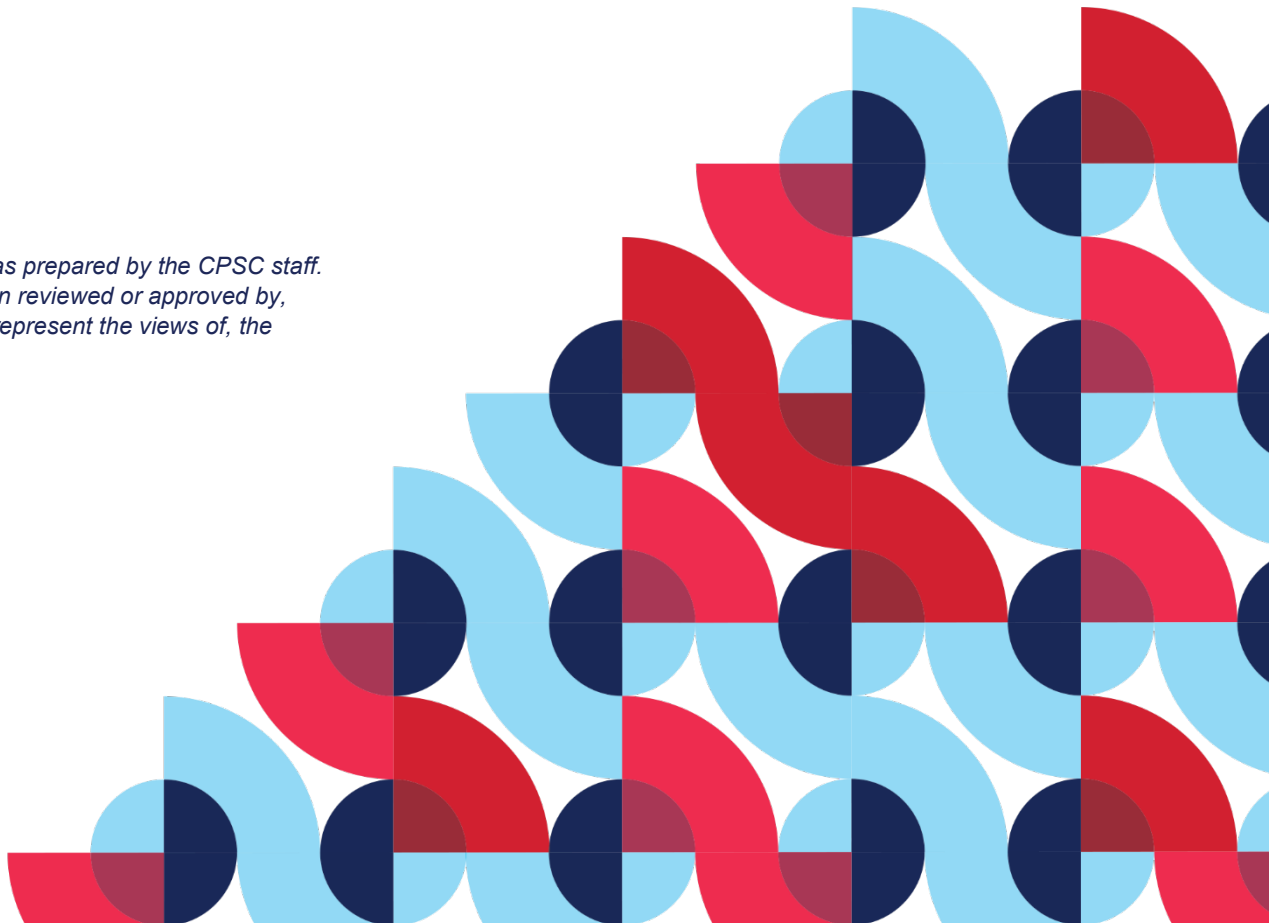
United States
Consumer Product Safety Commission

Organohalogen Flame Retardant Scope Document: Polyhalogenated Phenol Aliphatic Ether 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 phenol aliphatic ether (PHPhAE) 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 PHPhAE 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 PHPhAE 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 polyhalogenated phenol aliphatic ether (PHPhAE) 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 supports estimates of quantitative average daily dose(s) for human exposure, and
    - Modeled exposure data (emissions, occurrence, disposition), if such data demonstrate close agreement with empirical data, are acceptable to support this category, but such data are not required.

4.2. Inventory

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

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

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

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

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

4.3. Market and Use Research

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

4.3.1. Targeted Literature Search

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

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

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

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

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

4.3.2. Other Data Sources

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

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

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

4.4. Literature Survey

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

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

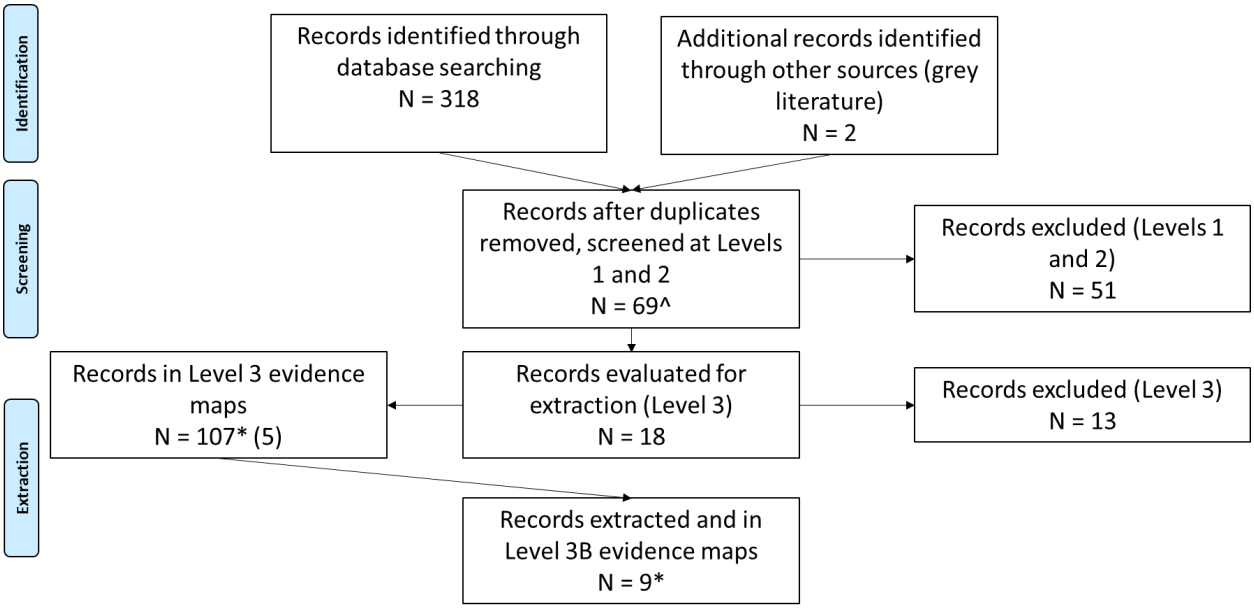
Briefly, for peer-reviewed and gray literature, **Level 1** screening was used to confirm that the reference might contain information about at least one OFR chemical and that the reference

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

was relevant to the PECO statement.[11] **Level 2** screening identified the OFR subclasses included in each reference and tagged the references for the types of data (hazard, exposure, risk). **Level 3** identified the specific OFR or analog chemicals in each reference and extracted more specific information about the types of hazard data, exposure data, or risk assessment information presented for each chemical. Finally, **Level 3B** tagging was performed on a subset of toxicity assessments, toxicity literature reviews, risk assessments, and exposure literature reviews selected from Level 3 to identify even more specific information for the chemicals in these references.

Similarly, data from databases were tagged for type of data using a database logic developed to provide consistency across different data sources. Finally, the tagged information was organized into evidence maps by OFR subclass and specific chemicals. Figure 4-1 shows the numbers of records initially identified and the number of records screened or extracted at each level.

Figure 4-1. Literature Flow Diagram



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

[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.

5. Scoping for PHPhAEs

5.1. PHPhAE Subclass Chemistry

The PHPhAE subclass generally consists of chemicals containing a halogenated phenyl ether with a functionalized alkyl substituent. The functional groups on the alkyl substituents include groups such as allyls, halogens, esters, and ethers. In particular, members of this subclass all have an ether chemical bond. The different functional groups on the alkyl substituents may lead to chemistry-based differences throughout this subclass despite structural similarities amongst the members.

Table 5-1 lists 11 individual chemicals in the PHPhAE subclass.

Table 5-1. List of Chemicals in PHPhAE Subclass

	CAS RN	Chemical Name	Abbreviation/ Synonyms	SMILES
1	20217-01-0	2,4-Dibromophenyl glycidyl ether	NA	C1C(O1)COC2=C(C=C(C=C2)Br)Br
2	2167063-57-0	1,2,3-Tribromo-4-[(prop-2-en-1-yl)oxy]benzene	(Allyloxy)tribromobenzene	C=CCOC1=C(C(=C(C=C1)Br)Br)Br
3	31977-87-4	1,1'-{[(2Z)-2,3-Dibromobut-2-ene-1,4-diyl]bis(oxy)}bis(2,4,6-tribromobenzene)	NA	C1=C(C=C(C(=C1Br)OCC(=C(COC2=C(C=C(C=C2Br)Br)Br)Br)Br)Br)Br
4	3278-89-5	1,3,5-Tribromo-2-(prop-2-en-1-yloxy)benzene	FR-913; TBP-AE	C=CCOC1=C(C=C(C=C1Br)Br)Br
5	35109-60-5	1,3,5-Tribromo-2-(2,3-dibromopropoxy)benzene	Bromkal 73-5PE	C1=C(C=C(C(=C1Br)OCC(CBr)Br)Br)Br
6	3555-11-1	Allyl pentabromophenyl ether	BRN 3338650; Flammex 5AE	C=CCOC1=C(C(=C(C(=C1Br)Br)Br)Br)Br
7	37853-59-1	1,2-Bis(2,4,6-tribromophenoxy)ethane	BTBPE; FireMaster 680; FireMaster FF 680	C1=C(C=C(C(=C1Br)OCCOC2=C(C=C(C=C2Br)Br)Br)Br)Br
8	607-99-8	2,4,6-Tribromoanisole	2,4,6-TBA, TBA	COC1=C(C=C(C=C1Br)Br)Br
9	61262-53-1	Benzene, 1,1'-[1,2-ethanediylbis(oxy)]bis[2,3,4,5,6-pentabromo-	FireMaster 695; Pyro-Chek 77B	C(COC1=C(C(=C(C(=C1Br)Br)Br)Br)Br)OC2=C(C(=C(C(=C2Br)Br)Br)Br)Br)Br
10	7347-19-5	Tribromophenoxyethyl acrylate	NA	C=CC(=O)OCCOC1=C(C=C(C=C1Br)Br)Br
11	99717-56-3	2-Bromoallyl 2,4,6-tribromophenyl ether	NA	C=C(COC1=C(C=C(C=C1Br)Br)Br)Br

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 PHPhAE chemicals are limited. One PHPhAE subclass member has experimental data and 11 PHPhAE members have predicted data. Well-studied chemicals in this subclass include 1,2-

bis(2,4,6-tribromophenoxy)ethane (BTBPE, CAS RN 37853-59-1) and 1,3,5-tribromo-2-(2,3-dibromopropoxy)benzene (Bromokal 73-5PE, CAS RN 35109-60-5). From this data set, studied PHPhAEs have predicted boiling points ranging from 251°C to 503 °C, and vapor pressures from $3.47E^{-11}$ to $1.35E^{-2}$ mm Hg. Data show water solubility values ranging from $4.90E^{-10}$ to $6.46E^{-4}$ mol/L. The octanol/water partition coefficient (K_{ow}) values, which are commonly expressed as log K_{ow}, range from 4.03 to 8.29.

5.2. Market and Use Summary for PHPhAEs

The OFR Market and Use Report, completed in March 2022, includes 11 PHPhAE chemicals.

- Ten PHPhAE chemicals had market and use information and one chemical had no market and use information.
- According to EPA data, four PHPhAE chemicals were identified to be on the TSCA chemical substance (active) inventory, three PHPhAE chemicals were identified on the TSCA (inactive) inventory, and none on the CDR and TRI program lists.
- No PHPhAE chemicals were identified in the Interstate Chemicals Clearinghouse (IC2) HPCDS.
- Five PHPhAE chemicals were identified in the targeted literature search.
- Nine PHPhAE chemicals had patent data.

5.2.1. PHPhAEs 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 10 PHPhAEs that are known to be or have been used in commerce, according to data available from these sources.

The one PHPhAE chemical that is not known to be used in commerce is: 1,1'-{[(2Z)-2,3-dibromobut-2-ene-1,4-diyl]bis(oxy)}bis(2,4,6-tribromobenzene) (CAS RN 31977-87-4).

Among the 10 PHPhAE chemicals used in commerce, seven can be found in the TSCA inventory. Four chemicals are in the TSCA active inventory and three PHPhAEs are in the TSCA inactive inventory. In Table 5-2, PHPhAE 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] Five PHPhAE chemicals appear in one or more of these international inventories. In Table 5-2, the number of

[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.

international registries for the PHPhAE chemical is listed in the “International Inventories” column.

Five PHPhAE 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.

Nine PHPhAE chemicals were mentioned in patents. The total count of patents is provided for each chemical in Table 5-2, and identified from a search of the associated Compound Identifier (CID) in PubChem.

Table 5-2. PHPhAE Chemicals Used in Commerce

CAS RN	Chemical Name	TSCA	International Inventories	Literature Cites	Patents
20217-01-0	2,4-Dibromophenyl glycidyl ether	Active	3	0	120
2167063-57-0	1,2,3-Tribromo-4-[(prop-2-en-1-yl)oxy]benzene	Not found	Not found	0	250
3278-89-5	1,3,5-Tribromo-2-(prop-2-en-1-yloxy)benzene	Active	2	6	153
35109-60-5	1,3,5-Tribromo-2-(2,3-dibromopropoxy)benzene	Inactive	Not found	5	36
3555-11-1	Allyl pentabromophenyl ether	Not found	Not found	0	36
37853-59-1	1,2-Bis(2,4,6-tribromophenoxy)ethane	Active	4	24	500
607-99-8	2,4,6-Tribromoanisole	Inactive	Not found	0	246
61262-53-1	Benzene, 1,1’-[1,2-ethanediylbis(oxy)]bis[2,3,4,5,6-pentabromo-	Inactive	1	2	329
7347-19-5	Tribromophenoxyethyl acrylate	Active	2	0	1,245
99717-56-3	2-bromoallyl 2,4,6-tribromophenyl ethe	Not found	Not found	2	0

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

5.2.2. PHPhAEs Used in Consumer Products

The Market and Use Report identified the use of PHPhAEs 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

[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.
[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.

articles as such or in complex objects (Products) (SCIP) database, and the IC2's HPCDS. Data on the uses and applications of PHPhAE chemicals were also found in the literature.

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

- Kitchen utensils (up to 0.11%)
- Resins and extruded polystyrene foams (0.0044% to 0.0216%)
- Construction materials, electrical and electronic devices, flooring, fabric, upholstery (detected in electrical and electronic devices at a maximum of 0.0000317%)
- Hard plastic toys, foam toys, rubber/soft plastic toys, textile and stuffed toys (median <0.00001%)
- Household and office products: detected in about half the products sampled (concentrations close to the detection limit)

Of the reported uses of PHPhAEs chemicals in products, chemicals were used in trace amounts, and in concentrations greater than 1,000 ppm (0.1%); levels below 0.1% are considered contaminant by CPSC staff.[15]

The following PHPhAE chemical was identified from the targeted literature search to have been used in consumer and children's products, and example uses are provided below:

CAS RN. 37853-59-1: Applications in HIPS, ABS, thermoplastics, thermoset resins, polycarbonate and coatings. Replacement for Octa-BDE in ABS, thermoplastics, polycarbonates and coatings.

HPCDS. Using the HPCDS reporting tool, private industry reports the use of chemicals of concern in products intended for use by children that are sold in select states.[16] From 2012 to 2020, 1,093 reports were submitted to HPCDS identifying the use of OFR chemicals from seven subclasses in children's products sold in two U.S. states, Washington and Oregon. Among the 1,093 reports submitted to HPCDS, none documented the use of PHPhAE chemicals in children's products.

SCIP. ECHA maintains a database of information through the REACH regulation, which was enacted in 2007 to improve the protection of human health from risks posed by chemicals. REACH applies to consumer products as well as to the chemicals industry. The REACH regulation requires suppliers of articles (products) containing potentially hazardous chemicals, including OFRs, to communicate down the supply chain and to consumers sufficient information

[15] 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.

[16] 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.

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

Table 5-3. PHPhAE Chemical Included in SCIP Database

CAS RN	Substance Name	EC No.	Number of Search Results Returned
37853-59-1	1,2-Bis(2,4,6-tribromophenoxy)ethane	253-692-3	191

As of May 2023, there were 191 search results for BTBPE (CAS RN 37853-59-1) in the SCIP database. Articles that contain this candidate list substance can be found in at least 14 article categories that can be used to help identify articles based on function and use. According to SCIP data, TBE can be found in vehicles with piston engines including those designed for traveling on snow, electrical conductors, electronic switches, and data-processing machinery, in forged or stamped iron or steel articles, and in tubes pipes and hoses with fittings. 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, PHPhAE chemicals have been used in a variety of product use categories for many years. Table 5-4 presents the commercial and consumer product uses of PHPhAE chemicals because CPSC needs to know the range of the product uses for these chemicals during the scoping phases.[17]

EPA changed the names of some product use categories between 2006 and 2012, and again in 2016, and so Table 5-4 presents the names of product use categories of PHPhAE 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

[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.

product use category names help maintain consistency over the period displayed in the table below without distorting product use.

According to the CDR, the most common uses of PHPhAE chemicals are in product use categories where the product description is not identified in public data, although PHPhAEs are reported to be used in rubber and plastic products and batteries as well.

Table 5-4. Report of PHPhAE Chemicals in CDR

Product Use Category	2006	2012	2016	Total
Product description, not identified	4	NR	NR	**4**
Rubber and plastic products	NR	1	NR	**1**
Batteries	NR	NR	1	**1**
Grand Total	**4**	**1**	**1**	**6**

Notes: Data listed as "Product description not identified" may be interpreted as one of any of the other product categories reported for PHPhAEs, 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 PHPhAE 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 PHPhAEs

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.

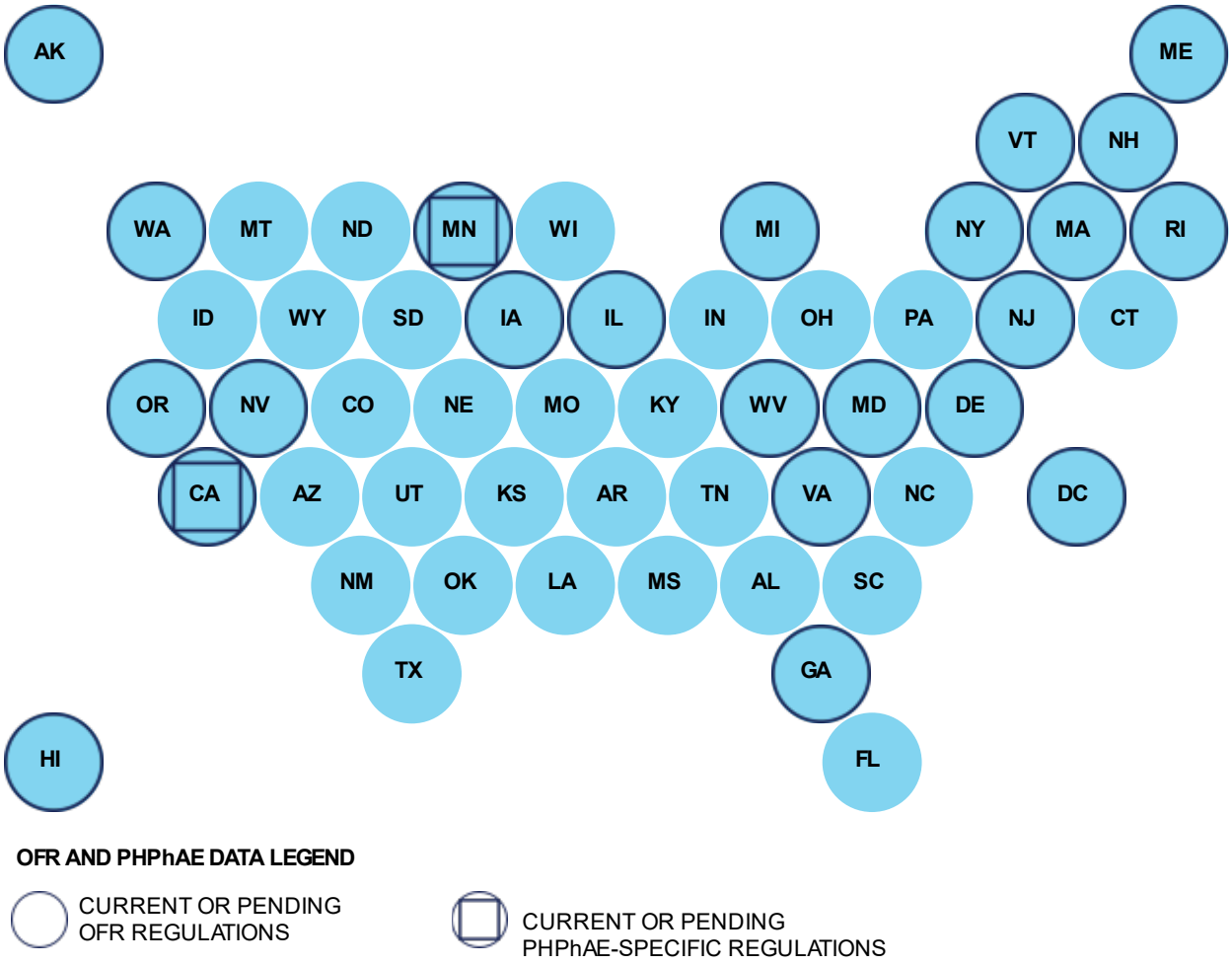
The Market and Use Report provides greater detail of legislative action taken in the United States, as well as action taken by other nations. Volume 2, Appendix R of the Market and Use Report provides detailed fact sheets describing specific pieces of legislation enacted or under consideration since 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]

According to the Market and Use Report, 22 states and the District of Columbia have current or pending OFR chemical regulations. State regulation of OFRs has tended to focus primarily on

[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.

the use of these chemicals in children's products, upholstered furniture, and mattresses. (See Market and Use Report Volume 1, Section 4.1.2.4 Summary of U.S. Regulatory Trends.) Among areas that have regulated the use of OFRs, two states have proposed or enacted regulation of PHPhAEs specifically. In the map below (Figure 5-1), states that regulate OFRs or have pending regulations are shown with a circle border and states that regulate PHPhAEs specifically or have pending PHPhAE-specific regulations are shown with a square within the circle. For more information on the state regulation of OFRs and PHPhAEs, see Volume 2 of the Market and Use Report, Appendix R.

Figure 5-1. U.S. States That Regulate the Use of OFR and PHPhAE 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:

- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had the most representation across toxicity categories for database and PDF reviews.
- The *QSAR, Read-across, Analog* category (QSAR = quantitative structure activity relationships) had broad representation with 100% of PHPhAE members and 100% of analogs having at least one data source at both Level 3 review and 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 11 PHPhAE members and for all 19 analogs. The PHPhAE members with the most data sources at Level 2 were 1,2-bis(2,4,6-tribromophenoxy)ethane; 1,3,5-tribromo-2-(2,3-dibromopropoxy)benzene; and 1,3,5-Tribromo-2-(prop-2-en-1-yloxy)benzene. Table 5-5 summarizes how many PHPhAE members and analogs had different degrees of data source abundance.

Table 5-5. 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	
	PHPhAE Chemicals (n = 11)	Analog Chemicals (n = 19)
21+	1	0
6–20	2	0
1–5	8	19
0	0	0

[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 "PHPhAE Level 2 Evidence Maps 12.6.22, Tab: Integrated" on the CPSC Organohalogen Flame Retardant Chemicals Assessment website or Docket No. CPSC-2015-0022.

5.3.2. Summary of Levels 3 and 3B

The "TOX_Integrated" tabs from each file in the evidence map files, 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 5-6 and Table 5-7 respectively summarize how many PHPhAE members and analogs had different degrees of Level 3 toxicity data source abundance.

Table 5-6. 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 PHPhAE Chemicals (n = 11)						
	Animal Toxicity or Accepted Alternative	Human Toxicity	Human, Animal, or Modeled Toxicokinetics (ADME)	Experimental Mechanistic	QSAR, Read-Across, Analog	Qualitative Hazard Characterization	Quantitative Hazard Characterization
21+	1	0	1	2	10	0	1
6–20	2	0	3	2	1	1	0
1–5	3	1	5	0	0	4	5
0	5	10	2	7	0	6	5

Animal Toxicity or Accepted Alternative data sources were available for six PHPhAE members and no analogs at Level 3 review. Six PHPhAE members and no analogs had data in the databases and PDFs at Level 3B review. Level 3B reviews provided additional detail for nine subcategories: Acute Toxicity, Systemic or Repeated Dose Toxicity, Neurotoxicity, Carcinogenicity, Mutagenicity/Genotoxicity, Reproductive Toxicity/Developmental Toxicity, Irritation, Sensitization, and Endocrine Disruption. CPSC staff observed the following:

[23] See evidence map file "PHPhAE Level 3 Evidence Maps 12.6.22, Tab: TOX Integrated" and "PHPhAE 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.

- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had data sources in all subcategories except Sensitization.
- PHPhAE member 2,4-dibromophenyl glycidyl ether had data sources for subcategories Acute Toxicity, Systemic or Repeated Dose Toxicity, and Mutagenicity/Genotoxicity.
- PHPhAE member 2,4,6-tribromoanisole had data sources for subcategories Acute Toxicity, Mutagenicity/Genotoxicity, and Irritation.
- The subcategory Acute Toxicity had data sources for four PHPhAE members.
- The subcategories Mutagenicity/Genotoxicity and Reproductive Toxicity/Developmental Toxicity each had data sources for three PHPhAE members.

Table 5-7. 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 PHPhAE Analogs (n = 19)						
	Animal Toxicity or Accepted Alternative	Human Toxicity	Human, Animal, or Modeled Toxicokinetics (ADME)	Experimental Mechanistic	QSAR, Read-Across, Analog	Qualitative Hazard Characterization	Quantitative Hazard Characterization
21+	0	0	0	0	7	0	0
1–5	0	0	7	1	12	0	0
0	19	19	12	18	0	19	19

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

- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had one data source for the subcategory Endocrine Disruption.
- No PHPhAE analogs had *Human Toxicity* data sources.

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

- No data sources were reported for any PHPhAE members or analogs under the subcategories Human Metabolism; Animal Metabolism; or In Vitro.
- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had data sources in three subcategories: Human Absorption, Distribution, Excretion; Chemical- or Class-Specific PBPK Model; and Chemical- or Class-Specific QSAR for an ADME Parameter.
- 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 eight PHPhAE members and seven analogs.

Experimental Mechanistic data sources were available for four PHPhAE members and one analog at Level 3 review. One PHPhAE member and no 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:

- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had one data source for the subcategory Study Does Not Make Connection to MOA and Potential Health Effect Specifically.
- No PHPhAE analogs had *Experimental Mechanistic* data sources.

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

- No data sources for PHPhAE members or analogs were identified for Neurotoxicity. The vast majority of data with the *QSAR, Read-across, Analog* tag are from the Danish QSAR Database, which does not include any data that are taggable as Neurotoxicity.
- Six PHPhAE members and seven analogs had data sources for all subcategories except Neurotoxicity.
- Twelve analogs had data sources in subcategories Acute Toxicity, Mutagenicity/ Genotoxicity, Reproductive Toxicity/Developmental Toxicity, and Endocrine Disruption.

Qualitative Hazard Characterization data sources were available for five PHPhAE members and none of the analogs at Level 3 review and had data in the databases and PDFs at Level 3B review. In contrast with all other data types, a tag for Qualitative Hazard Characterization indicates that a review/assessment was attempted, not necessarily that data were found (e.g., if a review/assessment clearly stated that authors looked for data for endpoint X for chemical Y but found none, chemical Y was tagged for Qualitative Hazard Characterization for endpoint X,

[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.

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:

- PHPhAE member 1,2-Bis(2,4,6-tribromophenoxy)ethane had data sources for subcategories Acute Toxicity, Carcinogenicity, Mutagenicity/Genotoxicity, and Endocrine Disruption.
- No PHPhAE members or analogs had data sources in subcategories Systemic or Repeated Dose Toxicity or Neurotoxicity.
- No analogs had data sources for Qualitative Hazard Characterization.

Quantitative Hazard Characterization data sources were available for six PHPhAE members and no analogs at Level 3 review and had data 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:

- PHPhAE member 1,2-Bis(2,4,6-tribromophenoxy)ethane had data sources for subcategories Acute Toxicity, Systemic or Repeated Dose Toxicity, Neurotoxicity, Carcinogenicity, Reproductive Toxicity/Developmental Toxicity.
- Subcategories Acute Toxicity and Reproductive Toxicity/Developmental Toxicity each had data sources for three PHPhAE members.
- No PHPhAE members or analogs had data sources in subcategories Neurotoxicity, Carcinogenicity, Sensitization, or Endocrine Disruption.
- No analogs had data sources for Quantitative Hazard Characterization.

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. PHPhAE 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 include:

- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had the most representation across exposure categories for database and PDF reviews.

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

5.4.1. Summary of Level 2

The MMDB database and PDF searches identified exposure data sources for eight of 11 PHPhAE members.[27] The PHPhAE members with the most data sources were 1,2-bis(2,4,6-tribromophenoxy)ethane; 1,3,5-tribromo-2-(2,3-dibromopropoxy)benzene; and 1,3,5-tribromo-2-(prop-2-en-1-yloxy)benzene. Table 5-8 summarizes how many PHPhAE members had different degrees of data source abundance. The PDFs provided more total data sources and covered more PHPhAE members than the database.

Table 5-8. 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
	PHPhAE Chemicals (n = 11)
21+	2
6–20	2
1–5	4
0	3

5.4.2. Summary of Levels 3 and 3B

The "EXP_Integrated" tabs from 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 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 5-9 summarizes how many PHPhAE members had different degrees of Level 3 exposure data source abundance.

[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.

Table 5-9. 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					
	PHPhAE Chemicals (n = 11)					
	Environmental Monitoring	Biomonitoring/ Personal Monitoring	Source Characterization	Epidemiology – Population Group	Modeled Concentrations	Modeled Human Dose
21+	1	1	2	0	0	1
6–20	3	0	1	0	0	1
1–5	1	2	5	3	1	2
0	6	8	3	8	10	7

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

- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had data sources in each of the subcategories except Soil and Drinking Water.
- PHPhAE member 1,3,5-tribromo-2-(prop-2-en-1-yloxy)benzene had data sources for subcategories Indoor/Personal Air, Indoor Dust, and Food/Dietary.
- Subcategory Indoor Dust had data sources for four PHPhAE members.
- Subcategories Indoor/Personal Air and Food/Dietary each had data sources for three PHPhAE members, and Outdoor air had data sources for two PHPhAE members.
- Subcategories Soil and Drinking Water had no data sources for any PHPhAE members.

Biomonitoring/Personal Monitoring data sources were available for three PHPhAE members at Level 3 review. One PHPhAE member had data 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). Staff noted the following observations:

- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had one data source in each of the Breast Milk/Lipids and Skin/Dermal subcategories.
- Subcategories Blood/Serum, Urine, and Human (Other) had no data sources for any PHPhAE members.

Source Characterization data sources were available for eight PHPhAE members at Level 3 review. Five PHPhAE 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. Staff noted the following observations:

- PHPhAE members 1,2-bis(2,4,6-tribromophenoxy)ethane; 1,3,5-tribromo-2-(prop-2-en-1-yloxy)benzene; 1,3,5-tribromo-2-(2,3-dibromopropoxy)benzene; allyl pentabromophenyl ether; and 2,4,6-tribromoanisole each had one to three data sources for subcategories Nonexperimental Product- or Chemical-Specific Modeling Inputs and Other Qualitative or Quantitative Description of Product Use or Class/Chemical.
- PHPhAE member 1,3,5-Tribromo-2-(prop-2-en-1-yloxy)benzene had 30 data sources for the subcategory Product Testing: Content Only.

Environmental Epidemiology[29] data sources were available for three PHPhAE members at Level 3 review. One PHPhAE member had data in the database and PDFs at Level 3B review. The subcategories were Children; Adult, Non-Occupational; and Other, Specify (with Suggestions). Staff noted the following observations:

- PHPhAE member 1,2-bis(2,4,6-tribromophenoxy)ethane had data sources in each of the subcategories Children and Adult, Non-Occupational.
- No PHPhAE members had data sources for subcategory Other, Specify (with Suggestions).

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

Modeled Human Dose data sources were available for four PHPhAE members at Level 3 review. Two PHPhAE members had data in the database and PDFs at Level 3B review. The subcategories were Children; Adult, Non-occupational; and Other, Specify (with Suggestions). Staff noted the following observations:

- PHPhAE member 1,2-Bis(2,4,6-tribromophenoxy)ethane had data sources for the subcategories Children and Adult, Non-occupational.
- PHPhAE member 2-bromoallyl 2,4,6-tribromophenyl ether had one hit for subcategory Adult, Non-occupational only.
- The subcategory Other, Specify (with Suggestions) had no hits for any PHPhAE members.

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

None of the "Database" (DB) tabs in the evidence maps 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.

[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.

5.5.1. Summary of Level 2

The “Integrated” tab in the risk evidence map file contains summed Level 2 risk data counts from PDF sources.[30] No risk data were found in the databases. One PHPhAE member and no analogs had PDF data sources for risk at Level 2 review. Table 5-10 summarizes how many PHPhAE members had different degrees of data source abundance. 1,2-Bis(2,4,6-tribromophenoxy)ethane was the only PHPhAE member with human health risk assessments available (n = 18).

Table 5-10. 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
	PHPhAE Chemicals (n = 11)
6–20	1
0	10

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 number of PDFs identified per chemical for each Noncancer and Cancer risk assessment. Table 5-11 summarizes how many PHPhAE members and analogs had different degrees of level 3 human health risk data source abundance.

Human Health Risk Assessment data were available for one PHPhAE member and no analogs at Level 3 review. One PHPhAE member and no analogs had data in the 25 selected PDFs at Level 3B review. The subcategories used were Noncancer Risk and Cancer Risk. Staff noted the following observations:

- PHPhAE member 1,2-Bis(2,4,6-tribromophenoxy)ethane had one Noncancer Risk data source.
- No PHPhAE members had Cancer Risk data sources.
- None of the 19 analogs had risk assessment data sources.

Table 5-11. 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
	PHPhAE Chemicals (n = 11)
6–20	1
0	10

[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.

5.6. Literature Survey Results: Key References

Among the literature survey results are several references from authoritative sources. Only one reference, from the U.S. EPA, contained useful information specifically for 1,1'-[1,2-ethanediylbis(oxy)]bis[2,4,6-tribromo- (CAS RN: 37853-59-1). This chemical is among the PHPhAEs noted in the market use report as found in consumer products, as well as in the literature survey results generally. This report demonstrates the existence of data about this chemical, including hazard and potential exposures and may be a useful reference for CPSC staff evaluations of this PHPhAE.

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 PHPhAE subclass and its analogs, and the criteria described in Section 4.1, Criteria for Scoping Determination, CPSC staff concludes, at the time of writing, that the PHPhAE 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 PHPhAE subclass includes three data rich chemicals and that a majority of PHPhAE chemicals and some analogs have some data. The evidence maps show that half of the PHPhAE chemicals have data in the Animal Toxicity or Accepted Alternative category, including among acute, systemic or repeated dose toxicity, or reproductive toxicity/developmental toxicity studies. In addition, a majority of PHPhAE chemicals and some analogs have data in the experimental, mechanistic, and QSAR categories, all of which may be used to support further analyses, including performing read-across analyses for predictions among class members with less available data.

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

CPSC staff concludes that the subclass includes up to four data rich chemicals and that a majority of chemicals have some data. In addition, according to available data sources, 10 of the 11 chemicals have market information for use in commerce.

Following the determination that the PHPhAE 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 PHPhAE 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 PHPhAEs, data rich PHPhAE analogs, PHPhAEs with some toxicity information, and PHPhAEs 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][32]) from the comprehensive literature search.
3. CPSC staff will refine the NAS analog list and characterize analog substances for the PHPhAE 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 PHPhAE 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 seven analogs.
4. CPSC staff will estimate major metabolites of PHPhAE 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 PHPhAE class members and analogs with available toxicity data can be used to read-across to PHPhAE 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 PHPhAE class are acute toxicity, mutagenicity/genotoxicity, and reproductive toxicity/developmental toxicity.

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

6. CPSC staff will identify a smaller number of endpoint(s) and studies that are candidates for identifying points of departure (POD) and generating toxicity reference values for multiple PHPhAE 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 PHPhAE class members.
8. CPSC staff will explore the variability and uncertainty associated with dose response values for PHPhAE chemicals within the class.
9. CPSC staff will use information developed in a class-based hazard assessment and dose-response assessment to support a class-based risk assessment for PHPhAEs.

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

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.

The oral LD50 for BTBPE is >10,000 mg/kg (EFSA, 2012) (Dong et al., 2021). The low acute oral toxicity may be related to low bioavailability, with <1% of a gavage dose being available systemically (EFSA, 2012; ECHA, 2022). The repeat dose toxicity of BTBPE appears to be low with “no obvious effect” seen in rats exposed in the diet at 35 mg/kg-day for 14 days (EFSA, 2012). In addition, acute inhalation toxicity is also reported to be low (Dong et al., 2021). Further details were not available, nor were data on longer duration or higher exposure levels. The acute toxicity of 2,4-dibromophenyl glycidyl ether is also low, based on the “acute toxic class method” (ECHA, 2018).

Koschier et al. (2011) treated rats with 28 daily oral gavage doses of 2,4,6 tribromoanisole (TBA) at 0 001, 0.01, 100, or 1,000 mg/kg-day. The only adverse effect was hyaline droplets in the renal cortical tubular epithelium of the males. This effect is commonly associated with α_{2u} globulin nephropathy, an MOA considered not relevant to humans (US EPA, 1991), although the study authors did not rigorously demonstrate this MOA. Hepatocellular hypertrophy in both sexes was considered an adaptive effect. Histopathology of the liver, adrenal gland, pituitary, and pancreas were reported in a 106-day feeding study of BTBPE in rats, but the study was conducted prior to the development of test guidelines and pneumonia could have affected the results. ECHA (2022) concluded that limited reporting means that the reliability of this study cannot be fully assessed. Similarly, ECHA (2022) concluded that the reliability of a 21-day inhalation study with BTBPE could not be fully assessed.

It is unclear whether BTBPE or other class members are endocrine active. In vitro studies reported that BTBPE showed anti-estrogenic activity, significantly induced the expression of CYP1A4/5 genes and suppressed the expression of thyroid hormone deiodinase (DIO) (ECHA, 2022). In addition, a screening study with the BTBPE metabolite 2,4,6-tribromophenol (2,4,6-TBP) found thymus atrophy and adrenal hypertrophy, suggesting potential endocrine-disrupting properties (ECHA, 2022). ECHA (2022) also noted the structural similarity between BTBPE and polybrominated diphenyl ethers (PBDEs), which affect the thyroid and reproductive systems.

No reproductive or developmental toxicity studies conducted according to test guidelines were identified for any class members. ECHA (2022) reported that oral exposures to BTBPE in mink found no effect on reproductive performance or on the survival and growth of the offspring. In a study conducted prior to the development of test guidelines, BTBPE was administered by gavage at doses up to 10,000 mg/kg-day on gestation days (GD) 6, 12, or 15 through GD 20. The study authors concluded that there was no developmental or maternal toxicity, but ECHA (2022) stated that it is difficult to draw a clear conclusion due to limited information and guideline deviations. ECHA (2022) also noted that concern has been raised about potential effects on perinatal development and developmental neurotoxicity of the BTBPE metabolite 2,4,6-TBP based on in vitro studies; additional support is needed from in vivo studies.

Genotoxicity results for class members are mixed. TBA was not mutagenic in a bacterial reverse mutation assay (Koschier et al., 2011). BTBPE was negative for mutagenicity in *Saccharomyces cerevisiae* and in the *Salmonella* reverse mutation assay, both in the presence and absence of exogenous metabolic activation (ECHA, 2022). However, 2,4-dibromophenyl glycidyl ether was positive in the mammalian cell gene mutation assay and gave inconsistent results in the bacterial reverse mutation test, with and without S9; ambiguous results were also obtained in an in vitro micronucleus assay (ECHA, 2018). Empirical genotoxicity or carcinogenicity data were not located for TBP-DBPE, but this chemical is considered a suspected carcinogen under REACH, with genotoxicity and nongenotoxicity alerts listed in the OECD toolbox (Zuiderveen et al., 2020).

Overall, it appears that there may be insufficient data for a class-based assessment of PHPhAEs based solely on data on the PHPhAEs because of the lack of repeat dose studies of adequate quality and adequate duration. However, it may be appropriate to combine some members of this class with other classes to ensure sufficiency for a class-based assessment. BTBPE is metabolized into 2,4,6-TBP (a member of the polyhalogenated phenol derivative class), which is in turn predicted to be metabolized to TBA, a member of this PHPhAE class (ECHA, 2016). In addition, at least some members of this class are structurally related to PBDEs. Grouping some or all of the PHPhAEs with members of other classes may ensure sufficient data for a class-based risk assessment.

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:

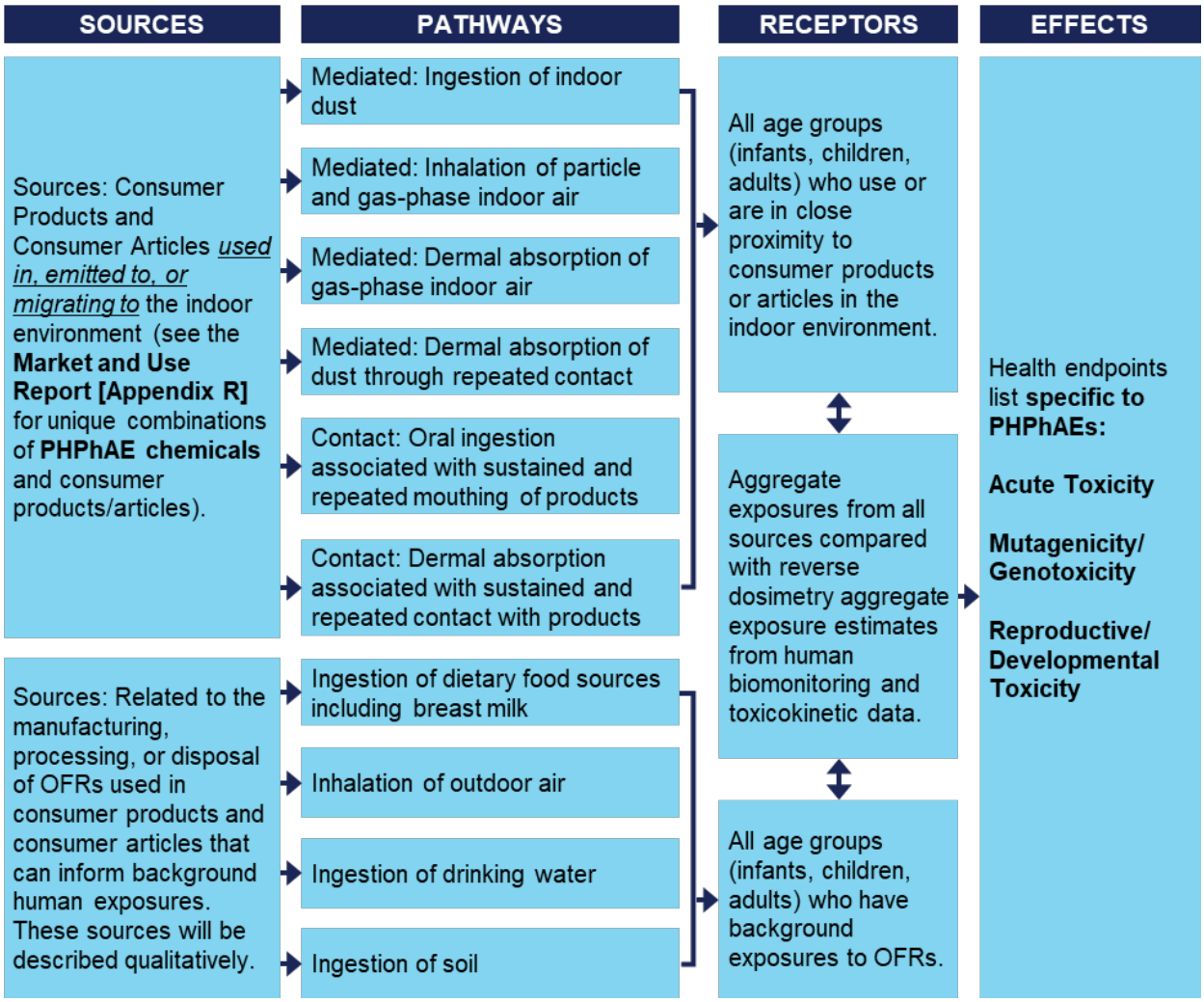
1. CPSC staff, in coordination with DTT staff, is working on a comprehensive literature search. Available exposure information from PHPhAE class members will be further summarized and integrated after this search is complete. After the search, staff will refine the list of data rich PHPhAEs, PHPhAEs with some exposure and use information, and PHPhAEs with no exposure and use information.
2. Using the market and use research, CPSC staff expects to compile a list of PHPhAE chemicals that have been or could be used in consumer products. While 10 of the 11 chemicals had some market-use information, four PHPhAE chemicals had more market and use information that could be used to inform analyses for PHPhAE chemicals with less information. CPSC staff will characterize uses for PHPhAEs 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 four and 10 PHPhAE subclass members.
4. Exposure pathways with likely higher potential for PHPhAE class members include contact and mediated exposures with consumer products, ingestion of drinking water and food. Exposure pathways with likely lower potential for PHPhAE class members include inhalation of indoor and ambient air and ingestion of soil. CPSC staff will review available environmental monitoring data to determine a range of potential concentrations to which people could be exposed. There are eight chemicals in the class with source characterization data, five chemicals in the class with environmental monitoring data, and five 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 PHPhAE 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 three chemicals in the class with source characterization data and no corresponding environmental monitoring data.

7. CPSC staff will explore the connection between reported or estimated environmental concentrations and reported exposures from human biomonitoring data. First, doses will be estimated using reported or estimated environmental concentrations and population specific exposure factors and activity patterns. Second, doses will be estimated using reported human biomonitoring data and reported or estimated toxicokinetic data. There are three PHPhAE 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 PHPhAEs.

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 PHPhAE 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 PHPhAEs are listed.

Figure 6-1. PHPhAE 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

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

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

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Market and Use Profile Supporting Files

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

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