHAs,[32] of which four were the subject of multiple technical reports and assessments. These seven chemicals are among the PHAs most frequently noted in the Market Use Report as found in consumer products, as well as in the literature survey results generally. These reports suggest the existence of data about these chemicals, including hazard and potential exposures, and may be useful references for CPSC staff evaluations of these and other PHAs.

[32] The seven PHAs included in one or more key references are (by CAS RN): 77-47-4; 25637-99-4; 3194-55-6; 134237-52-8; 134237-50-6; 134237-51-7; 3194-57-8.

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 PHA subclass and its analogs, and the criteria described in Section 3.1, Criteria for Scoping Determination, CPSC staff concludes, at the time of writing, that the PHA 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 PHA subclass includes 10 data-rich chemicals and that a majority of PHA chemicals and some analogs have some data. The evidence maps show that many PHA chemicals have data in the Animal Toxicity or Accepted Alternative category, including among acute, systemic or repeated dose toxicity, neurotoxicity, carcinogenicity, reproductive/developmental studies, and endocrine disruption. In addition, a majority of PHA 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 eight data-rich chemicals and that a majority of chemicals have some data. In addition, according to available data sources, 21 of the 22 chemicals have market information for use in commerce.

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

6.2. Next Steps for Class-Based Hazard Assessment

6.2.1. Analysis Plan

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

1. CPSC staff, in coordination with the Division of Translational Toxicology (DTT) at the National Institute of Environmental Health Sciences, is working on a comprehensive literature search. Available toxicity information from PHA 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 PHAs, data-rich PHA analogs, PHAs with some toxicity information, and PHAs 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][33]) from the comprehensive literature search.
3. CPSC staff will refine the NAS analog list and characterize analog substances for the PHA 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 PHA class members to be associated with them, will be deprioritized. CPSC staff's initial survey shows that both toxicity and toxicokinetic data are available for 17 analogs.
4. CPSC staff will estimate major metabolites of PHA 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 PHA class members and analogs with available toxicity data can be used to read-across to PHA 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 PHA class are acute toxicity, mutagenicity/genotoxicity, reproductive toxicity/developmental toxicity, and systemic repeat-dose toxicity.
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 PHA 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 PHA class members.
8. CPSC staff will explore the variability and uncertainty associated with dose response values for PHA chemicals within the class.

[33] 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.

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 PHAs.

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

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

Of the two PHA subclass members with the most data, the acute oral toxicity of HCCPD is somewhat higher than that of HBCDD. In contrast, HBCDD is essentially nontoxic following acute inhalation exposure, while HCCPD is "highly toxic" under the Federal Hazardous Substances Act (FHSA). The acute oral toxicity of multiple subclass members appears to be (relatively) low, with LD50s ≥ 2,000 mg/kg (HBCDD and PBCC; EFSA, 2021; OECD, 2007; U.S. EPA, 2016; ECHA, 2008) and between 505 and 1,500 mg/kg (HCCPD; ECHA, 2007). For inhalation toxicity, ECHA (2008) reports no deaths from HBCDD in rats exposed to 202 mg/L (202,000 mg/m^3) for 4 hours, while ECHA (2007) reports ~4-hour inhalation LC50s for HCCPD between 0.018 mg/L (18 mg/m^3)) and 0.041 mg/L (41 mg/m^3). While dermal toxicity for HBCDD appears to be low (LD50 >20,000 mg/kg; OECD, 2007; ECHA, 2008), for HCCPD it is higher (LD50s of 2,000 mg/kg and 3,200 mg/kg; ECHA, 2007). In addition, ECHA (2007) reports at least some mortality in all skin and eye irritation studies of HCCPD. TBCO is classified as harmful if swallowed, inhaled, or in contact with skin in the ECHA Annex Inventory III, although it is not clear if this classification is based on measured or modeled data (Zuiderveen et al., 2020).

HBCDD may be a mild eye irritant (OECD, 2007) although it does not meet EU labeling criteria (ECHA, 2008), and does not appear to be a skin or respiratory irritant (ECHA, 2008) or a skin sensitizer (OECD, 2007; ECHA, 2008). According to animal data, HCCPD is classified as an irritant (skin, eyes, and respiratory tract) and a possible sensitizer (ECHA, 2007). PBCC may be an eye irritant and a skin sensitizer (U.S. EPA, 2016). In the ECHA Annex Inventory III, DBE-DBCH and TrBTrCCH are classified as suspected skin irritants, DBE-DBCH as a suspected skin sensitizer, and TBCO as causing skin irritation and serious eye irritation, although it is not clear if these labels are based on measured or modeled data (Zuiderveen et al., 2020).

Repeated dose studies of HBCDD (EFSA, 2021; ECHA, 2008) and HCCPD (ECHA, 2007) found some consistency in the targets, with both affecting the liver, immune system, and reproductive system. HBCD also affected neurodevelopment and the thyroid, while HCCPD also affected the kidney following oral or inhalation exposure. Consistent with its irritative properties, HCCPD caused forestomach inflammation following gavage exposure (ECHA, 2007) and respiratory tract irritation following inhalation exposure (ECHA, 2007). None of these repeated dose studies for HCCPD, and only some of the studies for HBCD, met current test guidelines. Mice and rats exposed to alpha-HBCD, or to mixtures consisting of primarily alpha-HBCD or primarily gamma-HBCD, generally exhibited effects similar to those ascribed to HBCD (EFSA,

2021), although uptake and accumulation of alpha-HBCD may be higher than that of other isomers (Xu et al., 2018). A 13-week gavage study of HCCPD in both rats and mice identified increased relative kidney weight and kidney tubular necrosis (ECHA, 2007), but the kidney effects may have been due to contamination with a known nephrotoxin.

Liver may be a shared endpoint between HBCD, HCCPD, and DBE-DBCH. Increased (absolute or relative) liver weights were observed for HBCD in four 28-day oral studies at doses ≥20 mg/kg-day and in both adult and weanling rats in a two-generation dietary study (EFSA, 2021), and for HCCPD in rats and female mice exposed orally to 19 mg/kg-day (ECHA, 2007). A 5-day gavage study in rats observed centrilobular hypertrophy at the highest tested dose of HBCD (641 mg/kg-day) (EFSA, 2021), and a 30-week study observed "mild degenerative changes" in liver in rats, mice, rabbits, and guinea pigs exposed to 1.7 mg/m^3 (7 hours/day, 5 days/wk) (ECHA, 2007). A NOAEL of 50 mg/kg-day for oral exposures to DBE-DBCH was reported for rats that was based on liver histopathology indicative of inflammation (Dong et al., 2021; Curran et al., 2017). In vivo and in vitro studies indicate that the MOA for liver effects of HBCDs is mediated by activation of several cell receptors, including CAR, PXR, and AHR (EFSA, 2021). Data on MOA for liver effects were not identified for other PHA subclass members.

It appears that both HBCCD and HCCPD affect the immune system. Rats exposed orally to HBCD had lesions on the thyroid and spleen, and changes in both the cellular and humoral immune system parameters (EFSA, 2021). Similar targets were seen in a chronic inhalation study with HCCPD (ECHA, 2007). Data on immune effects were not identified for other PHA subclass members.

Multiple subclass members appear to affect the thyroid, although it is unclear whether this is through a consistent MOA. In vivo studies, in rats and mice, and in vitro studies (human liver cells, rat pituitary cells) are consistent with a MOA in which HBCD induces hepatic T4-UGT leading to increased clearance of T4 and compensatory induction of thyroid stimulating hormone (TSH) (EFSA, 2021; ECHA, 2008; Stubbings and Harrad, 2014). This MOA is considered relevant to humans for potential neurodevelopmental effects, but not for thyroid cancer (Dellarco et al., 2006). Female but not male rats exposed to TBECH for 28 days had increased serum levels of T3 and T4; TSH was not measured (Dong et al., 2021; Curran et al., 2017). It appears no data exist on the effects of HCCPD on thyroid hormones (ECHA, 2007).

Neurotoxicity (including neurodevelopment) may be a shared characteristic among some subclass members. However, it is unlikely that these effects are secondary to thyroid hormone effects, since the doses of HBCD affecting neurodevelopment have generally been an order of magnitude lower than those affecting the thyroid (EFSA, 2021). Neurodevelopmental effects have been observed in rats and mice exposed to HBCDs, and these effects are supported by mechanistic studies reporting effects on dopaminergic and glutaminergic neurons (EFSA, 2021). TBECH has inhibited electrical activity in rat Purkinje neurons in vitro (Dong et al., 2021). In contrast, HCCPD did not have effects on locomotor activity in offspring of exposed pregnant mice, up to 45 mg/kg-day on gestational days 8-12 (as opposed to the guideline of days 6-15; ECHA, 2007).

Reproductive and developmental effects may be a shared characteristic among some subclass members. Rats orally exposed to HBCD have exhibited reproductive and developmental effects

(Moreau and Nong, 2019; EFSA, 2021). Chronic exposure of mice to HCCPD led to ovarian inflammation (ECHA, 2007). Minor developmental effects of HCCPD have been observed in the presence of significant maternal toxicity, but HCCPD has not been observed to affect reproductive function (ECHA, 2007). TBECH had mixed effects on reproduction and development in zebrafish (Dong et al., 2021). HBCYD is listed in the ECHA Annex Inventory III as "suspected of damaging fertility or the unborn child" and "may cause harm to breastfed children," although it is not clear if this is based on measured or modeled data (Zuiderveen et al., 2020).

Neither of the two data-rich chemicals in this subclass are considered mutagenic. EFSA (2021) concluded that HBCD is not mutagenic, based on negative results from bacterial reverse mutation assay, chromosomal aberration tests, micronucleus tests, and DNA strand breaks in a Comet assay only at concentrations associated with increased cytotoxicity. ECHA (2007) determined that HCCPD is not mutagenic, based on negative results in bacterial and mammalian in vitro mutagenicity assays, as well as in a mouse micronucleus assay, and supported by a negative carcinogenicity study. HCCPD induced chromosomal aberrations in vitro, but only in the presence of high cytotoxicity (ECHA, 2007). It is not clear, however, whether the negative results for HBCD and HCCPD apply to the rest of the subclass. DBE-DBCH is listed as a suspected mutagen in the ECHA Annex Inventory III, although it is not clear if this is based on measured or modeled data (Zuiderveen et al., 2020).

EFSA (2021) concluded that there is no indication that HBCDs are carcinogenic, based on non-genotoxicity, the lack of carcinogenicity in the chronic mouse study, and MOA. Given the genotoxicity data and a lack of increased neoplasms in an NTP 2-year chronic inhalation study, ECHA (2007) determined that HCCPD is "of no concern with respect to carcinogenic activity," though they also noted a lack of data on carcinogenicity after dermal and oral exposures. A 2-year chronic/carcinogenicity study of PBCC in rats showed increased large intestine adenomas and carcinomas, with a weight of evidence call of "suggestive Evidence of Carcinogenic Potential" (U.S. EPA, 2016). DBE-DBCH and TrBTrCCH are listed as suspected carcinogens in the ECHA Annex Inventory III, although it is not clear if these labels are based on measured or modeled data (Zuiderveen et al., 2020).

In summary, HBCD seems to share more endpoints with other less data-rich members of the subclass than does HCCPD. HCCPD shares possible reproductive effects with HBCD and other less data-rich subclass members, and shares immune system effects with HBCD, although data on immune effects were not identified for other PHA subclass members. HBCD and HCCPD may also cause similar liver effects. Challenges for this subclass may be a lack of clarity in some studies regarding the composition of HBCD administered, and the lack of guideline compliance of most if not all HCCPD studies. However, it appears that a class-based assessment that includes at least some members of this subclass may be possible.

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:

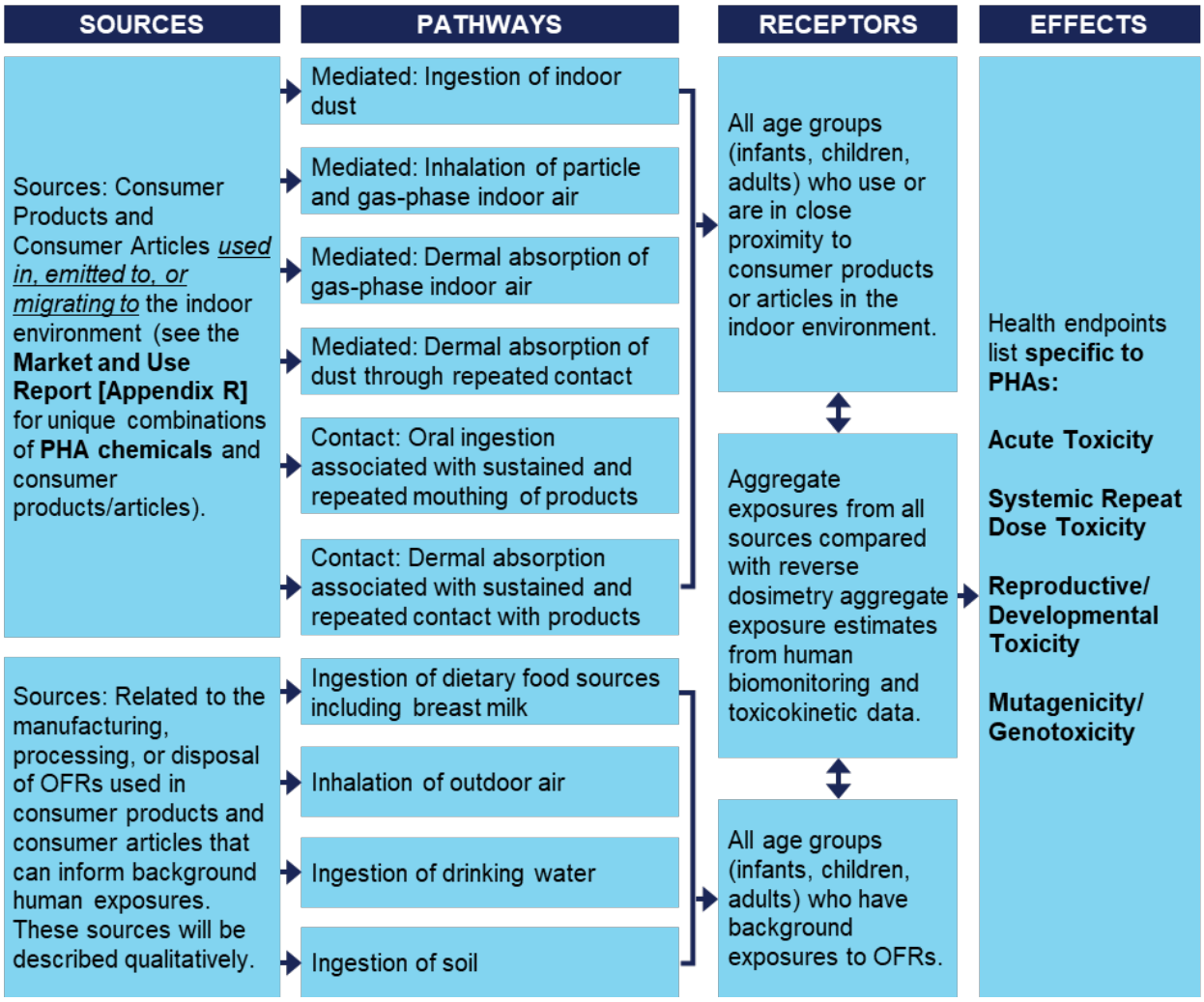
1. CPSC staff, in coordination with DTT staff, is working on a comprehensive literature search. Available exposure information from PHA class members will be further summarized and integrated after this search is complete. After the search, staff will refine the list of data-rich PHAs, PHAs with some exposure and use information, and PHAs with no exposure and use information.
2. Using the market and use research, CPSC staff expects to compile a list of PHA chemicals that have been or could be used in consumer products. While 21 of the 22 chemicals had some market-use information, 10 PHA chemicals had more market and use information that could be used to inform analyses for PHA chemicals with less information. CPSC staff will characterize uses for PHAs according to available information and consider temporal trends when developing exposure scenarios.
3. CPSC staff will characterize the uses identified in the market and use research and combine this information with likely exposure pathways and populations exposed to define unique combinations of exposure scenarios for chemical substances within the class. Depending on available information, CPSC may be able to quantify exposure scenarios for between 10 and 21 PHA subclass members.
4. Exposure pathways with likely higher potential for PHA class members include ingestion of indoor dust, ingestion of food, and mediated and contact exposures with consumer products. Exposure pathways with likely lower potential for PHA class members include ingestion of drinking water, ingestion of soil, and inhalation of indoor and ambient air. CPSC staff will review available environmental monitoring data to determine a range of potential concentrations to which people could be exposed. There are 18 chemicals in the class with source characterization data, 12 chemicals in the class with environmental monitoring data, and 12 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 PHA 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 six 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 11 PHA 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 PHAs.

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 PHA 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 PHAs are listed.

Figure 6-1. PHA 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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