Protocol for the Cancer Hazard Evaluation of Organohalogen Flame Retardants: Human Cancer and Experimental Animal Cancer Studies

Report on Carcinogens Monograph

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Introduction

Organohalogen flame retardants (OFRs) are a diverse group of halogen-containing chemicals added to commercial and industrial products, including furniture, mattresses, carpets, electronic devices, building and construction materials, and transportation products. These chemicals are categorized primarily by their functional use (i.e., fire retardation).

OFRs are frequently detected in U.S. biomonitoring studies due to their persistence in the environment and long half-lives in humans. Continuous exposure, primarily via ingestion of household dust and in the diet from treated consumer products is a concern for the entire U.S. population. Additionally, occupations in manufacturing, construction, and service industries (e.g., carpet installers, electronic scrap workers, gymnasium workers, chemical and foam manufacturers), and fire fighters may be at a higher risk of exposure to multiple OFRs (Estill et al. 2020). OFRs are prevalent in numerous consumer products. Determined to be health hazards in humans, some legacy OFRs have decreased because of restrictions and voluntary phase outs. Despite these efforts and an expanded list of replacement chemicals, continued exposure to contaminated products and biological persistence have raised new concerns for these chemicals.

The evaluation of OFRs is an important public health concern because of widespread exposure and concerns for carcinogenicity. For this reason, the National Institute of Environmental Health Sciences (NIEHS) is conducting cancer hazard evaluations of multiple OFRs for potential listing in the Report on Carcinogens (RoC), a congressionally mandated, science-based public health document. As part of the evaluation, NIEHS may choose to hone our assessment on one or a few brominated and/or chlorinated flame retardants, or an assessment may be expanded to other flame retardants if data are available to evaluate as a subclass.

Federal and state agencies have nominated multiple OFRs for cancer hazard evaluations. Currently, there are multiple OFRs identified as carcinogens (Table 1). Five OFRs have already been listed in the RoC as *reasonably anticipated to be human carcinogens*. Aside from the RoC, the International Agency for Research on Cancer (IARC) has listed multiple OFRs as *probably carcinogenic to humans* (Group 2A) or *possibly carcinogenic to humans* (Group 2B). Given the breadth of OFR compounds and subclasses, an approach adapted from the National Academies of Sciences (NAS) (2019) OFR scoping plan will be used to identify candidates for cancer hazard evaluations.

Table 1. Current OFR listings in Report on Carcinogens (RoC) and International Agency for Research on Cancer (IARC)

Subclass	RoC Listing	IARC Classification
Polyhalogenated bisphenol aliphatics and functionalized (PBAFs)	None	Tetrabromobisphenol A (TBBPA); Group 2A, probable human carcinogen (2018)[j]
Polyhalogenated diphenyl ethers (PHDEs)	None	Polybrominated diphenyl ethers (PBDEs); Group 3, not classifiable (2014)[i]

Subclass	RoC Listing	IARC Classification
Polyhalogenated organophosphates (PHOPs)	TDBPP (tris(2,3-dibromopropyl) phosphate)[k]; Reasonably anticipated to be a human carcinogen	TDBPP; Group 2A, probable human carcinogen (1979[b], 1987[c], 1999[g])*
		Tris (2-chloroethyl) phosphate (TCEP); Group 3, not classifiable (1990[e]; 1999[f])
Polyhalogenated carbocycles	Mirex[l]; Reasonably anticipated to be a human carcinogen	Mirex; Group 2B, possible human carcinogen (1979)[a]
	Chlorendic acid[m]; Reasonably anticipated to be a human carcinogen	Chlorendic acid; Group 2B, possible human carcinogen (1990)[d]
Polyhalogenated aliphatic chains	2,3-dibromo-1-propanol*,[n]; Reasonably anticipated to be a human carcinogen	2,3-dibromo-1-propanol*; Group 2B, possible human carcinogen (1999)[g]
	2,2-bis(bromomethyl)propane-1,3-diol[o]; Reasonably anticipated to be a human carcinogen	2,2-bis(bromomethyl)propane-1,3-diol; Group 2B, possible human carcinogen (2000[h])

*Note: 2,3-dibromo-1-propanol is both a metabolite of TDBPP and used as an intermediate to manufacture TDBPP
Sources: , IARC (1979a)[a], IARC (1979b)[b], IARC (1987)[c], IARC (1990a)[d], IARC (1990b)[e], IARC (1999c)[f], IARC (1999d)[g], IARC (2000)[h], IARC (2014)[i], IARC (2018b)[j], NTP (2021f)[k], NTP (2021e)[l], NTP (2021d)[m], NTP (2021c)[n], NTP (2021b)[o]

Identification of OFRs for Cancer Hazard Evaluations

Hundreds of OFR chemicals exist (Bevington et al. 2022). Though broadly categorized by their function (fire retardation), until recently, there has been inconsistent subcategorization of OFRs.

In 2019, a NAS committee, tasked by the US Consumer Product Safety Commission (CPSC), produced a scoping plan to determine if a class-based approach can be used to evaluate OFR compounds (NAS 2019). The NAS committee identified 168 chemicals classified as OFRs (Figure B-2 from NAS 2019; see Appendix A). To categorize these chemicals into subclasses, the NAS committee used chemical structure, physical and chemical properties, and predicted biological activity to group OFRs into 14 subclasses (see Table A-1 in Appendix A).

NIEHS approach

To identify OFR chemicals to pursue for full cancer hazard evaluations, we took a chemical and subclass agnostic approach through a first pass scoping of all 168 compounds to identify data-rich chemicals. NIEHS tailored the general NAS strategy for a class-based approach to hazard assessment of OFRs (Figure 2-1, NAS 2019, see Appendix A), which recommends identifying if sufficient toxicity data is available on any OFR compound within a subclass. Below, we outline our approach to identifying subclasses for cancer hazard evaluations.

Preliminary scoping approach: Subclass identification

Taking all 168 OFR compounds, we conducted a preliminary scoping of the frequency of human epidemiology, experimental animal, and mechanistic studies related to cancer in 2021 using the Chemical Risk Assessment and Biomedical Text Mining (CRAB) tool (http://www.lionproject.net/; Silins et al. 2012). This text mining tool conducts PubMed literatures searches for human, animal, cellular and other mechanistic data pertaining to chemical

cancer risk assessments and classifies them by evidence type for a broad snapshot of the literature. This tool was meant to be a broad, first-pass scoping tool to understand relative publication frequencies and trends within the overall body of literature; as such, a more robust literature search was conducted for chosen subclasses.

Using the CRAB text-mining tool, we produced a preliminary evidence map of all 168 OFRs to examine the frequency counts for human, animal, and mechanistic studies. This gave us a rough understanding of the literature without a full literature search on all 168 OFRs.

Subsequently, given the National Toxicology Program (NTP) has conducted cancer bioassay studies in experimental animal studies, we then searched NTP's Chemical Effects in Biological Systems (CEBS) database (https://cebs.niehs.nih.gov/cebs/) to identify if any of the 168 OFR chemicals had available two-year experimental animal studies.

Results from preliminary scoping approach

Based on the availability of human and/or experimental animal cancer data for at least one representative subclass OFR chemical not listed in the RoC, we identified the following NAS-defined OFR subclasses:

1. Polyhalogenated bisphenol aliphatics and functionalized (PBAFs) (11 compounds)
2. Polyhalogenated diphenyl ethers (PHDEs) (12 compounds)
3. Polyhalogenated organophosphates (PHOPs) (22 compounds)

These three subclasses were identified as the most likely candidates based on availability of data relevant to a cancer hazard evaluation for possible RoC listing.

Subsequent scoping on chemicals within each subclass

Based on our identification of the three subclasses, we then conducted a robust literature search on each chemical within the three chemical subclasses. Using defined search terms, we systematically searched for human cancer, experimental animal, and mechanistic studies in three literature databases. Further evidence mapping and scoping activities are described below in Section 1 (human cancer studies) and Section 2 (animal cancer studies). Scoping for mechanistic data will be described in a future protocol.

Description of OFR subclasses

Polyhalogenated bisphenol aliphatics and functionalized (PBAFs)

PBAFs subclass is best represented by tetrabromobisphenol A (TBBPA), a widely used brominated bisphenol A flame retardant, and, to a lesser extent, tetrachlorobisphenol A (TCBPA). Other members of this subclass are analogues of TBBPA. NTP has conducted animal cancer bioassay studies on TBBPA in 2014 (NTP 2014), and IARC has listed TBBPA as a Group 2A carcinogen (IARC 2018a).

Polyhalogenated diphenyl ethers (PHDEs)

PHDE subclass is a group of halogen-containing FR chemicals extensively used in consumer products, best represented by polybrominated diphenyl ethers (PBDEs). Depending on the structure and bromine atoms, this group of brominated hydrocarbons can contain up to 209

possible congeners, though are more frequently categorized by their homolog, or the number of bromine atoms from 2-10 bromines (i.e., diBDE, triBDE, tetraBDE, pentaBDE, hexaBDE, heptaBDE, octaBDE, nonaBDE, decaBDE).

PBDEs have been commercially available as mixtures of congeners. Common commercial mixtures include pentaBDE (primarily BDE-47, BDE-99, BDE-100), octaBDE (primarily BDE-183), and decaBDE (primarily BDE-209). NTP has conducted animal cancer bioassay studies of both decabromodiphenyl ether (BDE-209) and a commercial pentaBDE mixture, DE-71 (NTP 1986; 2016). PentaBDE, octaBDE, and decaBDE have all been added to the Stockholm Convention and largely phased out of production. Despite phase outs, detection of these chemicals is still ubiquitous. IARC has classified PBDEs as a Group 3 carcinogen due to lack of available evidence. EPA has listed decaBDE as "suggestive evidence of carcinogenic potential"; other homologs were not classified based on lack of available evidence.

Polyhalogenated organophosphates (PHOPs)

PHOP subclass encompasses an emerging group of halogen-containing organophosphate FRs, often used as replacement FR for previously phased out compounds. This subclass differs from the FR subclass of nonhalogenated organophosphate esters (though both compounds may share similar metabolites). The most researched compounds in this class include tris(2-chloroethyl) phosphate (TCEP), tris(2-chloropropyl) phosphate (TCPP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP), and tris(2,3-dibromopropyl) phosphate (TDBPP; tris-BP). NTP has conducted animal cancer bioassay studies on TDBPP (NCI 1978), TCEP (NTP 1991), and TCPP (NTP 2023).

TDBPP is already listed as *reasonably anticipated to be a human carcinogen* by RoC, and a probable human carcinogen (Group 2A) by IARC. Additionally, 2,3-dibromo-1-propanol, both a metabolite of TDBPP and used as an intermediate to manufacture TDBPP, is listed in the RoC (reasonably anticipated to be a human carcinogen; 2002) and IARC (Group 2B, possible human carcinogen; 1999) (IARC 1999a; NTP 2021a). We note that despite the relationship to TDBPP, 2,3-dibromo-1-propanol is listed by NAS in a separate subclass (polyhalogenated aliphatic chains) that we are not pursuing.

Protocol components

This protocol discusses the methods that will be used to prepare the cancer evaluation component of the draft monograph on OFRs.

- Section 1: Methods for Evaluating Human Cancer Studies
- Section 2: Methods for Evaluating Cancer Studies in Experimental Animals
- Section 3: Methods for Evaluating Mechanistic and Other Relevant Data (Forthcoming)
- Section 4: Methods for Data Integration (Forthcoming)

Appendix A provides the NAS strategy for a class-based approach to hazard assessment of OFRs and the list of 168 OFR chemicals by organized by subclass. Appendix B provides the literature search strings that are specific for OFRs, as well as the evaluation team members.

1. Evaluating Human Cancer Studies of Exposure to Organohalogen Flame Retardants

1.1. Overall Objective

To reach conclusions about the level of evidence of the carcinogenicity to organohalogen flame retardants (OFRs) provided by human cancer studies based on the RoC listing criteria. These include chemicals from the three subgroups of OFRs: polyhalogenated bisphenol aliphatics and functionalized (PBAFs), polyhalogenated diphenyl ethers (PHDEs), and polyhalogenated organophosphates (PHOPs).

Key questions

- Is there a credible association between exposure to one or more OFRs and cancer in humans?
    - In retrospective study designs using biomarkers of OFR exposure, is there reasonable certainty that OFR exposure occurred prior to cancer diagnosis?
- For each chemical subclass, are there cancer sites with a substantial number of human cancer studies for a review (i.e., >4 studies)?

1.1.1. Protocol contents and evaluation process

This document describes the (1) completed scoping and problem formulation steps used to develop the framework (Section 1.2) and (2) a discussion of the utility of human cancer studies based on the timing of exposure. The scoping and problem formulation methods are based on applying the specific issues relevant to OFRs to the procedures outlined in forthcoming update of the RoC Handbook; given the RoC Handbook is in press, we detail key steps in this protocol. The literature search terms are described in Appendix B.

1.2. Developing the Framework

Preliminary scoping and problem formulation activities informed the evaluation framework for the entire cancer hazard evaluation for OFRs, which includes the evaluation of human cancer studies using the methods described in this protocol, as well as evaluation of animal cancer studies and mechanistic studies in humans, animals, and cells.

These activities informed the research questions and the body of evidence to answer the research questions. The body of evidence for human cancer studies is defined by the PECO (Population, Exposure, Comparison Group, Outcome) statements.

The initial PECO was used to search and select the literature for OFRs. Based on evidence mapping and a review of the literature database, this initial PECO was refined into a final PECO (Table 1-1).

Table 1-1. Initial and Final PECO for Human Studies

	Initial PECO	Final PECO
Population	All populations (no restrictions)	All populations (no restrictions)
Exposure	Individual OFR compounds and OFR mixtures	Individual selected OFR, metabolites of parent compound, or mixtures of multiple OFRs Biomarkers (serum, tissue) Dietary exposure
Comparison	No or lower exposure to OFRs	Lower exposure to OFRs (all studies had detectable concentrations in comparison group)
Outcome	Cancer (any type)	Incident breast cancer Incident thyroid cancer

1.2.1. Identifying and Selecting the Literature

Biomedical citation databases, namely PubMed, Scopus, and Web of Science, were searched for human cancer studies and exposure to OFRs by combining search terms for exposure to chemicals within the three OFR subclasses (see Appendix B) with standard RoC search terms for cancer and human studies using the procedures outlined in the RoC Handbook.

Search results were processed in Endnote and imported into a content management system [e.g., Health Assessment Workplace Collaborative (HAWC)] software to select relevant literature (Shapiro et al. 2018).

We identified a tiered process for screening studies to consider for evaluation. First, a single reviewer screened studies against the initial PECO by title and abstract (Level 1). Study uncertainty underwent full text and/or second reviewer screen. Subsequently, a full text review was conducted to screen studies in greater detail (Level 2). No non-English studies for human or animal cancer were found. Studies were initially included if they meet the following preliminary inclusion criteria:

- Primary studies (analytical epidemiologic studies) meeting the initial PECO statement (Table 1-1).
    - Clearly indicate exposure to OFRs. Exposure to OFRs may include (a) OFRs measured in environmental media (e.g., environmental, occupational, food sources); (b) measured biomarkers of OFR exposure in humans, represented as a metabolite of OFRs as a surrogate of OFR exposure in available studies.
    - Report an effect estimate (or information to calculate an effect estimate) for cancer.
    - OFRs are evaluated as individual compounds or compounds within a mixture of compounds within a subclass.
    - Studies evaluating OFRs as a complex mixture containing compounds outside a subclass will be excluded from analysis.

Upon meeting the initial PECO, a full text review of the studies was conducted to determine the relevance and utility of the studies and if our initial PECO needed further refinement. One questionnaire study did not separate exposure to OFRs and other persistent organic pollutant (POP) chemicals (McElroy et al. 2004), and therefore did not meet our initial PECO criteria.

Based on this additional review, our criteria and initial PECO were revised to a final PECO (Table 1-1).

1.2.2. Mapping the Evidence

Substances from all three OFR subclasses had human cancer studies from six cancer types (Table 1-2). Of the six cancer types, only thyroid and breast cancers have more than four studies available. Human cancer studies from one or more compounds within each OFR subclass were identified based on the initial PECO (Table 1-3).

Table 1-2. Cancer sites of human cancer studies for three OFR subclasses

	Thyroid	Breast	Prostate	ALL/AML	NHL	Pancreas	Testicular	Gastrointestinal
PHDEs	6	7	1	2	2	1	1	0
PHOPs	3	0	0	0	0	0	1	1
PBAFs	0	1	0	0	0	0	0	0

*ALL = Acute lymphoblastic leukemia; AML = acute myeloid leukemia; NHL = Non-Hodgkin lymphoma; PHDEs = polyhalogenated diphenyl ethers; PHOPs = polyhalogenated organophosphates; PBAFs = polyhalogenated bisphenol aliphatics and functionalized.

Table 1-3. Overall study characteristics from thyroid and breast cancer studies for OPFR subclasses

Cancer type	Subclass	No. of studies	Compound(s) (or metabolite(s)) studied	Study design(s)	Location(s)	Study setting(s)	Exposure assessment type(s)
Thyroid	PHDEs	6	BDE-28 BDE-47 BDE-85 BDE-99 BDE-100 BDE-153 BDE-154 BDE-183 BDE-209 ΣPBDEs	Case-control Nested case-control	China USA	Hospital-based Population-based Occupation-based	Serum
	PHOPs	3	TCEP TCIPP or metabolites (BCIPP and BCIPHIPP) TDCIPP or metabolite (BDCIPP)	Case-control	China USA	Hospital-based Population-based	Serum

Cancer type	Subclass	No. of studies	Compound(s) (or metabolite(s)) studied	Study design(s)	Location(s)	Study setting(s)	Exposure assessment type(s)
Breast	PHDEs	7 (two from same cohort)	BDE-17 BDE-28 BDE-47 BDE-66 BDE-85 BDE-99 BDE-100 BDE-138 BDE-153 BDE-154 BDE-183 BDE-190 BDE-209 ΣPBDEs	Case-control Nested case-control	China France USA	Hospital-based Population-based Occupation-based	Serum Adipose tissue Questionnaire Dietary modeling
	PBAFs	1	TBBPA	Case-control	China	Hospital-based	Adipose tissue

*PHDEs = polyhalogenated diphenyl ethers; PHOPs = polyhalogenated organophosphates; PBAFs = polyhalogenated bisphenol aliphatics and functionalized; BDE = brominated diphenyl ether; TCEP = tris(2-chloroethyl)phosphate; TCIPP = tris(1-chloro-2-propyl) phosphate; BCIPP = bis(1-chloro-2-propyl) phosphate; BCIPHIPP = bis(1-chloro-2-propyl) 1- hydroxy-2-propyl phosphate; TDCIPP = tris(1,3-dichloro-2-propyl)phosphate; BDCIPP = bis(1,3-dichloro-2-propyl)phosphate; TBBPA = tetrabromobisphenol a

1.3. Informativeness of studies

Upon investigation of the 17 human cancer studies of breast and thyroid cancer, only two studies, both from the same cohort (Frenoy et al. 2022; Mancini et al. 2020), measured OFR concentrations prior to cancer diagnosis. The other 15 studies measured OFR concentrations following cancer diagnosis. Although our database of studies meets our final PECO, additional information can be obtained by applying an in-depth examination of the informativeness of these studies for reaching conclusions.

In an effort to provide additional insight and examination of the ability of these studies to inform conclusions, we have opted to modify our normal approach to a fit-for-purpose strategy by identifying key influential questions that are critical to determining study informativeness, as discussed by Savitz et al. (2019). This method is similar to our approach suggested in the Mechanistic Studies section of our forthcoming RoC Handbook (NTP 2025). By identifying the most influential questions for informing the quality of these studies, we are streamlining our study evaluations to address these key criteria vital to assessing study informativeness. Understandably, this is a deviation from our normal process as outlined in our RoC Handbook, and the additional information gained will support transparency and efficiency in the process. Should it be determined, however, that a full study informativeness evaluation be completed for all bias and sensitivity domains, as usually completed in a cancer hazard evaluation, we will modify our protocol and expand our approach. These key influential questions are below:

Key Influential Questions:

- Can temporality be reasonably assumed to assess the causal association between OFR exposure and outcome?
  - For studies measuring OFR exposure post-diagnosis, is there concern that presence of the outcome may potentially bias the exposure assessment (e.g., reverse causality)?
  - Are OFR biomarker studies adequately capturing pre-diagnosis exposure?
- Were there an adequate number of exposed cases in studies to detect an effect, if present?
- Can we reasonably rule out the potential for (or impact of) confounding by other co-exposures?

Based on the responses to the above key influential questions, a modified study informativeness evaluation will be completed. In addition to our determination of the potential for bias, an assessment of the impact of each bias (i.e., understanding the magnitude and direction of bias) will be conducted.

1.3.1. Overall Assessment of Study Informativeness

The overall informativeness of a study considers both bias (i.e., systematic flaws or limitations that may compromise interpretation of the results) and study sensitivity. Studies having elements with major concerns may still be considered in a cancer hazard assessment, but the findings should be interpreted with caution. It should also be noted that some concerns about a study element (such as inadequate observation and/or exposure period or statistical power) would decrease the study's sensitivity to detect an effect. If positive findings were described despite these limitations, these studies would inform a cancer hazard assessment. Studies with critical concerns about important issues (see "Inadequate" judgement below) generally are inadequate to inform the evaluation.

If a study's information is inadequate for a reviewer to answer a specific question, the impact on overall study quality evaluation depends on the extent and importance of the missing information and is evaluated on a case-by-case basis.

Study informativeness-level judgment

- **High**: no or minimal concerns about most potential biases; high or moderate study sensitivity. This includes high confidence that OFR exposure preceded outcome, low concern for confounding bias to impact study results, and enough exposed cases to detect an effect.
- **Moderate**: low, minimal, or some concerns about most potential biases. This includes some confidence that OFR exposure preceded outcome, and/or some concern for confounding bias to impact study results.
- **Low**: major concerns about several biases; study sensitivity rating varies. This includes low confidence that OFR exposure preceded outcome, some/major concern for confounding bias, and/or a small number of exposed cases to detect an effect. Depending on the direction and distortion of the potential biases, the study may still be informative for cancer hazard evaluation but should be viewed with caution.

- **Inadequate**: critical concerns about any bias; sensitivity rating varies. This includes an inability to determine if OFR exposure preceded the outcome leading to reverse causation or post-diagnosis OFR exposure, critical concerns for confounding, and/or an inadequate number of exposed cases to detect an effect.

1.3.2. Evidence Evaluation and Integration

Following the assessment of study informativeness, evidence from individual studies will be evaluated and integrated across studies to reach a level-of-evidence conclusion (sufficient, limited, or inadequate) about the carcinogenicity of the substance from studies in humans by applying the RoC criteria to the assessment. If a majority of studies are determined to have inadequate informativeness due to critical concerns of bias, we will qualitatively summarize each study. If the database is adequate for sensitivity analyses, we may explore heterogeneity by grouping studies by subclass (i.e., PHOPs, PHDEs), study setting (e.g., hospital-based, occupational-based, population-based case-control studies), and/or exposure assessment type (e.g., serum, adipose tissue biomarkers). In addition, we may also consider grouping studies by study informativeness, bias domains, or other key factors, as appropriate.

The assessment is made for each cancer outcome, and the overall conclusion is based on the highest level of evidence (i.e., if the level of evidence for one cancer type is sufficient, the overall level of evidence is considered sufficient; levels of evidence for the other cancer types are noted). The cancer hazard evaluation builds upon the assessment of study informativeness and assesses confidence in the findings from individual studies, which includes evaluating the impact of bias on the studies' findings (considering the magnitude and direction of the bias and the strength of the findings). The bias judgments (overall study judgment, domain judgment, and specific biases), effect modifiers, exposure metric, and other scientific issues are systematically explored across studies to evaluate consistency and potential sources of heterogeneity. Finally, triangulation approaches and consideration of other causality factors (e.g., Bradford-Hill considerations, causal inference) also guide the assessment, giving weight to the most informative studies and considering all the evidence.

2. Evaluating Animal Cancer Studies of Exposure to Organohalogen Flame Retardants

2.1. Overall Objective and Aims

2.1.1. Overall Objective

To reach conclusions about the level of evidence of the carcinogenicity to organohalogen flame retardants (OFRs) provided by animal cancer studies based on the RoC listing criteria. These include chemicals from three subgroups of OFRs: polyhalogenated bisphenol aliphatics and functionalized (PBAFs), polyhalogenated diphenyl ethers (PHDEs), and polyhalogenated organophosphates (PHOPs).

Primary question

- What is the level of evidence (i.e., sufficient or not sufficient) for the carcinogenicity of one or more OFRs from carcinogenicity studies in experimental animals?

Secondary questions

- Which animal cancer studies should be included in the review?
- What are key issues for evaluation of the studies?
- What are the most sensitive animal models?
    - Are any sites connected with modes of action generally recognized as not relevant to humans?
- How informative (e.g., bias analysis, study sensitivity) are the studies for the evaluation?
- What tumor sites are related to exposure for each OFR?
    - Are there common tumor sites related to a chemical subclass?

We note that for NTP technical report two-year cancer bioassays, we will be applying RoC criteria to NTP technical report conclusions. For consistency, we will still undergo a study quality evaluation of NTP studies given there are also non-NTP studies.

2.1.2. Protocol contents and evaluation process

This document describes the (1) completed scoping and problem formulation steps used to develop the framework and (2) proposed methods used to conduct the cancer hazard evaluation, including key considerations for animal studies, study evaluation parameters, and evidence integration of animal studies. The methods are based on applying the specific issues relevant to OFRs to the procedures outlined in the updated RoC Handbook, which has been moderately revised from the 2015 Handbook (NTP 2025). The literature search terms are described in Appendix B.

2.2. Developing the Framework

Preliminary scoping and problem formulation activities informed the evaluation framework for the entire animal cancer hazard evaluation for OFRs. The body of evidence to evaluate the level

of evidence of carcinogenicity from animal cancer studies is defined by the MECO (**M**odel, **E**xposure, **C**omparison Group, **O**utcome) statements.

2.2.1. Identifying and Selecting the Literature

Biomedical citation databases, namely PubMed, Scopus, and Web of Science, were searched for animal cancer studies and exposure to OFRs by combining search terms for exposure to chemicals within the three OFR subclasses (see Appendix A), cancer (see RoC Handbook), and animal studies (see RoC Handbook) using the procedures outlined in the RoC Handbook.

For comprehensiveness, we also conducted a manual search from authoritative sources for possible relevant studies and citations. Sources include:

- National Toxicology Program website.
- Health Canada's Updated Draft Screening Assessment - Certain Organic Flame Retardants Substance Grouping - 2-Propanol, 1-chloro-, phosphate (3:1) (TCPP) and 2-Propanol, 1,3-dichloro-, phosphate (3:1) (TDCPP) (Health Canada 2020)
- US EPA's Provisional Peer-Reviewed Toxicity Values for Tris(2-chloroethyl) phosphate (CASRN 115-96-8) (EPA 2009)
- IARC's Volume 71 Re-Evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide (IARC 1999a)
- National Research Council's Toxicological Risks of Selected Flame-Retardant Chemicals (NRC 2000).
- Chlorinated Phosphate Esters cluster – Docket ID Number EPA–HQ–OPPT-2015-0068
- Tetrabromobisphenol A cluster - Docket ID Number EPA–HQ–OPPT–2014-0730
- Cyclic Aliphatic Bromides cluster – Docket ID Number EPA–HQ–OPPT-2015-0081
- Brominated Phthalates cluster - Docket ID Number EPA–HQ–OPPT–2014-0491
- Toxicological Profile for Phosphate Ester Flame Retardants (ATDSR 2012)
- EU Risk Assessment Report: Tris (2-Chloroethyl) Phosphate, (TCEP) CAS No: 115-96-8 (EU 2009)
- EU Risk Assessment Report: Tris(2-Chloro-1-Methylethyl) Phosphate (TCPP) CAS No: 13674-84-5 (EU 2008a)
- EU Risk Assessment Report: Tris[2-Chloro-1-(Chloromethyl)Ethyl] Phosphate (TDCP) CAS No: 13674-87-8 (EU 2008b)

If a relevant study was manually identified, the reviewer then determined if the study met our final PECO. Search results were processed in Endnote and imported into a content management system [e.g., Health Assessment Workplace Collaborative (HAWC)] software to select relevant literature (Shapiro et al. 2018).

Studies included in an initial MECO measure neoplastic (benign, malignant) endpoints. We also consider the following as supporting studies, not included in the MECO:

- have non-cancer data that is informative for a cancer assessment, such as reporting preneoplastic lesions,

- describe non-neoplastic lesions that are considered part of a morphologic continuum to neoplasia,
- compounds previously listed in the RoC (i.e., TDBPP),
- studies dosing metabolites of the parent compound (e.g. Eustis et al. 1995; NTP 1991, TDBPP) as the primary exposure.

2.2.2. Mapping the Evidence

Seven OFRs or OFR mixtures had animal cancer studies (Table 2-1). Animal cancer studies from one or more compounds within each OFR subclass were identified based on the initial MECO (Table 2-2).

Table 2-1.Characteristics of experimental animal studies (cancer bioassay studies)

OFR Subclass	Compound/Metabolite	# Of Studies*	Route	Species (Strain)
PBAFs	Tetrabromobisphenol A	2	Gavage (2)	Mouse ($B6C3F_1$) Rat (Wistar Han)
PHDEs	Pentabromodiphenyl ether mixture (DE-71; technical grade)	2	Gavage (2)	Mouse ($B6C3F_1$) Rat (Wistar Han)
	Decabromodiphenyl oxide (BDE-209)	4	Feed (3), Gavage (1)	Mouse (2) ($B6C3F_1$, C57BL/6) Rat (2) (F344/N, Sprague Dawley)
PHOPs	Tris(2,3-dibromopropyl) phosphate	2	Feed (2)	Mouse ($B6C3F_1$) Rat (F344/N)
	Tris(2-chloroethyl) phosphate	3	Feed (1), Gavage (2)	Mouse (2) (Slc:ddY, $B6C3F_1$) Rat (F344/N)
	Tris(1,3-dichloro-2-propyl) phosphate	1	Feed (1)	Rat (Sprague Dawley)
	Tris(cholorpropyl) phosphate	2	Feed (2)	Mouse (B6C3F1/N) Rat (Sprague Dawley)

*Note: Some studies (e.g., NTP Technical Reports) may include multiple species. For the purposes of this assessment, the number of studies is defined as species-specific cancer bioassay studies (i.e., rats and mice counted separately), and not by publication.
*PHDEs = polyhalogenated diphenyl ethers; PHOPs = polyhalogenated organophosphates; PBAFs = polyhalogenated bisphenol aliphatics and functionalized

Characteristics of available animal studies include:

- Two species-specific studies in the PBAFs subclass, four in the PHDEs subclass, and eight in the PHOPs subclass had cancer bioassay study designs in sexually mature rats or mice.
- Routes of administration included gavage and feed.

- One study (NTP 2016) used a commercial mixture of multiple PBDE congeners within a subclass (DE-71).

Table 2-2. Initial and Final MECO (no changes made)

	Initial MECO	Final MECO
Models	All animal cancer models and species	Complete carcinogenicity models and species
Exposure	Individual selected OFR, or mixtures of multiple OFRs	Individual selected OFR, or mixtures of multiple OFRs
Comparison	No exposure to OFRs, but comparable study design with exposure to vehicle only	No exposure to OFRs, but comparable study design with exposure to vehicle only
Outcome	Tumors	Tumors

2.3. Study evaluation of individual animal cancer studies

Each primary study is systematically evaluated for its ability to inform the cancer hazard evaluation using five domains related to an analysis of various biases –study design, exposure conditions, outcome assessment, potential confounding, and analysis – and one additional sixth domain related to study sensitivity (or the ability of the study to detect a true effect) (Cooper et al. 2016) and includes study issues related to study design and exposure conditions. Specific signaling questions, along with guidance and response options for answering these questions are summarized in Tables 2-3 to 2-7. These tables highlight concerns scientists usually consider when evaluating study informativeness in animal cancer studies and are used to increase transparency but are not meant to be a checklist. The potential for a given bias in a study does not necessarily or automatically mean that the findings of the study should be disregarded. When adequate information is available, the magnitude of the bias and the direction of the bias (away or towards the null, or false positives or negatives) should be considered (referred to as the impact of bias).

In answering each question on whether there is a potential bias or limitation, reviewers provide their judgment by comparing the study elements with those of an *ideal* study for a specific end point. *Ideal* study elements have no to minimal concern for potential bias and are sensitive enough to detect an effect if present. In some cases, a rating may not be possible due to the complexity of the issues and will be captured by narrative text. Differences in reviewer judgments are resolved by discussion between the reviewers. A small subset of studies may be used in a "pilot" phase to discuss and resolve any ambiguity before proceeding with evaluation of the full set of studies. Study authors may be contacted by reviewers to obtain additional information needed for our evaluation. Reporting quality may also be noted (e.g., missing information).

Response to signaling questions

- **No or minimal concern**: The study design or methodologies are ideal or very close to the ideal study characteristics, and potential bias is unlikely or minor. These studies generally are considered informative for the cancer hazard evaluation.

- **Some concern**: The study design or methodologies indicate a possible low-to-moderate concern for bias. These studies generally are considered informative for the cancer hazard evaluation.
- **Moderate or major concern**: The study design or methodologies suggest a large potential for a specific type of bias. Depending on the direction and distortion of the potential bias, the study may still be informative for cancer hazard evaluation but should be viewed with caution.
- **Critical concern**: The distortion resulting from bias likely makes the study findings unreliable for hazard identification. This category is rare.
- **No information**: The information in the study is inadequate to evaluate the level of concern for the domain.
- **Direction of bias**:
  ↑ Away from the null, or overestimation of the effect.
  ↓ Towards the null, or underestimation of the effect.
  Not known (unable to determine).

Study Informativeness Evaluation Questions and Guidance

The study evaluation is used to assess the informativeness of the studies and in the interpretation of the study findings. Signaling questions and considerations for each of the different types of bias and for sensitivity are listed below.

2.3.1. Study design

The study design domain evaluates two questions on bias in the study and one question on the study's sensitivity (Table 2-3). Bias assessment includes questions on randomization and controls. Concurrent controls are the most relevant comparison group for evaluating potential exposure-related tumor effects. Evaluation of study sensitivity integrates study model, statistical power, and study duration.

Strain-specific considerations

Rat strains

Two-year studies in rats that met our initial MECO included inbred F344/N, outbred Wistar Han, and outbred Sprague Dawley [Hsd: Sprague Dawley SD] strains. For this database of OFR chemicals, no strain-specific concerns were identified for F344/N and Sprague Dawley rats based on initial scoping.

For Wistar Han rats, our scoping determined that most in this species are homologous for a mutant aryl hydrocarbon (AhR) receptor (Pohjanvirta et al. 1999), raising concern for the potential sensitivity of this rat strain to detect specific tumors. This mutation makes the Wistar Han resistant to the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and certain other ‘‘dioxin-like’’ chemicals, including resistance to dioxin-induced hepatocarcinogenesis. Two NTP studies, pentabromodiphenyl ether mixture (DE-71) (NTP 2016) and tetrabromobisphenol a (NTP 2014), used the Wistar Han strain in a two-year rat study. Given the unknown potential for both penta-BDE and TBBPA to operate via modulation of AhR receptor to induce tumor

formation, and potential for Tp53 mutations further consideration of the Wistar Han rat as an appropriate animal strain was given by NTP.

Given this potential concern, NTP conducted a separate DNA sequencing study on female Wistar Han [Crl:WI(Han)] rats (Merrick et al. 2016) to determine if the mutation of the AhR genotype was related to DE-71-induced liver tumor formation. NTP (2016) found that liver tumor formation was independent of AhR mutation; however, we will evaluate the results from this genotyping study as well as any additional information to better understand the potential tumor-specific sensitivities of this strain.

Mouse strains

For carcinogenicity studies in mice, hybrid B6C3F1, inbred Slc:ddY, and inbred C57BL/6 strains were used. The hybrid B6C3F1 strain is most commonly used by NTP and often an adequate strain to detect chemically-induced tumors. Of note, the inbred C57BL/6 strain of mice is known to be relatively resistant to many tumors via chemical induction, including liver tumor formation. The inbred Slc:ddy strain of mice are more susceptible to development of lymphomas and certain carcinomas (i.e., lung, mammary gland). As with the rat strains, we will evaluate the appropriateness of these mouse strains in the context of our study quality evaluation.

Table 2-3. Study design: questions and responses

Signaling questions	Guidance	Response options
	Bias Questions	
Randomization		
Is there concern that the methods by which animals were randomized to groups were inadequate?	Ideally, the randomization method was reported and was based on ensuring that all animals had an equal probability of being assigned to any given control or experimental group.	**No or minor concern** Animals were adequately randomized to control and experimental groups. **Some/major concern** Inadequate randomization to control and experimental groups. **Critical concern** There is evidence that animals were not randomized to control and experimental groups
Controls		**No or minor concern**
Is there concern that the concurrent control group was not adequate for evaluating effects across treatment groups? If no concurrent controls were used, were historical controls reported that could be used in place of concurrent controls?	Concurrent controls are considered to be the most relevant comparison group for evaluating potential exposure-related tumor effects. Ideally, the concurrent control group included at least as many animals as did each treatment group. However, in some cases, historical controls of the same animal strain/stock and from the same laboratory may serve in place of concurrent controls.	Controls were treated as similarly as possible to the exposed animals but without exposure to the test substance (e.g., appropriate vehicle controls were used). **Critical concern** No concurrent or relevant historical controls (that could be used in place of concurrent controls) were available.

Signaling questions	Guidance	Response options
	Sensitivity Question	
Is there concern that the study design (i.e., animal model, number of animals/dose group and control group, and study duration) was sensitive enough to adequately detect a neoplastic effect if present? This question considers these factors: • Animal model • Statistical power (number of animals/group) • Study duration	The sensitivity rating integrates the animal model, statistical power, and study design. To the extent possible, the study should use an animal model that is sensitive for detecting tumors (e.g., the background tumor rates for the tumor type are known, and the animal is sensitive to effects via the exposure route). Outcomes should be measured after an appropriate latency period, depending on tumor type. Adequate statistical power to detect an effect is based on sufficient numbers of animals in each treatment group surviving to the end of the study (e.g., minimum 50 animals allocated to each experimental group).	**No or minor concern** The study used an appropriate animal model with a sufficient number of animals and an appropriate study duration. **Major concern** The study used an inappropriate animal model, or too few animals per group, or an insufficient study duration.

2.3.2. Exposure conditions

The signaling questions in the exposure domain include one question that address the bias and one question on sensitivity (Table 2-4).

The bias question assesses the dose level, and the sensitivity question integrates information related to dose selection and exposure duration. Dose selection is considered as both a bias issue and a sensitivity issue. Aspects of exposure conditions that are specific to the candidate substance are defined in the protocol.

Table 2-4. Exposure: questions and responses

Signaling questions	Guidance	Response options
	Bias Questions	
Dose selection Is there concern that the dose level was too high (e.g., exceeded the maximum tolerated dose)?	Ideally, the authors should state their rationale for dose selection. This may include information from a prior dose finding study. The high dose should not cause excess toxicity (e.g., substantial decreases body weight), for the duration of the study.	**No or minor concern** Minimal treatment-related survival effects were seen (other than mortality related to tumors). **Major or critical concern** Severe toxicity was seen in all treatment groups. Toxicity was so high that survival was greatly reduced. (Reduced survival due to tumors is not a concern.)
	Sensitivity Questions	
Is there concern that the conditions of exposure to the test agent did not provide sufficient sensitivity to adequately detect a neoplastic effect, if present?	Selection of the dose may depend on the exposure duration. Ideally, exposure would last throughout or for a significant proportion of the animals' lifespan (i.e., 1 to 2 years for rodents). Doses should be high enough (i.e., achieving or approaching the maximum tolerable dose). Evaluation of dose response can contribute to confidence in the study findings and allow for evaluation of potential effects at lower doses. Ideally, studies should use multiple doses; however, for the purpose of hazard identification, multiple doses are not required if the dose selection provides sufficient sensitivity.	**No or minor concern** The study included an appropriately high dose (such as signs of mild toxicity) and an adequate observation period. **Major concern** There is evidence that the combined dose level (i.e., too low) and duration (i.e., short) were not adequate to detect an effect in the animal model.

2.3.3. Outcome Assessment and Measurement

The outcome domain consists of one signaling question (and related follow-up question) on the adequacy of the methods to assess tumor outcome in exposed and control animals (Table 2-5). This question addresses concerns about both bias and sensitivity. Evaluation of only a few organs for tumors, instead of all organs and tissues, can limit the study's sensitivity. Although blinding generally is considered important to reduce bias in the assessment of subjective outcomes (such as behavior), non-blinding may be preferred for cancer outcomes, to determine normal background histology. The NTP uses an informed approach to histopathological evaluation in its toxicity and carcinogenicity studies (Sills et al. 2019). This principle applies to non-NTP studies, provided that the necropsy and histology methods used were adequate and consistent.

Table 2-5. Outcome: questions and responses

Signaling questions Follow-up question	Guidance	Response options
Outcome Is there concern that the methods used to assess tumor outcome (necropsy, gross pathology, histology, or diagnosis) were not adequate to allow the effects to be attributed to the exposure? • Is there concern that not all treatment and control groups were assessed in the same way and in balanced blocks, to avoid bias?	Ideally, each study should include full gross necropsies of all tissues and histopathological examination of the majority of them. If a histopathological examination was conducted but is not reported, tumor type (and whether benign or malignant) should be reported. Ideally, the controls and all the treatment groups were treated the same. The control groups should be evaluated at necropsy to the same extent as the treatment groups.	**No or minor concern** Complete necropsies and gross pathology were reported for all tissues, and histopathological examination for most tissues. The control groups were treated the same as the treatment groups except for the presence of the test substance. The conduct of the evaluation by the pathologists was sound. **Major concern** Pathology was assessed on only some tissues. Histopathology was not assessed in tumors. The controls were treated differently from the treatment groups.

2.3.4. Potential for confounding

The confounding domain consists of two signaling questions and related follow-up question and addresses the quality of the chemical characterization and any other potential sources of confounding that could influence the study outcome other than the substance under evaluation (Table 2-6).

Table 2-6. Potential confounding: questions and responses

Signaling questions Follow-up questions	Guidance	Response options
Confounding Is there concern about potential confounding? • What is the relative impact of the confounding? **Chemical characterization** Is there concern that the characterization, dose formulations (e.g., homogeneity, purity, solubility, and stability), or delivery of the test agent (e.g., actual vs. desired dose) were not adequate to support attribution of any neoplastic effects to the substance under evaluation?	Sources of potential confounding in animal studies are the use of an impure chemical that contains other potential carcinogens, inadequate animal husbandry conditions, and lack of monitoring for pathogens. Food, water, and bedding should also be monitored for potential impurities. The purity of the test agent should be reported, and any contaminants listed. Animals should be homogenously exposed to the agent.	**No or minor concern** The study used a pure testing agent without contaminants and adequate animal husbandry conditions. The test agent is representative of the substance under evaluation. **Major or critical concern** Strong evidence of the presence of carcinogenic contaminants in the testing agent or poor animal husbandry conditions will substantially compromise interpretation of the findings, and there are no data to evaluate the extent of the confounding. The test agent is not representative of the substance under evaluation and/or contains carcinogenic contaminants at levels high enough to compromise the interpretation of the results.

2.3.5. Analysis

The analysis domain evaluates statistical methods and combining of tumor incidences and consists of two bias questions (Table 2-7). These questions address the methods for grouping the outcome (i.e., tumor types) and statistical methods to evaluate the findings. If statistical analysis was not performed, but tumor incidences were reported in enough detail, NIEHS can perform pairwise statistical calculations. Trend analysis across treatment groups (e.g., Cochran-Armitage trend test) can also be performed if there are three or more dose groups. It will be noted if statistical analyses were performed by NIEHS.

Table 2-7. Analysis: questions and responses

Signaling questions Follow-up questions	Guidance	Response options
Combined tumors Is there concern that different types of tumors were inappropriately combined in the analysis?	Analyses of benign and malignant tumors from the same tissue type should be reported both separately and combined. Tumors of the same cellular origin, which may appear at different organ sites (as seen with metastasis), should be combined.	**No or minor concern** Tumors of the same cellular origin are reported both individually and combined in the analysis. **Major concern** Tumor types of different cellular origins are combined, or tumors are specified only as benign or malignant for a particular organ, without reporting of their cellular origin.
Statistical analysis Is there concern that statistical analyses were inadequate or were not conducted to evaluate the results? • If statistical analyses were not conducted, were the results reported in sufficient detail to allow *ad hoc* analysis?	If statistical analyses were not reported, the study should at a minimum present incidence data for specific tumors, so that statistical tests (e.g., Fisher's exact test for pairwise comparisons) can be conducted. If there is evidence of a decreased survival effect, the studies should use adequate statistical methods, such as the poly-3 test (Bailer and Portier 1988), to control for decreased survival.	**No/minor concerns** The study reported appropriate methods of analysis using relevant data. Analyses were adjusted for survival (e.g., poly-3 test) where relevant. **Critical concerns** There is strong evidence that reporting of data and analytical methods were so limited that the findings are not interpretable.

2.3.6. Overall Assessment of Study Informativeness

The overall informativeness of a study considers both bias (i.e., systematic flaws or limitations that may compromise interpretation of the results) and study sensitivity (i.e., ability for study to detect a true effect). Studies having elements with major concerns may still be considered in a cancer hazard assessment, but the findings should be interpreted with caution. It should also be noted that some concerns about a study element (such as inadequate observation and/or exposure period or statistical power) would decrease the study's sensitivity to detect an effect. If positive findings were described despite these limitations, these studies would inform a cancer hazard assessment. Studies with critical concerns about important issues generally are inadequate to inform the evaluation.

If a study's information is inadequate for a reviewer to answer a specific question, the impact on overall study quality evaluation depends on the extent and importance of the missing information and is evaluated on a case-by-case basis.

Study informativeness-level judgment

- **High**: no or minimal concerns about most potential biases; high or moderate sensitivity.
- **Moderate**: low, minimal, or some concerns about most potential biases.
- **Low**: major concerns about several biases; sensitivity rating varies. Depending on the direction and distortion of the potential biases, the study may still be informative for cancer hazard evaluation but should be viewed with caution.
- **Inadequate**: critical concerns about any bias; sensitivity rating varies.

2.4. Evidence Interpretation and Integration

2.4.1. Interpretation of Evidence from Individual Studies

As noted above, for NTP technical report two-year cancer bioassays, we will be applying RoC criteria to NTP technical report conclusions. For consistency, we will still be undergoing a study quality evaluation of NTP studies given there are non-NTP studies.

The factors considered include statistical significance with respect to controls and dose-related trends, pre-neoplastic lesions, lesion progression, decreased latency, tumor multiplicity, tumor incidence, historical control range, animal survival, species, sex, strain, and rarity of tumor. For instance, an uncommon tumor type could be deemed treatment-related without a statistically significant increase in incidence. It is important to note that the shape of the dose-response curve may vary (i.e., may not always be monotonic), and various factors (e.g., metabolism and toxicokinetics of the substance or differences in animal survival among the treatment groups) can affect the shape of the curve (IARC 2019). In evaluating potential biases in an individual study, one should consider the magnitude of the effect, the adequacy of the controls, and whether a potential confounder could modify effects across exposure groups.

In addition, we will consider here the potential modifying effect of genetic mutations in specific animal strains (e.g., AhR mutation in Wistar Han rats).

External Validity

External validity addresses the extent to which conclusions from one study can be generalized to other situations (i.e., the relevance of experimental animal data to humans). We will assess the relevance each experimental animal cancer study for evaluating the potential for human carcinogenicity based on the following:

- Relevance of the route of exposure.
- Relevance of the species, sex, or animals' age.
- Relevance of the mechanism of tumor formation.

For this database of experimental animal studies, a few specific endpoints may require further investigation to determine relevance to humans. This includes:

- Chemical induction of renal tubule tumors in male rats via the accumulation of alpha 2u-globulin; and
- Activation of peroxisome proliferation-activated receptor (PPAR) leading to liver tumor formation in male rats.

We plan to assess supporting literature and additional guidance to determine the potential relevance of these animal tumors to humans. For example, IARC (1999b) provides criteria to determine whether kidney tumor formation is occurring via alpha 2u-globulin nephropathy as the sole mode of action.

2.4.2. Evidence Integration Across Animal Cancer Studies

The final steps in evaluating evidence from experimental animal cancer studies are integrating the evidence for treatment-related tumors across studies, applying the RoC listing criteria, and reaching a level-of-evidence conclusion from studies in experimental animals.

Because OFRs may potentially be defined as subclasses in addition to individual OFR conclusions, the application of the RoC listing criteria and preliminary level of evidence conclusions from studies in experimental animals for a subclass will not be discussed until the overall cancer hazard conclusions, which are completed after the evaluation of the mechanistic data.

RoC listing criteria for evaluating carcinogenicity from studies in experimental animals

Sufficient evidence of carcinogenicity from studies in experimental animals:
An increased incidence of malignant and/or a combination of malignant and benign tumors

- in multiple species, or
- at multiple tissue sites, or

- by multiple routes of exposure, or
- to an unusual degree with regard to incidence, site, or type of tumor or age at onset.

The first step in evidence integration is to evaluate the evidence across studies for each cancer site of interest. Here, we will rely on evidence-based tables to explore heterogeneity and organize evidence across studies. For most databases, heterogeneity in findings is often explained by differences in experimental conditions (e.g., species, sex, strain, doses, duration, route), and few studies have been conducted using exactly the same experimental conditions. As mentioned above, the most informative studies (highest quality and sensitivity) are given the most weight, and positive findings from these studies are considered to provide evidence of treatment-related tumor effects. Moderate- and low-quality studies can also be used in the assessment, especially when it is unlikely that biases (moderate) in the studies would cause false-positive results. Replication of findings across several studies also increases confidence in treatment-related effects.

In general, the RoC criteria for sufficient evidence of carcinogenicity from studies in experimental animals are fulfilled by (1) two studies (by different exposure routes or in different species) reporting positive findings of malignant or combined malignant and benign tumors or (2) one study reporting positive findings at multiple tissue sites. In addition, positive findings from one robust study can fulfill the criteria if the tumors are rare, have an early onset, or have a high incidence. The spectrum of neoplastic responses, from pre-neoplastic lesions and benign tumors to malignant neoplasms of a specific tumor type, is relevant for the evaluation of whether benign tumors observed at increased incidences are likely to progress to malignancy.

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Appendix A. NAS Approach to Identifying OFR Subclasses for Hazard Assessments

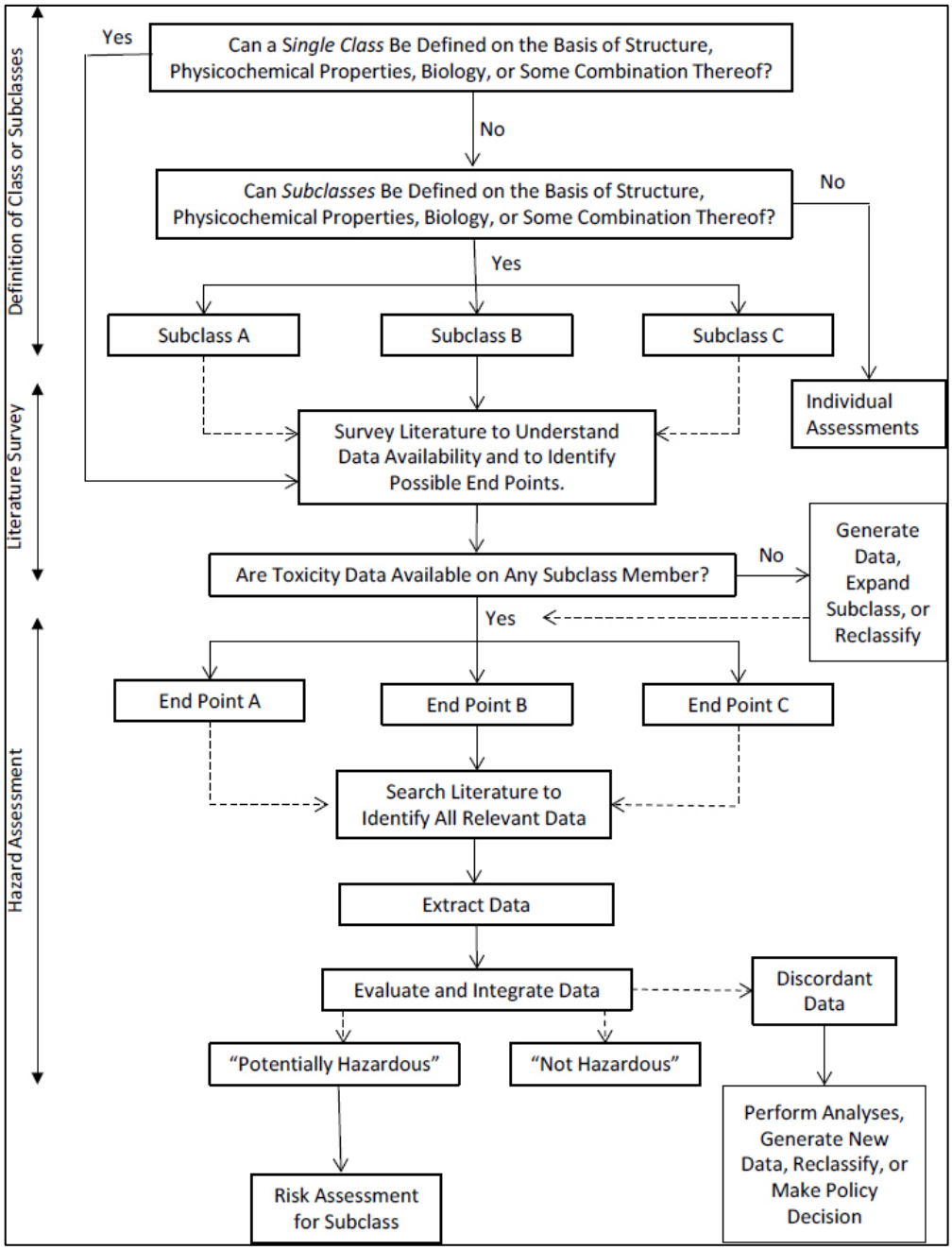

Figure A-1. Scoping approach to identifying subclasses of OFRs for potential health hazard assessments (Taken from Figure 2-1, NAS 2019).

Table A-1. Fourteen OFR subclasses formulated on the basis of chemotypes and predicted biological activity (NAS 2019)

OFR Subclass	No. Chemicals	CAS No. of Chemicals
Polyhalogenated alicycles	17	25495-98-1; 25637-99-4; 3194-55-6; 3194-57-8; 134237-50-6; 134237-51-7; 134237-52-8; 678970-17-7; 678970-16-6; 678970-15-5; 169102-57-2; 138257-19-9; 138257-18-8; 3322-93-8; 77-47-4; 87-84-3; 1837-91-8
Polyhalogenated aliphatic carboxylate	4	3066-70-4; 5445-17-0; 5445-19-2; 19660-16-3
Polyhalogenated aliphatic chains	12	52434-59-0; 1522-92-5; 3296-90-0; 3234-02-4; 96-13-9; 109678-33-3; 85535-84-8; 71011-12-6; 85535-85-9; 63449-39-8; 75-95-6; 79-27-6
Polyhalogenated benzene alicycles	4	1084889-51-9; 893843-07-7; 1025956-65-3; 155613-93-7
Polyhalogenated benzene aliphatics and functionalized	19	168434-45-5; 23488-38-2; 39569-21-6; 87-83-2; 85-22-3; 38521-51-6; 58495-09-3; 31780-26-4; 84852-53-9; 497107-13-8; 59447-55-1; 34571-16-9*; 855993-01-0*; 855992-98-2*; 147-82-0; 57011-47-9; 61368-34-1; 93-52-7; 39568-99-5
Polyhalogenated benzenes	19	608-90-2; 87-82-1; 84303-46-8; 60044-26-0; 67733-52-2; 67889-00-3; 69278-62-2; 59080-40-9; 13654-09-6; 36355-01-8; 92-66-0; 92-86-4; 115245-07-3; 60044-24-8; 59080-37-4; 77102-82-0; 16400-50-3; 67888-96-4; 59080-39-6
Polyhalogenated bisphenol aliphatics and functionalized	11	66710-97-2; 55205-38-4; 37853-61-5; 37419-42-4; 3072-84-2; 33798-02-6; 79-94-7; 25327-89-3; 21850-44-2; 4162-45-2; 79-95-8
Polyhalogenated carbocycles	15	13560-89-9; 51936-55-1; 13560-92-4; 34571-16-9*; 855993-01-0*; 855992-98-2*; 2385-85-5; 18300-04-4; 115-28-6; 1773-89-3; 1770-80-5; 115-27-5; 31107-44-5; 40703-79-5; 52907-07-0
Polyhalogenated diphenyl ethers	12	1163-19-5; 32534-81-9; 60348-60-9; 32536-52-0; 58965-66-5; 5436-43-1; 207122-16-5; 189084-67-1; 41318-75-6; 189084-64-8; 68631-49-2; 207122-15-4
Polyhalogenated organophosphates	22	114955-21-4*; 1373346-90-7*; 126-72-7; 19186-97-1; 115-96-8; 13674-84-5; 13674-87-8; 38051-10-4; 66108-37-0; 78-43-3; 6145-73-9; 33125-86-9; 49690-63-3; 7046-64-2; 5412-25-9; 53461-82-8; 61090-89-9; 140-08-9; 6749-73-1; 4351-70-6; 6294-34-4; 115-98-0
Polyhalogenated phenol derivatives	7	118-79-6; 608-71-9; 615-58-7; 42757-55-1; 39635-79-5; 70156-79-5; 25713-60-4*
Polyhalogenated phenol-aliphatic ethers	9	3278-89-5; 31977-87-4; 35109-60-5; 37853-59-1; 61262-53-1; 3555-11-1; 607-99-8; 26762-91-4; 20217-01-0

OFR Subclass	No. Chemicals	CAS No. of Chemicals
Polyhalogenated phthalates/benzoates/imides	11	32588-76-4; 183658-27-7; 90075-91-5; 82001-21-6; 20566-35-2; 26040-51-7; 7415-86-3; 55481-60-2; 632-79-1; 117-08-8; 57011-47-9
Polyhalogenated triazines	6	52434-90-9; 57829-89-7; 75795-16-3; 25713-60-4*; 114955-21-4*; 1373346-90-7*

*An asterisk indicates that the chemical occurs in more than one category
(Taken from Figure B-2, NAS 2019)

Appendix B. Search Terms and Evaluation Team Responsibilities

B1. Organohalogen Flame Retardant Search Terms for Human and Animal Cancer, and Mechanism Studies

Two sets of search strings were developed for the organohalogen flame retardant (OFR) searches. Table B-1 is a general OFR search string that includes general terms for OFRs, subclasses, and selected chemicals. Table B-2 are chemical specific terms that include all OFRs listed in Appendix A, along with aliases. Standard RoC search terms for human cancer, animal cancer, and mechanism terms are posted on the RoC website. All searches were conducted in three citations databases, PubMed, Scopus, and Web of Science.

For human cancer searches, the OFR general and specific terms were separately combined using "AND" with the RoC Animal Terms and RoC Cancer terms found in the standard search term document.

For animal cancer searches, the OFR general and specific terms were combined using "AND" with the RoC Animal Terms and RoC Cancer terms found in the standard search term document. In addition, we manually searched for additional relevant animal cancer studies and citations within documents from authoritative bodies and within existing databases, including those detailed in Section 2.2.1.

For mechanism searches, the OFR general and specific terms were combined using "AND" with the RoC KCC and RoC general mechanism search terms found in the standard search term document.

Table B-1. General OFR search terms

Database	Search String
Pubmed	(((flame OR fire) AND (retard* OR suppress*)) OR (Flame Retardants [MeSH]) OR (BCPP OR BCIPP OR TCIPP OR TCPP OR BCEP OR BCEtP OR BDCPP OR BDCIPP OR BCIPHIPP OR TBBPA OR PBDE) OR (polybrominated and ('diphenyl' OR diphenyl) and ('ethers' OR ether)) OR (‘polyhalogenated bisphenol aliphatic*’ OR ‘polybrominated bisphenol aliphatic*’ or ‘polychlorinated bisphenol aliphatic*’) OR (‘polyhalogenated diphenyl ether*’ OR ‘polychlorinated diphenyl ether*’) OR (‘polyhalogenated organophosphate*’ OR ‘polybrominated organophosphate*’ OR polychlorinated organophosphate* OR ‘organophosphate ester*’) OR ("tri-(2-chloroisopropyl)phosphate" [Supplementary Concept]) OR ("Halogenated Diphenyl Ethers"[Mesh]) OR ("polychlorinated diphenyl ethers" [Supplementary Concept]) OR ("tetrabromobisphenol A" [Supplementary Concept]))
Scopus	Title-abs-key((((flame OR fire) AND (retard* OR suppress*)) OR (Flame Retardants) OR (BCPP OR BCIPP OR TCIPP OR TCPP OR BCEP OR BCEtP OR BDCPP OR BDCIPP OR BCIPHIPP OR TBBPA OR PBDE) OR (polybrominated and ('diphenyl' OR diphenyl) and ('ethers' OR ether)) OR (‘polyhalogenated bisphenol aliphatic*’ OR ‘polybrominated bisphenol aliphatic*’ or ‘polychlorinated bisphenol aliphatic*’) OR (‘polyhalogenated diphenyl ether*’ OR ‘polychlorinated diphenyl ether*’) OR (‘polyhalogenated organophosphate*’ OR ‘polybrominated organophosphate*’ OR polychlorinated organophosphate* OR ‘organophosphate ester*’) OR ("tri-(2-chloroisopropyl)phosphate") OR ("Halogenated Diphenyl Ethers") OR ("polychlorinated diphenyl ethers") OR ("tetrabromobisphenol A")))
Web of Science	ts=((((flame OR fire) AND (retard* OR suppress*)) OR (Flame Retardants) OR (BCPP OR BCIPP OR TCIPP OR TCPP OR BCEP OR BCEtP OR BDCPP OR BDCIPP OR BCIPHIPP OR TBBPA OR PBDE) OR (polybrominated and ('diphenyl' OR diphenyl) and ('ethers' OR ether)) OR (‘polyhalogenated bisphenol aliphatic*’ OR ‘polybrominated bisphenol aliphatic*’ or ‘polychlorinated bisphenol aliphatic*’) OR (‘polyhalogenated diphenyl ether*’ OR ‘polychlorinated diphenyl ether*’) OR (‘polyhalogenated organophosphate*’ OR ‘polybrominated organophosphate*’ OR polychlorinated organophosphate* OR ‘organophosphate ester*’) OR ("tri-(2-chloroisopropyl)phosphate") OR ("Halogenated Diphenyl Ethers") OR ("polychlorinated diphenyl ethers") OR ("tetrabromobisphenol A")))

Table B-2. OFR Chemical Specific Search Terms

Database	Search String
Pubmed	(("Bis(p-acryloxyethoxy)tetrabromobisphenol A" OR "{(Propane-2,2-diyl)bis[(2,6-dibromo-4,1-phenylene)oxy]ethane-2,1-diyl} diprop-2-enoate" OR "2-Propenoic acid, (1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy-2,1-ethanediyl] ester" OR "66710-97-2"[EC/RN Number] OR "Tetrabromobisphenol A bis(2-hydroxyethyl) ether bis(acrylate)" OR "Tetrabromobisphenol A bis (2-hydroxyethyl)" OR "Ethoxylated Tetrabromo Bisphenol A Diacrylate" OR "TBBPA-BHEEBA") OR ("2,2',6,6'-Tetrachlorobisphenol A" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dichlorophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dichloro-" OR "79-95-8"[EC/RN Number] OR " (4,4'-isopropylidenebis(2,6-dichlorophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dichloro-" OR "Tetrachloro bisphenol A" OR "Tetrachlorobisphenol A" OR "Tetrachlorodian" OR "79-95-8" [EC/RN Number] OR "TCBPA") OR ("Tetrabromobisphenol A bis(2-hydroxyethyl) ether" OR "2,2'-{Propane-2,2-diylbis[(2,6-dibromo-4,1-phenylene)oxy]}di(ethan-1-ol)" OR "Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis-" OR "4162-45-2"[EC/RN Number] OR "Ethanol, 2,2'-((1-methylethylidene)bis((2,6-dibromo-4,1-phenylene)oxy))bis-" OR "Fire guard 3600" OR "Tetrabromobisphenol-A-bisethoxylate" OR "2,2-Bis(3,5-dibromo-4-(2-hydroxyethoxy)phenyl)propane" OR "Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis-" OR "Ethoxylated tetrabromobisphenol A" OR "Tetrabromobisphenol A bis(ethoxylate)" OR "TBBPA-BHEE") OR ("Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)" OR "1,1'-(Propane-2,2-diyl)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)-" OR "21850-44-2"[EC/RN Number] OR "TBBPA-DBPE" OR "1,1'-(Isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]" OR "Tetrabromobisphenol A dibromopropyl ether" OR "Tetrabromobisphenol A bis(dibromopropyl ether)" OR "TBBPA-BDBPE") OR ("Tetrabromobisphenol A diallyl ether" OR "1,1'-(Propane-2,2-diyl)bis{3,5-dibromo-4-[(prop-2-en-1-yl)oxy]benzene}" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-" OR "25327-89-3"[EC/RN Number] OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)-" OR "1,1'-(1-Methylethylidene)bis(3,5-dibromo-4-(2-propenyloxy)benzene" OR "Pyroguard SR 319" OR "2,2-bis(3,5-Dibromo-4-allyloxyphenyl)propane" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-" OR "Propane, 2,2-bis(4-(allyloxy)-3,5-dibromophenyl)-" OR "2,2′,6,6′-Tetrabromobisphenol A diallyl ether" OR "TBBPA-BAE") OR ("3,3',5,5'-Tetrabromobisphenol A" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-" OR "79-94-7"[EC/RN Number] OR "TBBPA" OR "Tetrabromobisphenol A") OR ("Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, 1,1'-diacetate" OR "(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) diacetate" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, diacetate" OR "33798-02-6"[EC/RN Number] OR "4,4'-Isopropylidenebis(2,6-dibromophenyl) diacetate" OR "TBBPA-BOAc") OR ("2,2'-[(1-Methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxymethylene]]bis[oxirane]" OR "2,2'-{Propane-2,2-diylbis[(2,6-dibromo-4,1-phenylene)oxymethylene]}bis(oxirane" OR "Oxirane, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxymethylene]]bis-" OR "3072-84-2"[EC/RN Number] OR "Tetrabromobisphenol A Diglycidyl Ether" OR "TBBPA-BGE") OR ("3,3',5,5'-Tetrabromobisphenol A bispropionate" OR "(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) dipropanoate" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, dipropanoate" OR "37419-42-4"[EC/RN Number] OR "TBBPA-BP") OR (Tetrabromobisphenol A dimethyl ether OR "1,1'-(Propane-2,2-diyl)bis(3,5-dibromo-4-methoxybenzene)" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-methoxy-" OR "37853-61-5"[EC/RN Number] OR "Benzene, 1, 1'- (1- methylethylidene) bis[3, 5- dibromo- 4- methoxy-" OR "1,1'-(1-Methylethylidene)bis[3,5-dibromo-4-methoxybenzene]" OR "2,2-Bis(3,5-dibromo-4-methoxyphenyl)propane" OR "Tetrabromobisphenol A methyl ether" OR "TBBPA-BME") OR ("(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) diprop-2-enoate" OR "2-Propenoic acid, (1-methylethylidene)bis-2,6-dibromo-4,1-phenylene ester" OR "55205-38-4"[EC/RN Number] OR "2,2',6,6'-Tetrabromobisphenol A diacrylate" OR "Tetrabromobisphenol A diacrylate" OR "TBBPA-BA") OR ("1,1'-Oxybis[2,3,4,5,6-pentabromobenzene]" OR "1,1'-Oxybis(pentabromobenzene)" OR

Database	Search String
	"Benzene, 1,1'-oxybis[2,3,4,5,6-pentabromo-" OR "1163-19-5"[EC/RN Number] OR "Ether, bis(pentabromophenyl)" OR "Benzene, 1,1'-oxybis[2,3,4,5,6-pentabromo-" OR "Decabromodiphenyl oxide) 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether" OR "BDE-209" OR "DE-83R" OR "BDE 209") OR ("2,2',4,4',5,6'-Hexabromodiphenyl ether" OR "1,3,5-Tribromo-2-(2,4,5-tribromophenoxy)benzene" OR "Benzene, 1,3,5-tribromo-2-(2,4,5-tribromophenoxy)-" OR "207122-15-4"[EC/RN Number] OR "BDE 154") OR ("1,2,3,4,5-Pentabromo-6-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,2,3,4,5-pentabromo-6-(2,4-dibromophenoxy)-" OR "189084-67-1"[EC/RN Number]) OR ("2,2',4,4',5,5'-Hexabromodiphenyl ether" OR "1,1'-Oxybis(2,4,5-tribromobenzene)" OR "Benzene, 1,1'-oxybis[2,4,5-tribromo-" OR "68631-49-2"[EC/RN Number] OR "BDE 153") OR ("2,2',4,4',6-Pentabromodiphenyl ether" OR "1,3,5-Tribromo-2-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,3,5-tribromo-2-(2,4-dibromophenoxy)-" OR "189084-64-8"[EC/RN Number] OR "BDE 100" OR "PBDE 100" OR "Benzene, 1,3,5-tribromo-2-(2,4-dibromophenoxy)-") OR ("2,4,4'-Tribromodiphenyl ether" OR "2,4-Dibromo-1-(4-bromophenoxy)benzene" OR "Benzene, 2,4-dibromo-1-(4-bromophenoxy)-" OR "41318-75-6"[EC/RN Number] OR "2,4-Dibromo-1-(4-bromophenoxy)benzene" OR "Benzene, 2,4-dibromo-1-(4-bromophenoxy)-" OR "Ether, p-bromophenyl 2,4-dibromophenyl" OR "BDE 28" OR "PBDE 28") OR ("2,2',3,4,4',5',6-Heptabromodiphenyl ether") OR ("2,2',4,4'-Tetrabromodiphenyl ether" OR "1,1'-Oxybis(2,4-dibromobenzene)" OR "Benzene, 1,1'-oxybis[2,4-dibromo-" OR "5436-43-1"[EC/RN Number] OR "BDE 47" OR "PBDE 47" OR "2,4-Dibromo-1-(2,4-dibromophenoxy)benzene" OR "bis(2,4-dibromophenyl) ether") OR ("Perbromo-1,4-diphenoxybenzene" OR "1,1'-[(2,3,5,6-Tetrabromo-1,4-phenylene)bis(oxy)]bis(pentabromobenzene)" OR "Benzene, 1,2,4,5-tetrabromo-3,6-bis(2,3,4,5,6-pentabromophenoxy)-" OR "58965-66-5"[EC/RN Number] OR "Benzene, 1,2,4,5-tetrabromo-3,6-bis(2,3,4,5,6-pentabromophenoxy)-" OR "Tetradecabromo-1,4-diphenoxybenzene") OR ("Octabromodiphenyl ether" OR "32536-52-0"[EC/RN Number] OR "Benzene, 1,1'-oxybis-, octabromo deriv." OR "DE-79") OR ("2,2',4,4',5-Pentabromodiphenyl ether" OR "1,2,4-Tribromo-5-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,2,4-tribromo-5-(2,4-dibromophenoxy)-" OR "60348-60-9"[EC/RN Number] OR "PBDE 99" OR "2,2',4,4',5-Pentabromodiphenyl oxide" OR "BDE 99" OR "BDE-99") OR ("Pentabromodiphenyl ether" OR "32534-81-9"[EC/RN Number] OR "Benzene, 1,1'-oxybis-, pentabromo deriv." OR "Bromkal G 1" OR "Pentabromodiphenyl oxide" OR "Saytex 125" OR "Oxyde de diphenyle, derive pentabrome" OR "diphenyl ether, pentabromo derivative" OR "Diphenylether, Pentabromderivat" OR "difenil eter, derivado pentabromado" OR "penta-BDE") OR ("diethyl (4,6-dichloro-1,3,5-triazin-2-yl)phosphonate" OR "Phosphonic acid, P-(4,6-dichloro-1,3,5-triazin-2-yl)-, diethyl ester" OR "114955-21-4"[EC/RN Number]) OR ("Phosphoric acid, 1,2-ethanediyl tetrakis(2-chloroethyl) ester" OR "Tetrakis(2-chloroethyl) ethane-1,2-diyl bis(phosphate)" OR "Phosphoric acid, tetrakis(2-chloroethyl) 1,2-ethanediyl ester" OR "33125-86-9"[EC/RN Number] OR “Ethylene bis(bis(2-chloroethyl)phosphate)”) OR ("Tris(2-chloropropyl) phosphate" OR "6145-73-9"[EC/RN Number] OR "1-Propanol, 2-chloro-, phosphate (3:1)" OR "TCPP") OR ("Tris(2,3-dichloropropyl)phosphate" OR "Tris(2,3-dichloropropyl) phosphate" OR "78-43-3"[EC/RN Number] OR “2,3-Dichloro-1-propanol phosphate”) OR ("Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester" OR "2,2-Bis(chloromethyl)propane-1,3-diyl tetrakis(2-chloroethyl) bis(phosphate)" OR "38051-10-4"[EC/RN Number] OR "Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester" OR "Phosphoric acid, P,P'-[2,2-bis(chloromethyl)-1,3-propanediyl] P,P,P',P'-tetrakis(2-chloroethyl) ester" OR “2,2-Bis(chloromethyl)-1,3-propanediyl bis(bis(2-chloroethyl) phosphate)”) OR ("Tris(1,3-dichloro-2-propyl) phosphate" OR "13674-87-8"[EC/RN Number] OR "2-Propanol, 1,3-dichloro-, phosphate (3:1)" OR "TDCPP" OR "Antiblaze 195" OR "Antiblaze WR 30LV" OR "CRP (fireproofing agent)" OR "Fyrol FR 2" OR "PF 38/3" OR "2-Propanol, 1,3-dichloro-, 2,2',2"-phosphate" OR "3PC-R" OR "FR 10" OR "Tris(1,3-dichloroisopropyl) phosphate" OR "Tris[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "tris[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "tris[2-chloro-1-chloromethyl)ethyl] phosphate" OR “Tris(1,3-dichloro-2-propyl)phosphate” OR “Tris (1,3-dichloroisopropyl)phosphate") OR ("2,2-Bis(bromomethyl)-3-chloropropyl bis[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "2,2-Bis(bromomethyl)-3-chloropropyl bis(1,3-

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	dichloropropan-2-yl) phosphate" OR "Phosphoric acid, 3-bromo-2-(bromomethyl)-2-(chloromethyl)propyl bis[2-chloro-1-(chloromethyl)ethyl] ester" OR "66108-37-0"[EC/RN Number] OR "MC 984" OR "Bis(1,3-dichloro-2-propyl)-3-chloro-2,2-dibromomethyl-1-propyl phosphate" OR "K6UU3AT81T") OR ("Tris(2-chloroisopropyl)phosphate" OR "13674-84-5"[EC/RN Number] OR ("TCPP NOT porphyrin") OR "2-Propanol, 1-chloro-, phosphate (3:1)" OR "Tris(1-chloro-2-propyl) phosphate" OR "Tris(2-chloro-1-methylethyl) phosphate") OR ("Tris(2-chloroethyl) phosphate" OR "115-96-8"[EC/RN Number] OR "Ethanol, 2-chloro-, phosphate (3:1)" OR ("TCEP" NOT "phosphine") OR "Ethanol, 2-chloro-, 1,1',1"-phosphate" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Trichlorethyl phosphate" OR "2-Chloroethanol phosphate") OR ("Diethylene glycol bis[bis(2-chloroethyl)phosphate]" OR "Tetrakis(2-chloroethyl) oxydi(ethane-2,1-diyl) bis(phosphate)" OR "Phosphoric acid, tetrakis(2-chloroethyl) oxydi-2,1-ethanediyl ester" OR "53461-82-8"[EC/RN Number] OR "Oxydiethylene tetrakis(2-chloroethyl) bisphosphate" OR "Diethylene glycol tetra(2-chloroethyl) phosphate") OR ("Phosphonic acid, P-[1-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]-, 1-[bis(2-chloroethoxy)phosphinyl]ethyl 2-chloroethyl ester" OR "1-[Bis(2-chloroethoxy)phosphoryl]ethyl 2-chloroethyl (1-{[(2-chloroethoxy)(2-chloroethyl)phosphoryl]oxy}ethyl)phosphonate (non-preferred name)" OR "4351-70-6" [EC/RN Number]OR "Phosgard c-22R") OR ("Tris(1,3-dichloropropan-2-yl) phosphite" OR "6749-73-1"[EC/RN Number] OR "2-Propanol, 1,3-dichloro-, phosphite (3:1)" OR "Tris(2-chloro-1-(chloromethyl)ethyl) phosphite") OR ("Tris(2-chloroethyl) phosphite" OR "140-08-9"[EC/RN Number] OR "Ethanol, 2-chloro-, phosphite (3:1)" OR "Ethanol, 2-chloro-, 1,1',1"-phosphite" OR "2-Chloroethanol phosphite (3:1)") OR ("2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-, 3,9-dioxide" OR "3,9-Bis[3-bromo-2,2-bis(bromomethyl)propoxy]-2,4,8,10-tetraoxa-3lambda~5~,9lambda~5~-diphosphaspiro[5.5]undecane-3,9-dion" OR "61090-89-9"[EC/RN Number] OR "UASQAKNFTHVEDR-UHFFFAOYSA-N" OR "3,9-Bis(3-bromo-2,2-bis(bromomethyl)propoxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro(5.5)undecane 3,9-dioxide" OR "3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-2,4,8,10-tetraoxa-3") OR ("Bis(2,3-dibromopropyl) hydrogen phosphate" OR "5412-25-9"[EC/RN Number] OR "1- Propanol, 2, 3-dibromo- , 1, 1'- (hydrogen phosphate)" OR "1-Propanol, 2,3-dibromo-, hydrogen phosphate" OR "Bis(2,3-dibromopropyl) phosphate" OR "NSC 3239" OR "bis(2,3-dibromopropyl) hydrogen phosphate" OR "Bis(2,3-dibromopropyl) phosphate") OR ("Tris(2,4,6-tribromophenyl) phosphate" OR "Phenol, 2,4,6-tribromo-, compd. with phosphoric acid (1:1)" OR "7046-64-2"[EC/RN Number] OR "Phenol, 2,4,6-tribromo-, phosphate") OR ("Tris(2,3-dibromophenyl) phosphate" OR "49690-63-3"[EC/RN Number]) OR ("Bis(2-chloroethyl) vinylphosphonate" OR "Phosphonic acid, P-ethenyl-, bis(2-chloroethyl) ester" OR "115-98-0"[EC/RN Number] OR "Vinifos" OR "Fyrol Bis beta") OR ("Bis(2-chloroethyl) 2-chloroethylphosphonate" OR "Bis(2-chloroethyl) (2-chloroethyl)phosphonate" OR "Phosphonic acid, P-(2-chloroethyl)-, bis(2-chloroethyl) ester" OR "6294-34-4"[EC/RN Number] OR "Phosphonic acid, P-(2-chloroethyl)-, bis(2-chloroethyl) ester" OR "Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester" OR "Bis(2-Chloroethyl) (2-Chloroethyl)Phosphonate") OR ("Tris(tribromoneopentyl)phosphate" OR "Tris[3-bromo-2,2-bis(bromomethyl)propyl] phosphate" OR "19186-97-1"[EC/RN Number] OR "TPB 3070" OR "1-Propanol, 3-bromo-2,2-bis(bromomethyl)-, 1,1',1"-phosphate" OR "Tris[2,2-bis(bromomethyl)-3-bromopropyl] phosphate") OR ("Tris(2,3-dibromopropyl) phosphate" OR "126-72-7"[EC/RN Number] OR "TDBPP") OR ("dimethyl {[(4,6-dichloro-1,3,5-triazin-'organophospate ester2-yl)oxy]methyl}phosphonate" OR "Phosphonic acid, P-[[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]methyl]-, dimethyl ester" OR "1373346-90-7" [EC/RN Number]) OR "organophospate ester")
Scopus	TITLE-ABS-KEY((("Bis(p-acryloxyethoxy)tetrabromobisphenol A" OR "{(Propane-2,2-diyl)bis[(2,6-dibromo-4,1-phenylene)oxy]ethane-2,1-diyl} diprop-2-enoate" OR "2-Propenoic acid, (1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy-2,1-ethanediyl] ester" OR "66710-97-2"

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	OR “Tetrabromobisphenol A bis(2-hydroxyethyl) ether bis(acrylate)” OR “Tetrabromobisphenol A bis (2-hydroxyethyl)” OR “Ethoxylated Tetrabromo Bisphenol A Diacrylate” OR “TBBPA-BHEEBA”) OR ("2,2',6,6'-Tetrachlorobisphenol A" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dichlorophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dichloro-" OR "79-95-8"OR "(4,4'-isopropylidenebis(2,6-dichlorophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dichloro-" OR "Tetrachloro bisphenol A" OR “Tetrachlorobisphenol A” OR “Tetrachlorodian” OR “79-95-8” OR “TCBPA”) OR ("Tetrabromobisphenol A bis(2-hydroxyethyl) ether" OR "2,2'-{Propane-2,2-diylbis[(2,6-dibromo-4,1-phenylene)oxy]}di(ethan-1-ol)" OR "Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis-" OR "4162-45-2"OR "Ethanol, 2,2'-((1-methylethylidene)bis((2,6-dibromo-4,1-phenylene)oxy))bis-" OR "Fire guard 3600" OR "Tetrabromobisphenol-A-bisethoxylate" OR "2,2-Bis(3,5-dibromo-4-(2-hydroxyethoxy)phenyl)propane" OR "Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis-" OR “Ethoxylated tetrabromobisphenol A” OR “Tetrabromobisphenol A bis(ethoxylate)” OR “TBBPA-BHEE”) OR ("Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)" OR "1,1'-(Propane-2,2-diyl)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)-" OR "21850-44-2"OR "TBBPA-DBPE" OR "1,1'-(Isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]" OR “Tetrabromobisphenol A dibromopropyl ether” OR “Tetrabromobisphenol A bis(dibromopropyl ether)” OR “TBBPA-BDBPE”) OR ("Tetrabromobisphenol A diallyl ether" OR "1,1'-(Propane-2,2-diyl)bis{3,5-dibromo-4-[(prop-2-en-1-yl)oxy]benzene}" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-" OR "25327-89-3"OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)-" OR "1,1'-(1-Methylethylidene)bis(3,5-dibromo-4-(2-propenyloxy)benzene" OR "Pyroguard SR 319" OR "2,2-bis(3,5-Dibromo-4-allyloxyphenyl)propane" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-" OR "Propane, 2,2-bis(4-(allyloxy)-3,5-dibromophenyl)-" OR "2,2′,6,6′-Tetrabromobisphenol A diallyl ether" OR “TBBPA-BAE”) OR ("3,3',5,5'-Tetrabromobisphenol A" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-" OR "79-94-7"OR "TBBPA" OR “Tetrabromobisphenol A”) OR ("Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, 1,1'-diacetate" OR "(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) diacetate" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, diacetate" OR "33798-02-6"OR “4,4’-Isopropylidenebis(2,6-dibromophenyl) diacetate” OR “TBBPA-BOAc”) OR ("2,2'-[(1-Methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxymethylene]]bis[oxirane]" OR "2,2'-{Propane-2,2-diylbis[(2,6-dibromo-4,1-phenylene)oxymethylene]}bis(oxirane" OR "Oxirane, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxymethylene]]bis-" OR "3072-84-2"OR “Tetrabromobisphenol A Diglycidyl Ether” OR “TBBPA-BGE”) OR

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	("3,3',5,5'-Tetrabromobisphenol A bispropionate" OR "(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) dipropanoate" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, dipropanoate" OR "37419-42-4"OR “TBBPA-BP”) OR (Tetrabromobisphenol A dimethyl ether OR "1,1'-(Propane-2,2-diyl)bis(3,5-dibromo-4-methoxybenzene)" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-methoxy-" OR "37853-61-5"OR "Benzene, 1, 1'- (1- methylethylidene) bis[3, 5- dibromo- 4- methoxy-" OR "1,1'-(1-Methylethylidene)bis[3,5-dibromo-4-methoxybenzene]" OR "2,2-Bis(3,5-dibromo-4-methoxyphenyl)propane" OR "Tetrabromobisphenol A methyl ether" OR “TBBPA-BME”) OR ("(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) diprop-2-enoate" OR "2-Propenoic acid, (1-methylethylidene)bis-2,6-dibromo-4,1-phenylene ester" OR "55205-38-4"OR “2,2’,6,6’-Tetrabromobisphenol A diacrylate” OR “Tetrabromobisphenol A diacrylate” OR “TBBPA-BA”) OR ("1,1'-Oxybis[2,3,4,5,6-pentabromobenzene]" OR "1,1'-Oxybis(pentabromobenzene)" OR "Benzene, 1,1'-oxybis[2,3,4,5,6-pentabromo-" OR "1163-19-5"OR "Ether, bis(pentabromophenyl)" OR "Benzene, 1,1'-oxybis[2,3,4,5,6-pentabromo-" OR "Decabromodiphenyl oxide) 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether" OR "BDE-209" OR "DE-83R" OR "BDE 209") OR ("2,2',4,4',5,6'-Hexabromodiphenyl ether" OR "1,3,5-Tribromo-2-(2,4,5-tribromophenoxy)benzene" OR "Benzene, 1,3,5-tribromo-2-(2,4,5-tribromophenoxy)-" OR "207122-15-4"OR "BDE 154") OR ("1,2,3,4,5-Pentabromo-6-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,2,3,4,5-pentabromo-6-(2,4-dibromophenoxy)-" OR "189084-67-1") OR ("2,2',4,4',5,5'-Hexabromodiphenyl ether" OR "1,1'-Oxybis(2,4,5-tribromobenzene)" OR "Benzene, 1,1'-oxybis[2,4,5-tribromo-" OR "68631-49-2"OR "BDE 153") OR ("2,2',4,4',6-Pentabromodiphenyl ether" OR "1,3,5-Tribromo-2-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,3,5-tribromo-2-(2,4-dibromophenoxy)-" OR "189084-

Database	Search String
	64-8"OR "BDE 100" OR "PBDE 100" OR "Benzene, 1,3,5-tribromo-2-(2,4-dibromophenoxy)-") OR ("2,4,4'-Tribromodiphenyl ether" OR "2,4-Dibromo-1-(4-bromophenoxy)benzene" OR "Benzene, 2,4-dibromo-1-(4-bromophenoxy)-" OR "41318-75-6"OR "2,4-Dibromo-1-(4-bromophenoxy)benzene" OR "Benzene, 2,4-dibromo-1-(4-bromophenoxy)-" OR "Ether, p-bromophenyl 2,4-dibromophenyl" OR "BDE 28" OR "PBDE 28") OR ("2,2',3,4,4',5',6-Heptabromodiphenyl ether") OR ("2,2',4,4'-Tetrabromodiphenyl ether" OR "1,1'-Oxybis(2,4-dibromobenzene)" OR "Benzene, 1,1'-oxybis[2,4-dibromo-" OR "5436-43-1"OR "BDE 47" OR "PBDE 47" OR "2,4-Dibromo-1-(2,4-dibromophenoxy)benzene" OR "bis(2,4-dibromophenyl) ether") OR ("Perbromo-1,4-diphenoxybenzene" OR "1,1'-[(2,3,5,6-Tetrabromo-1,4-phenylene)bis(oxy)]bis(pentabromobenzene)" OR "Benzene, 1,2,4,5-tetrabromo-3,6-bis(2,3,4,5,6-pentabromophenoxy)-" OR "58965-66-5"OR "Benzene, 1,2,4,5-tetrabromo-3,6-bis(2,3,4,5,6-pentabromophenoxy)-" OR "Tetradecabromo-1,4-diphenoxybenzene") OR ("Octabromodiphenyl ether" OR "32536-52-0"OR "Benzene, 1,1'-oxybis-, octabromo deriv." OR "DE-79") OR ("2,2',4,4',5-Pentabromodiphenyl ether" OR "1,2,4-Tribromo-5-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,2,4-tribromo-5-(2,4-dibromophenoxy)-" OR "60348-60-9"OR "PBDE 99" OR "2,2',4,4',5-Pentabromodiphenyl oxide" OR "BDE 99" OR "BDE-99") OR ("Pentabromodiphenyl ether" OR "32534-81-9"OR "Benzene, 1,1'-oxybis-, pentabromo deriv." OR "Bromkal G 1" OR "Pentabromodiphenyl oxide" OR "Saytex 125" OR "Oxyde de diphenyle, derive pentabrome" OR "diphenyl ether, pentabromo derivative" OR "Diphenylether, Pentabromderivat" OR "difenil eter, derivado pentabromado" OR "penta-BDE") OR ("diethyl (4,6-dichloro-1,3,5-triazin-2-yl)phosphonate" OR "Phosphonic acid, P-(4,6-dichloro-1,3,5-triazin-2-yl)-, diethyl ester" OR "114955-21-4") OR ("Phosphoric acid, 1,2-ethanediyl tetrakis(2-chloroethyl) ester" OR "Tetrakis(2-chloroethyl) ethane-1,2-diyl bis(phosphate)" OR "Phosphoric acid, tetrakis(2-chloroethyl) 1,2-ethanediyl ester" OR "33125-86-9"OR "Ethylene bis(bis(2-chloroethyl)phosphate)") OR ("Tris(2-chloropropyl) phosphate" OR "6145-73-9"OR "1-Propanol, 2-chloro-, phosphate (3:1)" OR "TCPP") OR ("Tris(2,3-dichloropropyl)phosphate" OR "Tris(2,3-dichloropropyl) phosphate" OR "78-43-3"OR "2,3-Dichloro-1-propanol phosphate") OR ("Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester" OR "2,2-Bis(chloromethyl)propane-1,3-diyl tetrakis(2-chloroethyl) bis(phosphate)" OR "38051-10-4"OR "Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester" OR "Phosphoric acid, P,P'-[2,2-bis(chloromethyl)-1,3-propanediyl] P,P,P',P'-tetrakis(2-chloroethyl) ester" OR "2,2-Bis(chloromethyl)-1,3-propanediyl bis(bis(2-chloroethyl) phosphate)") OR ("Tris(1,3-dichloro-2-propyl) phosphate" OR "13674-87-8"OR "2-Propanol, 1,3-dichloro-, phosphate (3:1)" OR "TDCPP" OR "Antiblaze 195" OR "Antiblaze WR 30LV" OR "CRP (fireproofing agent)" OR "Fyrol FR 2" OR "PF 38/3" OR "2-Propanol, 1,3-dichloro-, 2,2',2"-phosphate" OR "3PC-R" OR "FR 10" OR "Tris(1,3-dichloroisopropyl) phosphate" OR "Tris[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "tris[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "tris[2-chloro-1-chloromethyl)ethyl] phosphate" OR "Tris(1,3-dichloro-2-propyl)phosphate" OR "Tris (1,3-dichloroisopropyl)phosphate") OR ("2,2-Bis(bromomethyl)-3-chloropropyl bis[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "2,2-Bis(bromomethyl)-3-chloropropyl bis(1,3-dichloropropan-2-yl) phosphate" OR "Phosphoric acid, 3-bromo-2-(bromomethyl)-2-(chloromethyl)propyl bis[2-chloro-1-(chloromethyl)ethyl] ester" OR "66108-37-0"OR "MC 984" OR "Bis(1,3-dichloro-2-propyl)-3-chloro-2,2-dibromomethyl-1-propyl phosphate" OR "K6UU3AT81T") OR ("Tris(2-chloroisopropyl)phosphate" OR "13674-84-5"OR ("TCPP NOT porphyrin") OR "2-Propanol, 1-chloro-, phosphate (3:1)" OR "Tris(1-chloro-2-propyl) phosphate" OR "Tris(2-chloro-1-methylethyl) phosphate") OR ("Tris(2-chloroethyl) phosphate" OR "115-96-8"OR "Ethanol, 2-chloro-, phosphate (3:1)" OR ("TCEP" NOT "phosphine") OR "Ethanol, 2-chloro-, 1,1',1"-phosphate" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Trichlorethyl phosphate" OR "2-Chloroethanol phosphate") OR ("Diethylene glycol bis[bis(2-chloroethyl)phosphate]" OR "Tetrakis(2-chloroethyl) oxydi(ethane-2,1-diyl) bis(phosphate)" OR "Phosphoric acid, tetrakis(2-chloroethyl) oxydi-2,1-ethanediyl ester" OR "53461-82-8"OR "Oxydiethylene tetrakis(2-chloroethyl) bisphosphate" OR "Diethylene glycol tetra(2-chloroethyl) phosphate") OR ("Phosphonic acid, P-[1-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]-, 1-[bis(2-chloroethoxy)phosphinyl]ethyl 2-chloroethyl ester" OR "1-[Bis(2-chloroethoxy)phosphoryl]ethyl 2-

Database	Search String
	chloroethyl (1-{[(2-chloroethoxy)(2-chloroethyl)phosphoryl]oxy}ethyl)phosphonate (non-preferred name)" OR "4351-70-6" [EC/RN Number]OR "Phosgard c-22R") OR ("Tris(1,3-dichloropropan-2-yl) phosphite" OR "6749-73-1"OR "2-Propanol, 1,3-dichloro-, phosphite (3:1)" OR "Tris(2-chloro-1-(chloromethyl)ethyl) phosphite") OR ("Tris(2-chloroethyl) phosphite" OR "140-08-9"OR "Ethanol, 2-chloro-, phosphite (3:1)" OR "Ethanol, 2-chloro-, 1,1',1"-phosphite" OR "2-Chloroethanol phosphite (3:1)") OR ("2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-, 3,9-dioxide" OR "3,9-Bis[3-bromo-2,2-bis(bromomethyl)propoxy]-2,4,8,10-tetraoxa-3lambda~5~,9lambda~5~-diphosphaspiro[5.5]undecane-3,9-dion" OR "61090-89-9"OR "UASQAKNFTHVEDR-UHFFFAOYSA-N" OR "3,9-Bis(3-bromo-2,2-bis(bromomethyl)propoxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro(5.5)undecane 3,9-dioxide" OR "3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-2,4,8,10-tetraoxa-3") OR ("Bis(2,3-dibromopropyl) hydrogen phosphate" OR "5412-25-9"OR "1-Propanol, 2, 3- dibromo- , 1, 1'- (hydrogen phosphate)" OR "1-Propanol, 2,3-dibromo-, hydrogen phosphate" OR "Bis(2,3-dibromopropyl) phosphate" OR "NSC 3239" OR "bis(2,3-dibromopropyl) hydrogen phosphate" OR "Bis(2,3-dibromopropyl) phosphate") OR ("Tris(2,4,6-tribromophenyl) phosphate" OR "Phenol, 2,4,6-tribromo-, compd. with phosphoric acid (1:1)" OR "7046-64-2"OR "Phenol, 2,4,6-tribromo-, phosphate") OR ("Tris(2,3-dibromophenyl) phosphate" OR "49690-63-3") OR ("Bis(2-chloroethyl) vinylphosphonate" OR "Phosphonic acid, P-ethenyl-, bis(2-chloroethyl) ester" OR "115-98-0"OR "Vinifos" OR "Fyrol Bis beta") OR ("Bis(2-chloroethyl) 2-chloroethylphosphonate" OR "Bis(2-chloroethyl) (2-chloroethyl)phosphonate" OR "Phosphonic acid, P-(2-chloroethyl)-, bis(2-chloroethyl) ester" OR "6294-34-4"OR "Phosphonic acid, P-(2-chloroethyl)-, bis(2-chloroethyl) ester" OR "Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester" OR "Bis(2-Chloroethyl) (2-Chloroethyl)Phosphonate") OR ("Tris(tribromoneopentyl)phosphate" OR "Tris[3-bromo-2,2-bis(bromomethyl)propyl] phosphate" OR "19186-97-1"OR "TPB 3070" OR "1-Propanol, 3-bromo-2,2-bis(bromomethyl)-, 1,1',1"-phosphate" OR "Tris[2,2-bis(bromomethyl)-3-bromopropyl] phosphate") OR ("Tris(2,3-dibromopropyl) phosphate" OR "126-72-7"OR "TDBPP") OR ("dimethyl {[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]methyl}phosphonate" OR "Phosphonic acid, P-[[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]methyl]-, dimethyl ester" OR "1373346-90-7") OR "organophospate ester"))
Web of Science	TS=((("Bis(p-acryloxyethoxy)tetrabromobisphenol A" OR "{(Propane-2,2-diyl)bis[(2,6-dibromo-4,1-phenylene)oxy]ethane-2,1-diyl} diprop-2-enoate" OR "2-Propenoic acid, (1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy-2,1-ethanediyl] ester" OR "66710-97-2" OR "Tetrabromobisphenol A bis(2-hydroxyethyl) ether bis(acrylate)" OR "Tetrabromobisphenol A bis (2-hydroxyethyl)" OR "Ethoxylated Tetrabromo Bisphenol A Diacrylate" OR "TBBPA-BHEEBA") OR ("2,2',6,6'-Tetrachlorobisphenol A" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dichlorophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dichloro-" OR "79-95-8"OR "(4,4'-isopropylidenebis(2,6-dichlorophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dichloro-" OR "Tetrachloro bisphenol A" OR "Tetrachlorobisphenol A" OR "Tetrachlorodian" OR "79-95-8" OR "TCBPA") OR ("Tetrabromobisphenol A bis(2-hydroxyethyl) ether" OR "2,2'-{Propane-2,2-diylbis[(2,6-dibromo-4,1-phenylene)oxy]}di(ethan-1-ol)" OR "Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis-" OR "4162-45-2"OR "Ethanol, 2,2'-((1-methylethylidene)bis((2,6-dibromo-4,1-phenylene)oxy))bis-" OR "Fire guard 3600" OR "Tetrabromobisphenol-A-bisethoxylate" OR "2,2-Bis(3,5-dibromo-4-(2-hydroxyethoxy)phenyl)propane" OR "Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis-" OR "Ethoxylated tetrabromobisphenol A" OR "Tetrabromobisphenol A bis(ethoxylate)" OR "TBBPA-BHEE") OR ("Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)" OR "1,1'-(Propane-2,2-diyl)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)-" OR "21850-44-2"OR "TBBPA-DBPE" OR "1,1'-(Isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]" OR "Tetrabromobisphenol A dibromopropyl ether" OR "Tetrabromobisphenol A bis(dibromopropyl ether)" OR "TBBPA-BDBPE") OR

Database	Search String
	("Tetrabromobisphenol A diallyl ether" OR "1,1'-(Propane-2,2-diyl)bis{3,5-dibromo-4-[(prop-2-en-1-yl)oxy]benzene}" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-" OR "25327-89-3"OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)-" OR "1,1'-(1-Methylethylidene)bis(3,5-dibromo-4-(2-propenyloxy)benzene" OR "Pyroguard SR 319" OR "2,2-bis(3,5-Dibromo-4-allyloxyphenyl)propane" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-" OR "Propane, 2,2-bis(4-(allyloxy)-3,5-dibromophenyl)-" OR "2,2′,6,6′-Tetrabromobisphenol A diallyl ether" OR "TBBPA-BAE") OR ("3,3',5,5'-Tetrabromobisphenol A" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-" OR "79-94-7"OR "TBBPA" OR "Tetrabromobisphenol A") OR ("Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, 1,1'-diacetate" OR "(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) diacetate" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, diacetate" OR "33798-02-6"OR "4,4'-Isopropylidenebis(2,6-dibromophenyl) diacetate" OR "TBBPA-BOAc") OR ("2,2'-[(1-Methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxymethylene]]bis[oxirane]" OR "2,2'-{Propane-2,2-diylbis[(2,6-dibromo-4,1-phenylene)oxymethylene]}bis(oxirane" OR "Oxirane, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxymethylene]]bis-" OR "3072-84-2"OR "Tetrabromobisphenol A Diglycidyl Ether" OR "TBBPA-BGE") OR ("3,3',5,5'-Tetrabromobisphenol A bispropionate" OR "(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) dipropanoate" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, dipropanoate" OR "37419-42-4"OR "TBBPA-BP") OR (Tetrabromobisphenol A dimethyl ether OR "1,1'-(Propane-2,2-diyl)bis(3,5-dibromo-4-methoxybenzene)" OR "Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-methoxy-" OR "37853-61-5"OR "Benzene, 1, 1'- (1- methylethylidene) bis[3, 5- dibromo- 4- methoxy-" OR "1,1'-(1-Methylethylidene)bis[3,5-dibromo-4-methoxybenzene]" OR "2,2-Bis(3,5-dibromo-4-methoxyphenyl)propane" OR "Tetrabromobisphenol A methyl ether" OR "TBBPA-BME") OR ("(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) diprop-2-enoate" OR "2-Propenoic acid, (1-methylethylidene)bis-2,6-dibromo-4,1-phenylene ester" OR "55205-38-4"OR "2,2',6,6'-Tetrabromobisphenol A diacrylate" OR "Tetrabromobisphenol A diacrylate" OR "TBBPA-BA") OR ("1,1'-Oxybis[2,3,4,5,6-pentabromobenzene]" OR "1,1'-Oxybis(pentabromobenzene)" OR "Benzene, 1,1'-oxybis[2,3,4,5,6-pentabromo-" OR "1163-19-5"OR "Ether, bis(pentabromophenyl)" OR "Benzene, 1,1'-oxybis[2,3,4,5,6-pentabromo-" OR "Decabromodiphenyl oxide) 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether" OR "BDE-209" OR "DE-83R" OR "BDE 209") OR ("2,2',4,4',5,6'-Hexabromodiphenyl ether" OR "1,3,5-Tribromo-2-(2,4,5-tribromophenoxy)benzene" OR "Benzene, 1,3,5-tribromo-2-(2,4,5-tribromophenoxy)-" OR "207122-15-4"OR "BDE 154") OR ("1,2,3,4,5-Pentabromo-6-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,2,3,4,5-pentabromo-6-(2,4-dibromophenoxy)-" OR "189084-67-1") OR ("2,2',4,4',5,5'-Hexabromodiphenyl ether" OR "1,1'-Oxybis(2,4,5-tribromobenzene)" OR "Benzene, 1,1'-oxybis[2,4,5-tribromo-" OR "68631-49-2"OR "BDE 153") OR ("2,2',4,4',6-Pentabromodiphenyl ether" OR "1,3,5-Tribromo-2-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,3,5-tribromo-2-(2,4-dibromophenoxy)-" OR "189084-64-8"OR "BDE 100" OR "PBDE 100" OR "Benzene, 1,3,5-tribromo-2-(2,4-dibromophenoxy)-") OR ("2,4,4'-Tribromodiphenyl ether" OR "2,4-Dibromo-1-(4-bromophenoxy)benzene" OR "Benzene, 2,4-dibromo-1-(4-bromophenoxy)-" OR "41318-75-6"OR "2,4-Dibromo-1-(4-bromophenoxy)benzene" OR "Benzene, 2,4-dibromo-1-(4-bromophenoxy)-" OR "Ether, p-bromophenyl 2,4-dibromophenyl" OR "BDE 28" OR "PBDE 28") OR ("2,2',3,4,4',5',6-Heptabromodiphenyl ether") OR ("2,2',4,4'-Tetrabromodiphenyl ether" OR "1,1'-Oxybis(2,4-dibromobenzene)" OR "Benzene, 1,1'-oxybis[2,4-dibromo-" OR "5436-43-1"OR "BDE 47" OR "PBDE 47" OR "2,4-Dibromo-1-(2,4-dibromophenoxy)benzene" OR "bis(2,4-dibromophenyl) ether") OR ("Perbromo-1,4-diphenoxybenzene" OR "1,1'-[(2,3,5,6-Tetrabromo-1,4-phenylene)bis(oxy)]bis(pentabromobenzene)" OR "Benzene, 1,2,4,5-tetrabromo-3,6-bis(2,3,4,5,6-pentabromophenoxy)-" OR "58965-66-5"OR "Benzene, 1,2,4,5-tetrabromo-3,6-bis(2,3,4,5,6-pentabromophenoxy)-" OR "Tetradecabromo-1,4-diphenoxybenzene") OR ("Octabromodiphenyl ether" OR "32536-52-0"OR "Benzene, 1,1'-oxybis-, octabromo deriv." OR "DE-79") OR ("2,2',4,4',5-Pentabromodiphenyl ether" OR "1,2,4-Tribromo-5-(2,4-dibromophenoxy)benzene" OR "Benzene, 1,2,4-tribromo-5-(2,4-dibromophenoxy)-" OR "60348-60-9"OR "PBDE 99" OR "2,2',4,4',5-Pentabromodiphenyl oxide" OR "BDE 99" OR "BDE-99")

Database	Search String
	OR ("Pentabromodiphenyl ether" OR "32534-81-9"OR "Benzene, 1,1'-oxybis-, pentabromo deriv." OR "Bromkal G 1" OR "Pentabromodiphenyl oxide" OR "Saytex 125" OR "Oxyde de diphenyle, derive pentabrome" OR "diphenyl ether, pentabromo derivative" OR "Diphenylether, Pentabromderivat" OR "difenil eter, derivado pentabromado" OR "penta-BDE") OR ("diethyl (4,6-dichloro-1,3,5-triazin-2-yl)phosphonate" OR "Phosphonic acid, P-(4,6-dichloro-1,3,5-triazin-2-yl)-, diethyl ester" OR "114955-21-4") OR ("Phosphoric acid, 1,2-ethanediyl tetrakis(2-chloroethyl) ester" OR "Tetrakis(2-chloroethyl) ethane-1,2-diyl bis(phosphate)" OR "Phosphoric acid, tetrakis(2-chloroethyl) 1,2-ethanediyl ester" OR "33125-86-9"OR "Ethylene bis(bis(2-chloroethyl)phosphate)") OR ("Tris(2-chloropropyl) phosphate" OR "6145-73-9"OR "1-Propanol, 2-chloro-, phosphate (3:1)" OR "TCPP") OR ("Tris(2,3-dichloropropyl)phosphate" OR "Tris(2,3-dichloropropyl) phosphate" OR "78-43-3"OR "2,3-Dichloro-1-propanol phosphate") OR ("Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester" OR "2,2-Bis(chloromethyl)propane-1,3-diyl tetrakis(2-chloroethyl) bis(phosphate)" OR "38051-10-4"OR "Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester" OR "Phosphoric acid, P,P'-[2,2-bis(chloromethyl)-1,3-propanediyl] P,P,P',P'-tetrakis(2-chloroethyl) ester" OR "2,2-Bis(chloromethyl)-1,3-propanediyl bis(bis(2-chloroethyl) phosphate)") OR ("Tris(1,3-dichloro-2-propyl) phosphate" OR "13674-87-8"OR "2-Propanol, 1,3-dichloro-, phosphate (3:1)" OR "TDCPP" OR "Antiblaze 195" OR "Antiblaze WR 30LV" OR "CRP (fireproofing agent)" OR "Fyrol FR 2" OR "PF 38/3" OR "2-Propanol, 1,3-dichloro-, 2,2',2"-phosphate" OR "3PC-R" OR "FR 10" OR "Tris(1,3-dichloroisopropyl) phosphate" OR "Tris[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "tris[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "tris[2-chloro-1-chloromethyl)ethyl] phosphate" OR "Tris(1,3-dichloro-2-propyl)phosphate" OR "Tris (1,3-dichloroisopropyl)phosphate") OR ("2,2-Bis(bromomethyl)-3-chloropropyl bis[2-chloro-1-(chloromethyl)ethyl] phosphate" OR "2,2-Bis(bromomethyl)-3-chloropropyl bis(1,3-dichloropropan-2-yl) phosphate" OR "Phosphoric acid, 3-bromo-2-(bromomethyl)-2-(chloromethyl)propyl bis[2-chloro-1-(chloromethyl)ethyl] ester" OR "66108-37-0"OR "MC 984" OR "Bis(1,3-dichloro-2-propyl)-3-chloro-2,2-dibromomethyl-1-propyl phosphate" OR "K6UU3AT81T") OR ("Tris(2-chloroisopropyl)phosphate" OR "13674-84-5"OR ("TCPP NOT porphyrin") OR "2-Propanol, 1-chloro-, phosphate (3:1)" OR "Tris(1-chloro-2-propyl) phosphate" OR "Tris(2-chloro-1-methylethyl) phosphate") OR ("Tris(2-chloroethyl) phosphate" OR "115-96-8"OR "Ethanol, 2-chloro-, phosphate (3:1)" OR ("TCEP" NOT "phosphine") OR "Ethanol, 2-chloro-, 1,1',1"-phosphate" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Trichlorethyl phosphate" OR "2-Chloroethanol phosphate") OR ("Diethylene glycol bis[bis(2-chloroethyl)phosphate]" OR "Tetrakis(2-chloroethyl) oxydi(ethane-2,1-diyl) bis(phosphate)" OR "Phosphoric acid, tetrakis(2-chloroethyl) oxydi-2,1-ethanediyl ester" OR "53461-82-8"OR "Oxydiethylene tetrakis(2-chloroethyl) bisphosphate" OR "Diethylene glycol tetra(2-chloroethyl) phosphate") OR ("Phosphonic acid, P-[1-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]-, 1-[bis(2-chloroethoxy)phosphinyl]ethyl 2-chloroethyl ester" OR "1-[Bis(2-chloroethoxy)phosphoryl]ethyl 2-chloroethyl (1-{[(2-chloroethoxy)(2-chloroethyl)phosphoryl]oxy}ethyl)phosphonate (non-preferred name)" OR "4351-70-6" [EC/RN Number]OR "Phosgard c-22R") OR ("Tris(1,3-dichloropropan-2-yl) phosphite" OR "6749-73-1"OR "2-Propanol, 1,3-dichloro-, phosphite (3:1)" OR "Tris(2-chloro-1-(chloromethyl)ethyl) phosphite") OR ("Tris(2-chloroethyl) phosphite" OR "140-08-9"OR "Ethanol, 2-chloro-, phosphite (3:1)" OR "Ethanol, 2-chloro-, 1,1',1"-phosphite" OR "2-Chloroethanol phosphite (3:1)") OR ("2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-, 3,9-dioxide" OR "3,9-Bis[3-bromo-2,2-bis(bromomethyl)propoxy]-2,4,8,10-tetraoxa-3lambda~5~,9lambda~5~-diphosphaspiro[5.5]undecane-3,9-dion" OR "61090-89-9"OR "UASQAKNFTHVEDR-UHFFFAOYSA-N" OR "3,9-Bis(3-bromo-2,2-bis(bromomethyl)propoxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro(5.5)undecane 3,9-dioxide" OR "3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-2,4,8,10-tetraoxa-3") OR ("Bis(2,3-dibromopropyl) hydrogen phosphate" OR "5412-25-9"OR "1-Propanol, 2, 3- dibromo- , 1, 1'- (hydrogen phosphate)" OR "1-Propanol, 2,3-dibromo-, hydrogen phosphate" OR "Bis(2,3-dibromopropyl) phosphate" OR "NSC 3239" OR "bis(2,3-dibromopropyl) hydrogen phosphate" OR "Bis(2,3-dibromopropyl) phosphate") OR ("Tris(2,4,6-tribromophenyl) phosphate" OR "Phenol, 2,4,6-tribromo-, compd. with phosphoric acid (1:1)" OR

Database	Search String
	"7046-64-2"OR "Phenol, 2,4,6-tribromo-, phosphate") OR ("Tris(2,3-dibromophenyl) phosphate" OR "49690-63-3") OR ("Bis(2-chloroethyl) vinylphosphonate" OR "Phosphonic acid, P-ethenyl-, bis(2-chloroethyl) ester" OR "115-98-0"OR "Vinifos" OR "Fyrol Bis beta") OR ("Bis(2-chloroethyl) 2-chloroethylphosphonate" OR "Bis(2-chloroethyl) (2-chloroethyl)phosphonate" OR "Phosphonic acid, P-(2-chloroethyl)-, bis(2-chloroethyl) ester" OR "6294-34-4"OR "Phosphonic acid, P-(2-chloroethyl)-, bis(2-chloroethyl) ester" OR "Phosphonic acid, (2-chloroethyl)-, bis(2-chloroethyl) ester" OR "Bis(2-Chloroethyl) (2-Chloroethyl)Phosphonate") OR ("Tris(tribromoneopentyl)phosphate" OR "Tris[3-bromo-2,2-bis(bromomethyl)propyl] phosphate" OR "19186-97-1"OR "TPB 3070" OR "1-Propanol, 3-bromo-2,2-bis(bromomethyl)-, 1,1',1"-phosphate" OR "Tris[2,2-bis(bromomethyl)-3-bromopropyl] phosphate") OR ("Tris(2,3-dibromopropyl) phosphate" OR "126-72-7"OR "TDBPP") OR ("dimethyl {[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]methyl}phosphonate" OR "Phosphonic acid, P-[[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]methyl]-, dimethyl ester" OR "1373346-90-7") OR "organophospate ester"))

B2. Evaluation team

Evaluation teams are composed of federal staff and contractor staff. Procedures are in place to avoid actual or perceived conflicts of interest. Members of the evaluation team have experience or training in conducting literature searches and/or evaluating occupational and environmental epidemiology studies, animal toxicology studies, or mechanism studies.

Project Leader

Develops research concept, rationale, and framework; serves as a researcher:

- Suril S. Mehta, DrPH, NIEHS

Protocol authors

- Suril S. Mehta, DrPH, Ruth M. Lunn, DrPH, Whitney D. Arroyave, PhD, and Mona Sethi, PhD

Information specialist

Develop search terms, conduct literature searches, and manage literature (e.g., endnote libraries, HAWC uploads):

- Rachel Kalsch, ILS - an Inotiv Company

Scientific Researchers (Toxicologists and Epidemiologists)

Primary researchers

Screen and map literature, extract mechanistic data and human and animal cancer data, conduct study evaluation (bias assessment, study sensitivity), conduct qualitative evidence integration, or draft the monographs sections:

- Suril S. Mehta, DrPH, NIEHS (project lead, epidemiologist)
- Ruth M. Lunn, DrPH, NIEHS (epidemiologist)
- Whitney D. Arroyave, PhD, ILS – an Inotiv Company (epidemiologist)
- Stanley Atwood, MS, ILS (toxicologist, retired, no longer part of team)
- Danila Cuomo, PhD, ILS – an Inotiv Company (toxicologist, lead mechanistic studies)
- Sanford Garner, PhD, ILS (toxicologist, retired, no longer part of team)
- Alton Peters, MS, ILS – an Inotiv Company (exposure assessment)
- Mona Sethi, PhD, ILS – an Inotiv Company (toxicologist, lead animal studies)

Data visualization

Create data visualization in Tableau:

- Whitney D. Arroyave, PhD, ILS – an Inotiv Company
- Tracy Saunders, ILS – an Inotiv Company

Protocol Peer Reviewers

Reviewed draft protocol in December 2024 and their comments were used to produce February 2025 version:

- June Dunnick, PhD, NIEHS
- Arun Pandiri, PhD, NIEHS
- Kristen Ryan, PhD, NIEHS
- Kyla Taylor, PhD, NIEHS