

Report on Carcinogens Protocol: Methods for Preparing the Draft Report on Carcinogens Monograph on Organohalogen Flame Retardants

Part II: Evaluating Mechanistic Studies

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National Institute of Environmental Health Sciences
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3. Evaluating Mechanistic Evidence

Overall Objective, Organization, and Process

Overall Objective

To reach conclusions about the level of evidence of the carcinogenicity to one or more organohalogen flame retardant compounds (OFRs) from mechanistic studies based on the [RoC listing criteria](#).

As referenced in Section 1 of the OFR Protocol (see [Protocol](#)), these include chemicals from the three subgroups of OFRs: polyhalogenated bisphenol aliphatics and functionalized (PBAFs), polyhalogenated diphenyl ethers (PHDEs), and polyhalogenated organophosphates (PHOPs).

Protocol Organization

We note here and throughout the protocol that we are conducting distinct evaluations for select individual compounds identified during scoping, while grouping compounds by subclass (i.e., PBAF, PHDE, and PHOP subclasses) for organizational purposes. We will continue to group chemicals belonging to each subclass for organizational purposes but acknowledge that these are different compounds.

As mentioned below, our overall goal is to conduct cancer hazard evaluations on OFR subclasses (rather than individual compounds within an OFR subclass). We will publish a forthcoming read-across strategy to evaluate data-poor compounds within an OFR subclass.

Sections of Protocol

The first section (Section 3.1) details our overall process, framework development (including identification and selection of relevant literature, Section 3.1.1), and general scoping and follow-up questions that apply to all OFR compounds in all subclasses (Section 3.1.2).

Subsequently, we provide subclass-specific scoping results organized by the PBAF subclass (Section 3.1.3), PHDE subclass (Section 3.1.4), and PHOP subclass (Section 3.1.5). Within each subclass-specific scoping results section, we provide interactive systematic evidence maps, organized by select Key Characteristics of Carcinogens (KCCs) and scoping results to help identify individual compounds with mechanistic data to pursue an evaluation. Within the PBAF and PHDE sections, we also detail proposed mechanisms of action (MOAs) identified through our scoping. In addition, each section identifies influential questions and influential literature that will help guide us through our fit-for-purpose, compound-specific evaluation.

Section 3.2 provides an overview of the studies being evaluated, as well as study informativeness questions that will guide systematic reviewers during their critical evaluation of individual studies. Section 3.3 describes our process for evaluating evidence from individual studies, and integrating evidence across studies and across

KCCs to reach a level of evidence conclusion of carcinogenicity from mechanistic evidence for each individual compound identified during scoping. Given that the approach to assessing study informativeness, evidence, and evidence integration applies to all compounds regardless of subclass, we will present these sections together.

Many of the mechanistic studies on OFRs evaluate not only individual compounds within a subclass, but mixtures of multiple compounds within a subclass. Our intention is to ultimately pursue a class-based cancer hazard evaluation, as suggested by the National Academy of Sciences (NAS) (2019). A first step, however, is to assess hazard from individual compounds based on the strength of the available mechanistic data. In absence of a current read-across strategy to evaluate multiple compounds within a subclass (which is forthcoming), we are approaching our hazard conclusions as providing judgements on individual compounds within one of the three identified subclasses.

In Section 3.4, we note that a forthcoming read-across strategy for our three OFR subclasses will be pursued. A read-across strategy will evaluate mechanistic data across compounds within a subclass, and we will use the data from our scoping of all compounds below to help inform this forthcoming strategy.

Overall Evaluation Process

The methods and strategies in this protocol come from the updated RoC Handbook (NTP 2025).

Briefly, the new methods use a fit-for-purpose approach that uses scoping activities (e.g., broad-based literature searches, iterative scoping questions, and evidence mapping) to develop the framework and identify key influential questions and corresponding literature (defined as study sets) to answer those questions (Figure 3-1). Key influential questions address scientific issues specific to the substance(s) under the evaluation that (1) are critical for understanding cancer mechanisms, biological plausibility, and human relevance, and (2) are most likely to impact the level-of-evidence (LoE) conclusions. The next step in the process is to conduct the study informativeness assessment. The rigor (depth) of the study informativeness assessment (see “Study Informativeness Assessment section in Figure 3-1) depends on how impactful the evidence is to the overall evaluation based on guidance outlined in the RoC Handbook. The overall LoE for carcinogenicity from mechanistic studies is reached by integrating confidence in the evidence across the database using a three-step process.

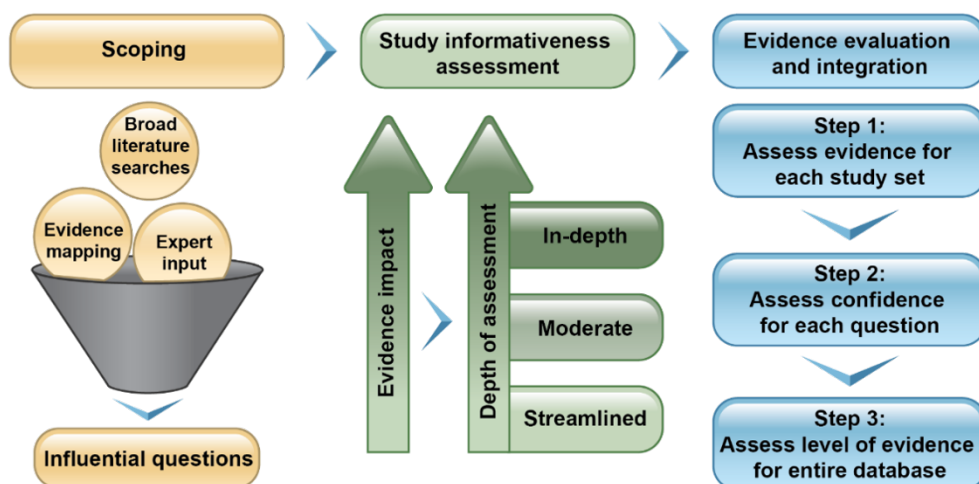


Figure 3-1. Fit-for-purpose evaluations to assess mechanistic evidence.

Key influential questions are identified from broad, unbiased literature searches. For each question, the relevant literature (e.g., multiple study sets) is identified and evaluated; the rigor (a streamlined to an in-depth level of assessment) of the study informativeness and evidence assessment depends on how impactful (e.g., low to high) a study set is to the overall evaluation. Each study set is defined by the type of evidence (e.g., exposed humans or animals, in vitro), exposure, comparison group, and endpoint (e.g., a specific biomarker or similar biomarkers). Lastly, we integrate the evidence across study sets to reach a confidence judgment for each question and across questions for an LoE conclusion.

3.1. Developing the Framework

Preliminary scoping and problem formulation activities informed the evaluation framework for the entire cancer hazard evaluation for OFRs (see Introduction Section of [Protocol](#)).

Scoping activities began with a review of authoritative reviews and other scientific information sources, and additional literature searches to gather mechanistic information for the substances and develop the initial EECO (Evidence stream, Exposure, Comparison Group, Outcome) statements for determining the LoE of carcinogenicity from mechanistic studies. Next, broad-based systematic literature searches, mapping the evidence from literature searches (e.g., by key characteristics of carcinogens [KCCs], evidence stream, or mode of action) and review of authoritative reports helped to identify the most influential mechanistic questions and literature.

3.1.1. Identifying and Selecting the Literature

We used the KCCs (Box 3-1) as a framework to organize and evaluate mechanistic evidence identified from broad literature searches. The KCCs were developed by an International Agency for Research on Cancer (IARC) working group (Smith et al. 2016; Guyton et al. 2018; Smith et al. 2020) to provide an unbiased framework to identify and organize relevant literature on carcinogenic mechanisms without relying on prespecified modes of action in isolation. Note that the RoC has broadened the KCC “induces chronic inflammation” to include “or immune activation”.

A mode or mechanism of action (MoA) includes the sequence of obligatory (key) biological events from cellular interaction with the chemical to a functional or biological effect within a living system (Kienzler et al. 2017). These include a molecular initiating event (MIE) and subsequent key events (KEs). As per our 2025 RoC Handbook, our literature searching by KCC may also identify any relevant proposed MoAs for any of the compounds within the three subclasses. Searches using the KCCs may serve as providing relevant information for steps within a proposed MOA. Please see an expanded discussion of MOAs in the 2025 RoC Handbook.

Biomedical citation databases, namely PubMed, Scopus, and Web of Science, were searched for mechanistic studies of exposure to OFRs by combining search terms for the exposure (see Appendix A) and KCC or general mechanistic terms (see RoC Handbook 2025). We also searched cited references.

In addition to biomedical citation databases, we evaluated authoritative sources for any relevant citations. These include:

- PBAF Subclass: [IARC](#) and [European Food Safety Authority \(EFSA\)](#) evaluations of tetrabromobisphenol A (TBBPA);
- PHOP Subclass: [U.S. Environmental Protection Agency \(EPA\) risk evaluation of tris\(2-chloroethyl\) phosphate \(TCEP\)](#) and California EPA hazard assessment of tris(1,3-dichloro-2-propyl) phosphate [TDCPP](#); and
- PHDE Subclass: [Agency for Toxic Substances and Disease Registry \(ATSDR\)](#), EPA, European Commission, and Health Canada evaluations for polybrominated diphenyl ethers (PBDEs).

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 are selected for possible inclusion in the

Box 3-1. Key Characteristics of Carcinogens

- KCC 1. Is electrophilic or can be metabolically activated to electrophiles
- KCC 2. Is genotoxic
- KCC 3. Alters DNA repair and causes genomic instability
- KCC 4. Induces epigenetic alterations
- KCC 5. Induces oxidative stress
- KCC 6. Induces chronic inflammation
- KCC 7. Is immunosuppressive
- KCC 8. Modulates receptor-mediated effects
- KCC 9. Causes immortalization
- KCC 10. Alters cell proliferation, cell death or nutrient supply

Source: (Smith et al. 2016; Smith et al. 2020)

evaluation if they meet the following EECO statement (Table 3-1). This EECO applies to all subclasses.

Table 3-1. Initial EECO statement

Evidence stream	Exposure	Comparison group	Outcome
Exposed humans	One or more OFRs	Low or no exposure to one or more OFRs	All KCCs (biomarkers and indicators)
Experimental animals (all species)	One or more OFRs	Low or no exposure to one or more OFRs	All KCCs
<i>In vitro</i> (or cell free)	One or more OFRs	Low or no exposure to one or more OFRs	All KCCs MoA or AoP

AoP = adverse outcome pathway; EECO = evidence stream, exposure, comparison group, outcome statement; KCC = key characteristics of carcinogens; MOA = mechanism of action; OFR = organohalogen flame retardant.

3.1.2. Overall Scoping Questions

Based on initial review of the selected studies and tagging, a review of authoritative literature, and of the available human cancer and animal cancer data, we developed primary scoping questions and additional guiding questions to identify the key influential mechanistic questions and evidence needed for evaluations and inform protocol development.

Primary scoping questions

- What are the proposed mechanisms by which OFRs are associated with cancer?
- What biological effects have an adequate database for review?

Additional guiding questions

- Which OFR compounds within each subclass have an adequate database of literature for an evaluation?
- Which KCC or KCCs, relevant to specific OFR compounds within each subclass, have an adequate database of literature for an evaluation?
- What types of evidence (evidence stream [e.g., experimental animal, exposed human], exposure variable, biomarkers evaluated) are available for each KCC?
 - What evidence streams should be evaluated (e.g., human, animal, in vitro)?
 - Which evidence streams are more influential for the review?
- What are the results (e.g., is a compound within an OFR subclass positively associated with genotoxicity, oxidative stress, chronic inflammation, immune modulation, receptor-mediated effects, altered cell proliferation)?

Note that these primary and additional scoping questions apply to compounds in all three OFR subclasses. In the following sections, we provide scoping results specific to compounds within each subclass.

3.1.3. Scoping Results: PBAF Subclass

We searched the mechanistic literature for the 11 compounds identified by the National Academy of Sciences (NAS 2019) that comprise the PBAF subclass. These include PBAF compounds tetrabromobisphenol A (TBBPA) and nine additional compounds where TBBPA is the base compound (i.e., TBBPA-BHEE, TBBPA-DBPE), as well as a chlorinated TBBPA analogue, tetrachlorobisphenol A (TCBPA). Apart from TBBPA, the database for TCBPA and the other TBBPA compounds with a functional group added are less commonly researched.

Systematic Evidence Mapping of KCCs

Below is an overall systematic evidence map of PBAF mechanistic studies with data subtypes for each KCC by evidence stream (Figure 3-2). We conducted a phased approach for PBAFs, starting with a search for all mechanistic data on all PBAF compounds. For TBBPA specifically, we tagged if studies were additionally evaluated in the IARC publication of TBBPA mechanistic data (IARC 2018). The purpose of this additional tagging was to determine whether additional mechanistic studies, if any, were conducted since IARC's TBBPA publication.

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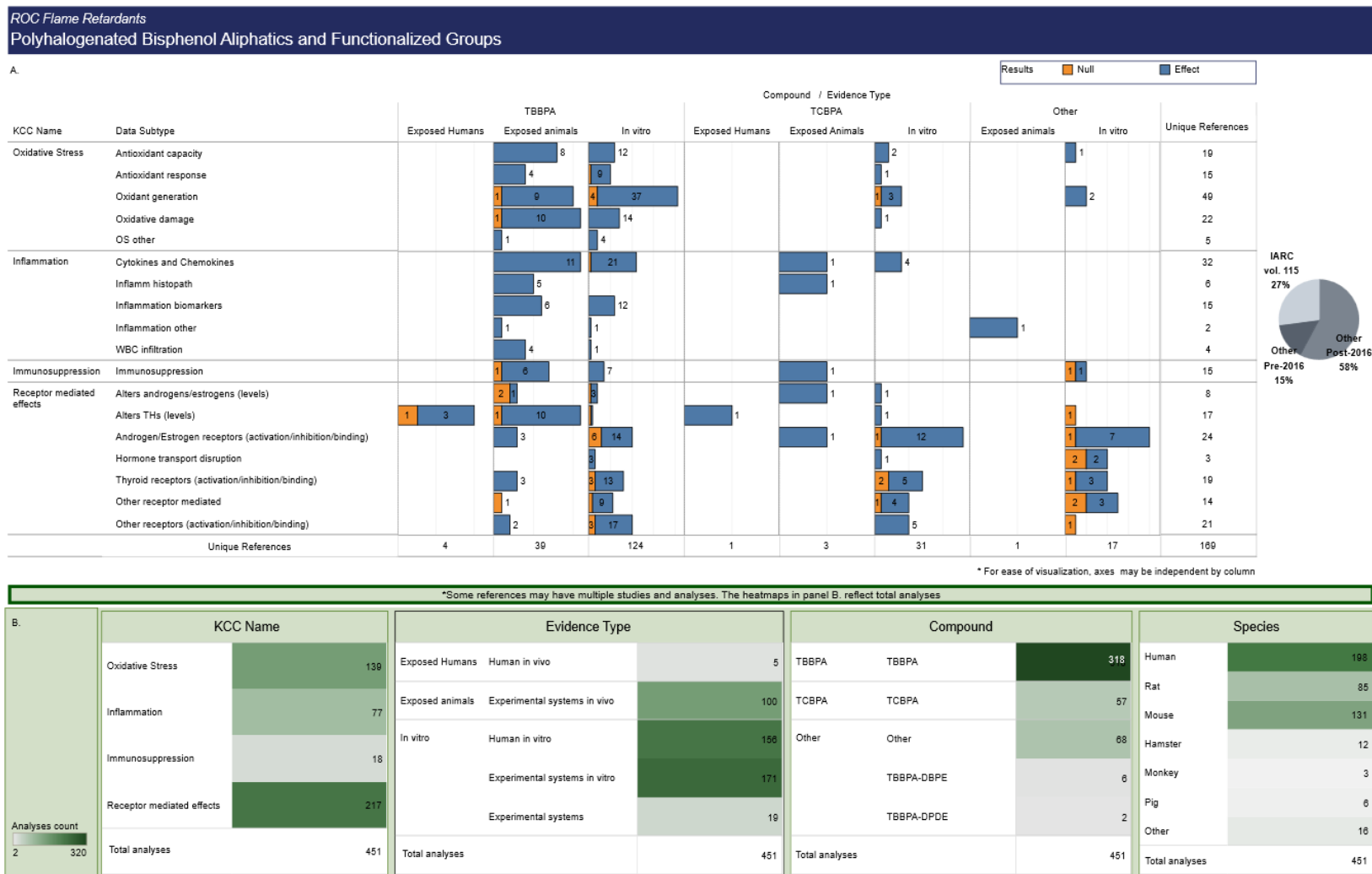


Figure 3-2. Systematic evidence map (SEM) of mechanistic studies of PBAFs, organized by select KCCs and evidence stream ([Evidence Map](#)).

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This SEM provides an overview of mechanistic data for TBBPA, TCPBA, and the nine other compounds in the PBAF subclass. In Section A (above), the rows depict the type of effect, organized by select KCC and KCC subtype. The columns, organized by compound, depict the number of studies by evidence type (exposed animal, exposed human, or in vitro). The bar charts in the SEM depict the number of unique references that show an effect or a null effect. In our evidence map, we indicate whether an effect or null result was reported. In this context for the purposes of our scoping exercise, an “effect” indicates that exposure to a chemical was associated with an effect on the outcome, regardless of direction (e.g., a negative or positive association). In Section B (below), we provide an analysis by key organizational bins of relevance, including KCC, evidence type, compound, and species. The linked and expanded SEM allows the user to interactively explore data by various topics, e.g., KCC, KCC biomarker type, PBAF compound, evidence type, species, and if study was included in IARC (2018), by selecting on table elements or using filters seen below.

Overall, 183 PBAF studies were identified across all KCCs (Figure 3-2). The majority were studies on TBBPA (N=171), with a substantially smaller number of publications for TCBPA (N=34, mostly in vitro studies) and other compounds in the PBAF subclass (N=20, mostly in vitro studies). Across all compounds, in vitro studies represented the largest proportion of evidence type (N=143), followed by exposed animals (N=47) and exposed humans (N=5). An initial screen of the study results indicated an effect was detected for most studies.

Focusing on just TBBPA, the compound with the most evidence, most studies reported on PBAFs and biomarkers of oxidative stress, chronic inflammation, immunosuppression, receptor-mediated effects, and cell proliferation/cell death. Most studies were exposed animals, human in vitro, and non-human in vitro studies. Notably, KCCs identified as “weak” or “moderate” by IARC (2018) include 4 additional studies on DNA damage and 17 additional studies on inflammation. Given the lack of additional influential data on genotoxicity (i.e., only in vitro DNA damage studies available), we will not evaluate this KCC for TBBPA. The additional studies on chronic inflammation, however, warrant further evaluation.

Modes/mechanisms of action (MOA) or adverse outcome pathways (AOPs) for PBAFs

Our search also identified multiple hypothesized MOAs for TBBPA and cancer, including induction of uterine tumors via inhibition of estrogen sulfotransferases and disruption of the thyroid hormone homeostasis leading to thyroid tumors (Lai et al. 2015). Of these two proposed MOAs, only the former (uterine tumor induction) also has two-year animal bioassay data. Given this, we detail the proposed MOA for TBBPA and uterine tumors below.

Proposed MOA for TBBPA in the induction of uterine tumors in female rats via inhibition of estrogen sulfotransferases

In addition to our scoping of studies by KCCs, we identified five studies proposing a MOA for TBBPA-induced uterine tumors observed in female rat bioassay results (Dunnick et al. 2015; Lai et al. 2015; Borghoff et al. 2016; Sanders et al. 2016; Wikoff et al. 2016). The proposed MOA involves an indirect pathway in which enzyme inhibition causes an increase in estrogen hormone levels in the uterus, leading to cell proliferation and ultimately tumor growth (Figure 3-3).

High circulating levels of unbound estrogen hormones is one of the strongest predictors for the development of uterine tumors in humans (Felix and Brinton 2018). Under normal phase II metabolism, conjugation of endogenous estrogen occurs via sulfation and glucuronidation, thereby reducing estrogen activity and contributing to their excretion. For example, serum estradiol forms estradiol sulfate by binding with a sulfate group, allowing for both estrogen inactivation and for excretion of the now conjugated estradiol sulfate. This process helps regulate estrogen homeostasis and tumor development.

The proposed molecular initiating event (MIE) for TBBPA involves the inhibition of the sulfation of estradiol via competitive binding to enzymes including estrogen sulfotransferase (SULT1E1). Specifically, TBBPA binds to estrogen sulfotransferase in the same location as estradiol. This, in turn, prevents estradiol sulfation and leads to an

increase in bioavailable unconjugated estradiol in uterine tissue. Long-lasting bioactive estrogen hormones overstimulate estrogen receptors and change gene expression linked to estrogen function and cell growth. This may lead to increased cell proliferation in uterine tissue, hyperplasia, and, ultimately, tumor formation.

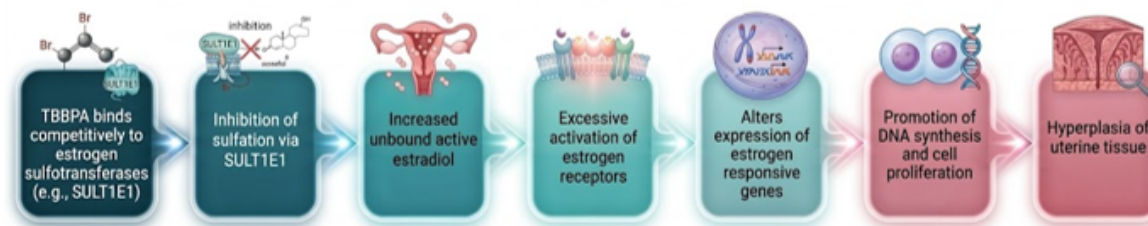


Figure 3-3. Overview of proposed MOA for TBBPA-induced uterine tumors via indirect pathway of estrogen hormone enzyme inhibition (made with Google Gemini).

This causal diagram describes a hypothesized MOA for TBBPA exposure leading to uterine cancer via competitive binding of estrogen sulfotransferases, leading to excess estrogen in uterine tissue.

Overall, the relevant steps for this evaluation include:

- MIE: TBBPA is competitively binding with sulfotransferases
- Key Event (KE)1: Increase in unbound estrogen in uterine tissue
- KE2: Unbound estrogen excessively activates estrogen receptors in uterine tissue
- KE3: Bioavailable estrogen changes gene expression linked to estrogen function and cell growth
- KE4: Promotion of DNA synthesis and cell proliferation
- KE5: Hyperplasia of uterine tissue

Identification of PBAF compounds for further evaluation

Of the 11 compounds identified, only TBBPA had a substantial literature database to evaluate. The other 10 compounds, including TCBPA and TBBPA compounds with additional functional groups, did not each have enough of a study database to individually evaluate. This information, however, may be informative for pursuing a read-across approach to listing chemicals within the PBAF subclass.

As such, all information below, including identification of influential questions, study informativeness, and conclusions on mechanistic data will apply only to TBBPA.

Key influential questions and literature, and study sets for influential questions for TBBPA

Based on our scoping of existing literature, we have identified key influential questions pertinent to evaluating relevant mechanisms for TBBPA. Additionally, we have outlined corresponding evidence that will be able to answer these questions (i.e., study sets).

KCC-specific influential questions and literature

- What is the confidence that TBBPA is causing oxidative stress? What oxidative stress biomarkers have the strongest evidence?

- What is the confidence that TBBPA is causing chronic inflammation? What chronic inflammation biomarkers have the strongest evidence?
- What is the confidence that TBBPA is causing immunosuppression? What immunosuppression biomarkers have the strongest evidence?
- What is the confidence that TBBPA modulates receptor-mediated effects?
 - What is the confidence that TBBPA causes thyroid hormone disruption, and which biomarkers have the strongest evidence?
 - What is the confidence that TBBPA is estrogenic or androgenic/anti-androgenic and which biomarkers have the strongest evidence?

The studies associated with each specific question are available in the interactive map by filtering on the specific KCC and evidence stream ([Evidence Map](#)). To streamline our process, we may choose to use the text descriptions of studies described by IARC (2018) for select KCCs that saw an overwhelming effect (i.e., oxidative stress, immunosuppression, receptor-mediated effects) to independently evaluate and apply our own judgement and RoC criteria. We will also incorporate any new studies or studies not described by IARC.

Table 3-2. Final EECO for mechanistic studies of TBBPA

Evidence type	Exposure	Outcome
Exposed humans (influential)	TBBPA exposure biomarkers (serum thyroid)	Q1. Oxidative stress: Oxidants generation, antioxidant status, antioxidant response, oxidative damage, redox sensitive pathways; studies primarily in experimental animals
Experimental animals (influential)	TBBPA exposure	
In vitro (or cell-free) Streamlined data extraction	TBBPA exposure	Q2. Inflammation effects: Inflammation biomarkers like pro-inflammatory cytokines, WBCs and subsets; histopathology (inflammation); studies primarily in experimental animals Q3: Immunosuppressive effects: Increased viral infection, impaired immune function (decreased NK cell activity); studies in experimental animals Q4: Receptor-mediated effects: Thyroid hormone disruption; estrogenic, androgenic, anti-androgenic effects; studies in exposed humans and animals

MOA-specific influential questions and literature

Regarding the proposed MOA, we have identified influential questions for the proposed MOA individually. See below:

Overall: What is the confidence that TBBPA is inhibiting estrogen conjugation by binding with sulfotransferases, leading to an increase in bioavailable unconjugated estrogen in uterine tissue which increases risk of hyperplasia?

- Does TBBPA bind to and activate sulfotransferases?
- Does TBBPA inhibit enzyme activity by altering estrogen hormones availability or metabolism?
- Is TBBPA associated with estrogen receptor activation and changes in estrogen-related gene expression?
- Does TBBPA increase hyperplasia in uterine tissue?

The study sets or EECO for each question are below for the identified KCCs and for the proposed MOA (Table 3-2).

For the MOA of TBBPA and uterine tumors, relevant literature for each step of the MOA are as follows:

- MIE - TBBPA binding and activation to sulfotransferases: (a) in vitro TBBPA studies on competitive binding potential and/or inhibition of enzyme estrogen sulfotransferases, (b) exposed animal and in vitro saturation of conjugated TBBPA sulfate.
- KE - TBBPA indirectly increasing unconjugated estrogen hormones/reducing estrogen hormone sulfation: In vitro and in vivo animal studies, measured indirectly via estrogen concentrations (note: assays measuring ratios of conjugated vs. unconjugated estrogen is limited)
- KE - TBBPA associated with estrogen receptor activation and changes in estrogen-related gene expression: In vitro and in vivo transcriptomics studies.
- KE - TBBPA increasing hyperplasia in uterine tissue: Exposed animal experimental studies evaluating pathology (cell proliferation in endometrial cells) and physiological change in uterine tissue (e.g., uterine weight, hyperplasia).

3.1.4. Scoping Results: PHDE Subclass

NAS (2019) identified 12 compounds in the PHDE subclass. These include common polybrominated diphenyl ether (PBDE) congeners including PBDE-47, PBDE-99, PBDE-100, PBDE-153, PBDE-154, and PBDE-209. For ease of interpretation, we have grouped brominated PHDEs (i.e., PBDEs) by number of bromines, i.e., mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and deca-BDE. Each bromine grouping contains one or more PBDE congeners represented by one CASRN (e.g., BDE-40 to BDE-81 all encompass tetraBDE, with a CASRN 40088-47-9; please see [Table 4-1](#) of ATSDR 2017).

Of these groupings, tetraBDE, pentaBDE, and decaBDE are the compounds most identified in the literature. Often, but not always, there is co-occurrence of multiple PBDE congeners across congener groupings to commercial mixtures, debromination of higher brominated PBDEs, or environmental sources. Matrices for evaluating these compounds, including environmental and biological samples, often yields mixtures of these compounds. Therefore, we have also included in our scoping an evaluation of PBDE mixtures. For pentabromodiphenyl ether (pentaBDE), our SEM has also included DE-71, a pentabromodiphenyl ether technical grade mixture, given this product also has been evaluated as a 2-year cancer bioassay.

Apart from brominated PHDEs, the subclass also contains polychlorinated diphenyl ethers (PCDEs), which are less commonly researched. We group all PCDEs across congener groupings together given the low frequency of studies. We note that although metabolites of these compounds (e.g., hydroxylated PBDE metabolites) are frequently evaluated as exposure biomarkers of PHDE exposure to study KCC-related effects, we are focusing this evaluation on parent PHDE compounds only and using metabolite studies as exposure proxies/indicators to parent compounds.

Systematic Evidence Mapping of KCCs

Below is an overall systematic evidence map of PHDE mechanistic studies with data subtypes for select KCC by evidence stream (Figure 3-4).

Our scoping identified >450 studies evaluating one or more PHDE compounds and one or more of the ten KCCs. In Figure 3-4 below, we present select KCCs with the most data. TetraBDE (N=215), pentaBDE/pentaBDE mixture (N=178), and decaBDE (N=146) were the PBDE congener groups most represented in the database. Across the other six PBDE congener groups, there were 116 studies, and there were 101 mixtures studies. There was a much lower number of studies measuring chlorinated PHDEs (i.e., PCDE, N=9). KCCs with the highest frequency of studies include modulation of receptor-mediated effects (N=295), chronic inflammation (N=69), oxidative stress (N=102), and genotoxicity/altered DNA repair (N=45). All evidence stream types were represented, though most studies were in exposed experimental animals (N=201) and human in vitro studies (N=104). Observational biomarker studies in both exposed humans and exposed animals were largely relegated to evaluating receptor-mediated effects. There were 195 in vitro studies, most of which were evaluating oxidative stress and receptor mediated effects.

Preliminary scoping suggests studies reported an effect for exposure to PBDEs and biomarkers of oxidative stress and inflammation, with a greater proportion of the overall evidence for each KCC in exposed animals.

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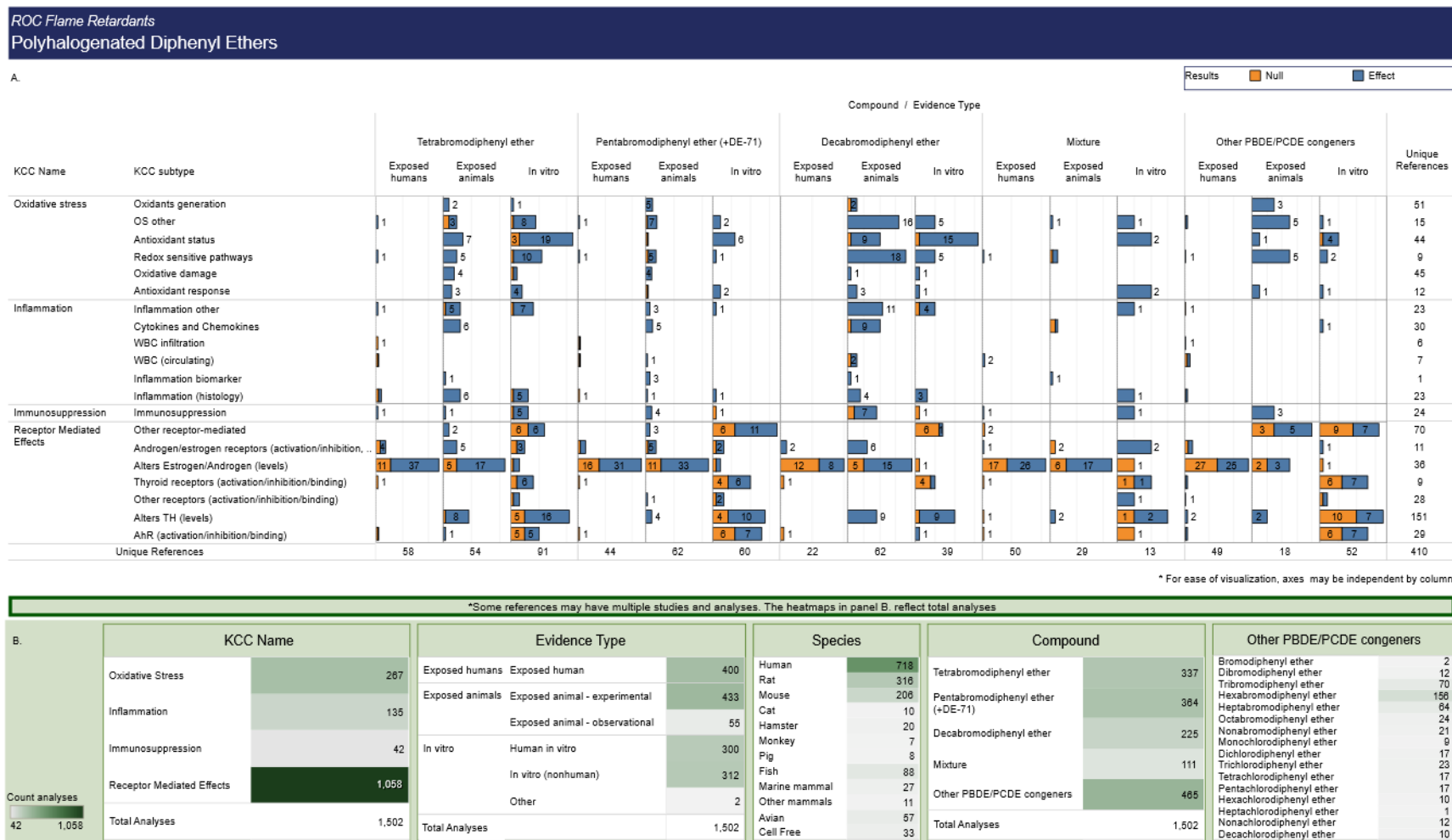


Figure 3-4. Systematic evidence map of PHDEs and priority KCCs, organized by data subtype for select KCCs with sufficient data (Evidence Map).

RoC Protocol: Mechanistic Studies of Organohalogen Flame Retardants

This SEM provides an overview of mechanistic data for tetrabromodiphenyl ether, pentabromodiphenyl ether and pentabromodiphenyl ether mixtures (e.g., DE-71), decabromodiphenyl ether, other PBDE and PCDE congeners in the PHDE subclass, and mixtures of PHDEs. In Section A (above), the rows depict the type of effect, organized by KCC and KCC subtype. The columns, organized by compound, depict the number of studies by evidence type (exposed animal, exposed human, or in vitro). The bar charts in the SEM depict the number of unique references that show an effect or a null effect. In our evidence map, we indicate whether an effect or null result was reported. In this context for the purposes of our scoping exercise, an “effect” indicates that exposure to a chemical was associated with an effect on the outcome, regardless of direction (e.g., a negative or positive association). In Section B (below), we provide an analysis by key organizational bins of relevance, including KCC, evidence type, compound, and species. The online interactive SEM allows the user to explore data by various topics, e.g., KCC, KCC biomarker type, PHDE compound, evidence type, and species, by selecting on table elements or using filters seen below

Modes/mechanisms of action (MOA) or adverse outcome pathways (AOPs) for PHDEs

Our search identified multiple hypothesized MOAs for PHDEs and cancer, most commonly disruption of the thyroid hormone (TH) homeostasis leading to thyroid tumors (Zhang et al. 2009). In determining which, if any, hypothesized MOAs or AOPs to pursue, the addition of tumor endpoint data from animal cancer and/or human cancer epidemiology studies adds an additional data point to evaluate. Given data on thyroid tumors is available from both an experimental animal cancer study and human cancer epidemiology studies, we plan to evaluate this hypothesized MOA, as detailed below.

Proposed mode of action (MOA) for PBDE-induced thyroid tumor induction via thyroid hormone disruption

A hypothesized MOA for PBDE exposure inducing thyroid tumors via thyroid hormone disruption has been suggested (Zhang et al. 2008; Gorini et al. 2018; Wang et al. 2023). Specifically, disruption of the hypothalamic-pituitary-thyroid (HPT) axis results in a sustained decrease in circulating TH concentrations, including thyroxine (T4), which can lead to an increase in hypertrophy and hyperplasia in thyroid tissue (Figure 3-5).

Prolonged decrease in thyroid hormones has been associated with hyperplasia in rodents and has been suggested in humans. In normally functioning mammals, the hypothalamic-pituitary-thyroid (HPT) axis highly regulates thyroid hormone homeostasis via a feedback loop. In particular, the hypothalamus releases thyrotropin-releasing hormone (TRH), which encourages secretion of thyroid stimulating hormone (TSH) in the pituitary gland, which increases production of triiodothyronine (T3) and T4 in the thyroid gland. Thyroid hormones are excreted via the kidneys and bile duct through phase II metabolism. Enzymatic conjugation of T3 and T4 is done by adding glucuronic acid (via UDP-glucuronosyltransferases) and/or a sulfate group (via sulfotransferases) to create a water-soluble compound that can be excreted. Transthyretin (TTR) and thyroxine binding globulin (TBG) are serum carrier proteins that bind and transport circulating T3 and T4, allowing for prevention of conjugation and excretion of thyroid hormones. When there is an increase in circulating thyroid hormones, negative feedback via the inhibition of TRH and TSH regulate further release of T3 and T4, allowing for homeostasis to occur.

As part of phase I oxidative biotransformation via cytochrome p450 enzyme catalysis, PBDEs are metabolized by adding a hydroxyl group to the aromatic phenyl ring of PBDEs to form hydroxylated PBDEs (OH-PBDEs). These metabolites are more biologically active and may disrupt the endocrine system. Importantly, these OH-PBDEs are structurally similar to endogenous thyroid hormones in the body, acting as competitors. In phase II metabolism, enzymatic conjugation of OH-PBDEs occurs by adding glucuronic acid and/or a sulfate group for elimination.

The proposed MIE for PBDEs involves mechanisms that can increase thyroid hormone clearance and decrease circulating thyroid hormones. PBDEs can induce UDP-glucuronosyltransferases in the liver, increasing glucuronidation of T4 for hepatic clearance. Additionally, OH-PBDEs can competitively bind to TTR, which can potentially increase the availability of serum T4 to undergo conjugation and elimination.

When elimination of conjugated T4 exceeds the rate of T4 synthesis, circulating concentrations of T4 decrease. This, in turn, activates the feedback loop of the HPT axis. Namely, the hypothalamus increases thyrotropin releasing hormone (TRH), and the pituitary gland increases secretion TSH. Elevated TSH activates TSH receptors in thyroid follicular epithelial cells, leading to cell proliferation. Sustained cell proliferation in thyroid cells can lead to hyperplasia of thyroid tissue, leading to thyroid cancer.

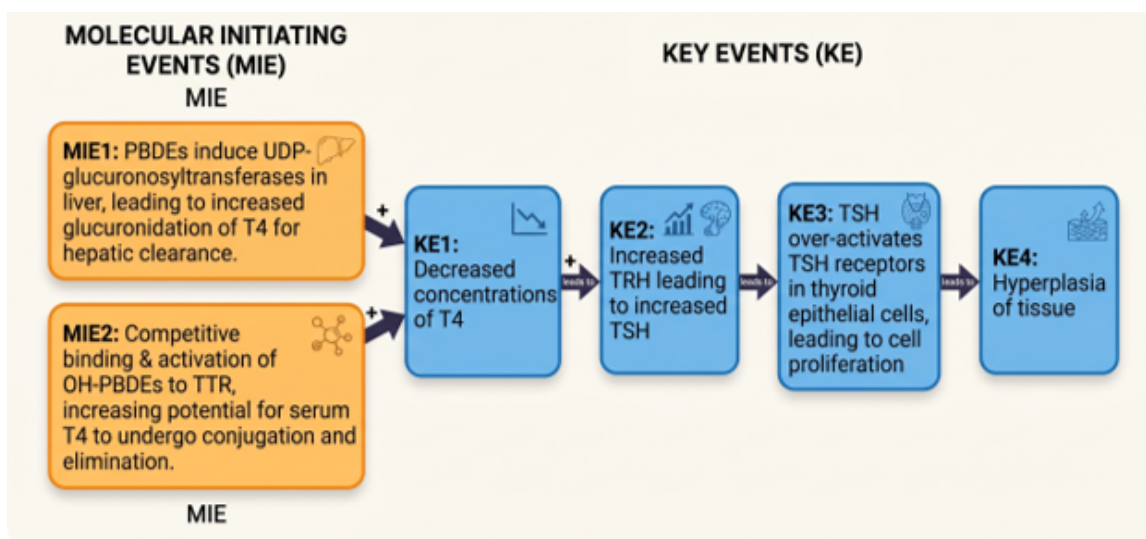


Figure 3-5. Overview of proposed MOA for PBDEs and thyroid tumors via thyroid hormone disruption (made with Google Gemini).

This causal diagram describes a hypothesized MOA for PBDE exposure leading to thyroid cancer via disruption of the body's thyroid hormone regulatory system. The proposed MOA includes two parallel MIEs and four KEs.

Overall, the relevant steps for this evaluation include:

- MIE:
 - MIE1: PBDEs induce UDP-glucuronosyltransferases in the liver which lead to increase in glucuronidation of T4 for hepatic clearance
 - MIE2: Competitive binding and activation of OH-PBDEs to TTR, which increases the potential for serum T4 to undergo conjugation and elimination.
- KE1: Decreased concentrations of T4
- KE2: Increased TRH leading to increased TSH
- KE3: TSH over-activates TSH receptors in thyroid follicular epithelial cells, leading to cell proliferation
- KE4: Hyperplasia of tissue

Identification of PHDE compounds for further evaluation

Of the 12 compounds identified in the PHDE subclass, only PBDEs had a substantial literature database to evaluate. Specifically, of the PBDEs, only the PBDE congeners represented by tetraBDE, pentaBDE, and decaBDE have substantial evidence to evaluate. Apart from the brominated PHDEs, the chlorinated PHDE compound PCDE did not each

have enough of a study database to individually evaluate this compound. This information, however, may be informative to pursuing a read-across approach to listing chemicals within the PHDE subclass. Similarly, evaluating PBDE mixture studies may help inform a class-based approach in a forthcoming read-across strategy, but out of scope for this section.

As such, all information below, including identification of influential questions, study informativeness, and conclusions on mechanistic data will apply only to tetraBDE, pentaBDE, and decaBDE.

Key influential questions and literature, and study sets for influential questions for tetraBDE, pentaBDE, and decaBDE

Based on our scoping of existing literature, we have identified key influential questions pertinent to evaluating relevant mechanisms for tetraBDE, pentaBDE, and decaBDE. Additionally, we have outlined corresponding evidence that will be able to answer these questions (i.e., study sets).

- What is the confidence that PBDEs are causing oxidative stress? What oxidative stress biomarkers have the strongest evidence?
- What is the confidence that PBDEs are causing chronic inflammation? What chronic inflammation biomarkers have the strongest evidence?
- What is the confidence that tetraBDE, pentaBDE, and decaBDE cause receptor mediated effects (i.e, thyroid hormone, estrogenic or androgenic/anti-androgenic effects), and which biomarkers have the strongest evidence?

The studies associated with each specific question are available in the interactive map by filtering on the specific KCC subtype and evidence stream (Evidence Map). The study sets or EECO for each question are below for the identified KCCs (Table 3-3).

Table 3-3. Final EECO for mechanistic studies of PBDEs

Evidence type	Exposure	Outcome
Exposed humans (influential)	PBDE exposure biomarkers (serum thyroid, adipose tissue)	Q1. Oxidative stress: Oxidants generation, antioxidant status, antioxidant response, oxidative damage, redox sensitive pathways; studies primarily in experimental animals
Experimental animals (influential)	PBDE exposure	Q2. Inflammation effects: Inflammation biomarkers like pro-inflammatory cytokines, WBCs and subsets; histopathology (inflammation); studies primarily in experimental animals
<i>In vitro</i> (or cell-free) Streamlined data extraction	PBDE exposure	Q3: Receptor-mediated effects: Thyroid hormone disruption; estrogenic, androgenic, anti-androgenic effects; studies in exposed humans and animals

MOA-Specific Influential Questions and Literature

Regarding the proposed MOA, we have identified influential questions below.

What is the confidence that tetraBDE, pentaBDE, and/or decaBDE disrupt normal thyroid hormone functioning regulated by the hypothalamic-pituitary-thyroid (HPT) axis, resulting in a chronic decrease in circulating TH concentrations, including thyroxine (T4), leading ultimately to an increase in hypertrophy and hyperplasia?

- Do PBDEs induce UDP-glucuronosyltransferases in the liver?
- Do hydroxylated PBDEs competitively bind to TTR?
- Are PBDEs associated with a decrease in thyroid hormone concentrations, specifically T4?
- Are PBDEs associated with increased TRH and increased TSH?
- Are PBDEs associated with an over-activation of TSH receptors in thyroid follicular epithelial cells?
- Are PBDEs associated with hyperplasia in thyroid tissue?
- Are the thyroid hormone disruption effects seen in exposed animals relevant to humans?

For the MOA of tetraBDE, pentaBDE, and decaBDE and thyroid hormone disruption, relevant literature for each step of the MOA is as follows:

- MIE –
 - (a) PBDEs inducing hepatic enzymes (UDP-glucuronosyltransferases) leading to increased TH clearance: experimental animal and in vitro studies
 - (b) hydroxylated PBDEs competitive binding to TTR: experimental animal and in vitro studies
- KE1 - PBDEs decreasing thyroid hormone concentrations: exposed humans, experimental animal, and in vitro studies
- KE2 - PBDEs activating HPT axis (e.g., increased TRH, increased TSH): exposed humans, experimental animal, and in vitro studies (mostly will be TSH concentration studies)
- KE3 – Chronic thyroid follicular cell stimulation due to increased TSH: Exposed animal and in vitro studies
- KE4 – Thyroid follicular hyperplasia: Exposed animal studies

3.1.5. Scoping Results: PHOP Subclass

NAS (2019) identified 22 compounds in the PHOP subclass. Compounds with the most mechanistic studies include tris(2-chloroethyl) phosphate (TCEP), tris(chloropropyl) phosphate (TCPP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP), and tris(2,3-dibromopropyl) phosphate (TDBPP). We note that our scoping results exclude TDBPP as it has already been listed in the RoC as reasonably anticipated to be a human carcinogen. Other compounds in this subclass include bis(2,3-dibromopropyl) phosphate and bis(1,3-dichloro-2-propyl)-3-chloro-2,2-dibromomethyl-1-propyl phosphate. Given that TDCPP, TCPP, and TCEP often co-occur in environmental or biological media as a mixture of

chlorinated organophosphates, many studies evaluate the mixtures effect of these compounds.

Systematic Evidence Mapping of KCCs

Scoping results are available as an interactive systematic evidence map of PHOP mechanistic studies with data subtypes for select KCC by evidence stream (Figure 3-6).

Our scoping identified 77 publications evaluating one or more PHOP compounds across relevant KCCs. Most of the studies within this subclass were on TDCPP (N=47), TCEP (N=41), and TCPP (N=38). Apart from the three chlorinated organophosphates, there were few studies on other PHOP compounds or mixtures.

When examining each compound by evidence type, we identified that most studies were in exposed humans and in in vitro models. KCCs with at least some data included genotoxicity/altering DNA repair, oxidative stress, inflammation, and modulation of receptor-mediated effects. Among the studies of receptor-mediated effects, most are specific to thyroid, estrogen, and androgen hormone regulation. When stratifying by evidence stream, only modulation of receptor mediated effects had >8 studies in exposed humans and exposed animals.

RoC Protocol: Mechanistic Studies of Organohalogen Flame Retardants

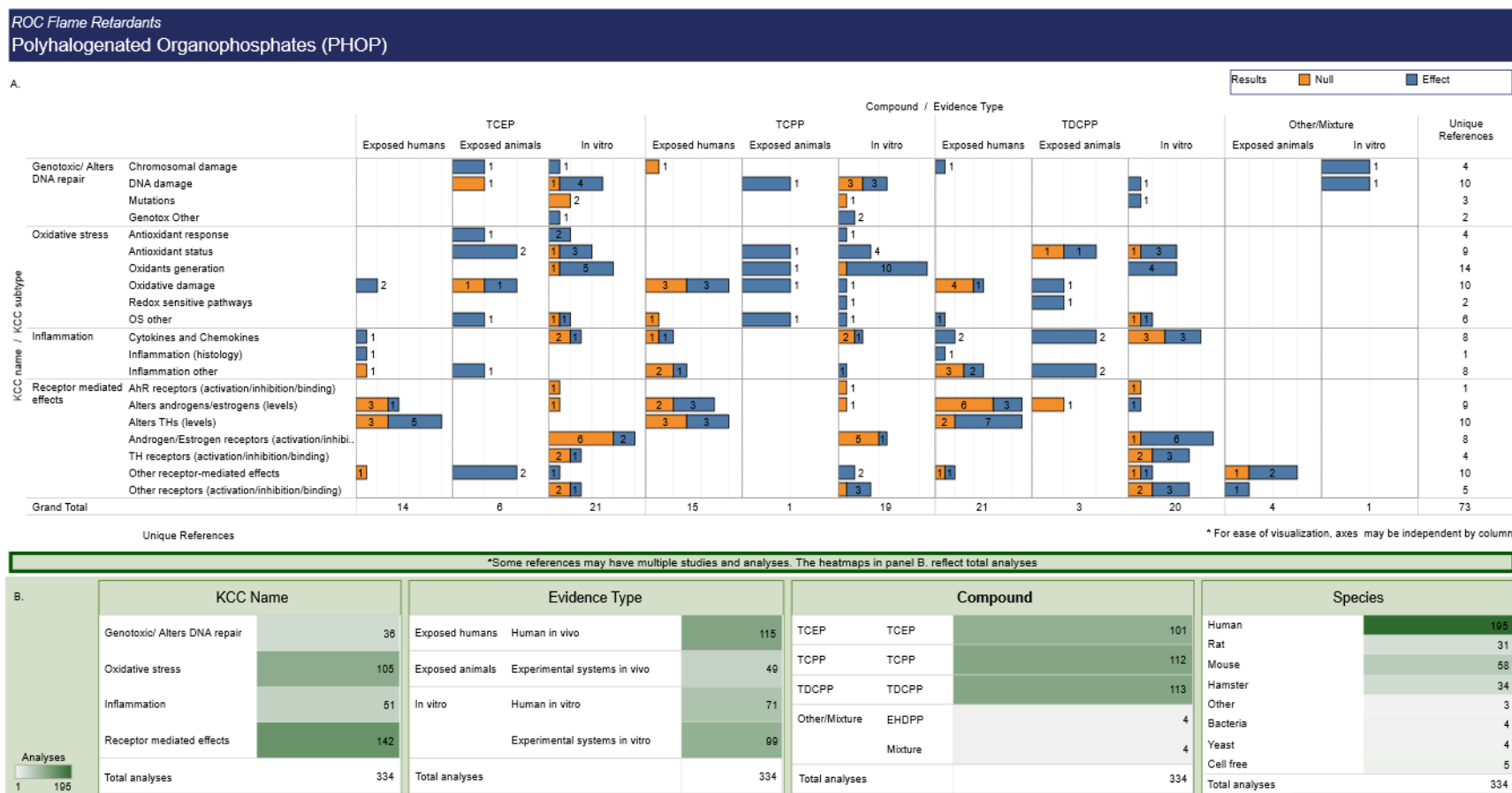


Figure 3-6. Systematic evidence map of PHOPs, organized by priority KCCs (Evidence Map).

This SEM provides an overview of mechanistic data for TCEP, TCPP, TDCPP, other PHOP compounds, and PHOP mixtures. In Section A (above), the rows depict the type of effect, organized by KCC and KCC subtype. The columns, organized by compound, depict the number of studies by evidence type (exposed animal, exposed human, or in vitro). The bar charts in the SEM depict the number of unique references that show an effect or a null effect. In our evidence map, we indicate whether an effect or null result was reported. In this context for the purposes of our scoping exercise, an “effect” indicates that exposure to a chemical was associated with an effect on the outcome, regardless of direction (e.g., a negative or positive association). In Section B (below), we provide an analysis by key organizational bins of relevance, including KCC, evidence type, compound,

RoC Protocol: Mechanistic Studies of Organohalogen Flame Retardants

and species. This interactive online SEM allows the user to explore data by various topics, e.g., KCC, KCC biomarker type, PHOP compound, evidence type, and species, by selecting on table elements or using filters seen below

Modes/mechanisms of action (MOA) or adverse outcome pathways (AOPs) for PHOPs

Our search did not find many publications outlining a consistent hypothesized MOA or AOP for one or more compounds in the PHOP subclass. Therefore, we are not pursuing an additional investigation of a proposed MOA/AOP for this subclass.

Identification of PHOP compounds for further evaluation

Of the 22 compounds identified in the PHOP subclass, only TCEP, TCPP, and TDCPP had a substantial literature database to evaluate (excluding TDBPP which has already been listed in the RoC). Other PHOP compounds did not individually have enough of a study database to evaluate. This information, however, may be informative to pursuing a read-across approach to listing chemicals within the PHOP subclass.

As such, all information below, including identification of influential questions, study informativeness, and conclusions on mechanistic data will apply only to TCPP, TCEP, and TDCPP.

Key influential questions and literature, and study sets for influential questions for TCPP, TCEP, and TDCPP

Based on our scoping of existing literature, we have identified key influential questions pertinent to only one KCC, receptor-mediated effects, to formally conduct a systematic evaluation for TCPP, TCEP, and TDCPP. Further, given that hormonal disruption appears to be a relevant characteristic across all OFRs evaluated, we will conduct a formal evaluation. Data on select other relevant KCCs will be summarized but not undergo a study informativeness evaluation as described in Section 1.2. We have outlined corresponding evidence that will be able to answer these questions (i.e., study sets).

- What is the confidence that TCPP, TCEP, or TDCPP cause thyroid hormone disruption, and which biomarkers that have the strongest evidence?
- What is the confidence that TCPP, TCEP, or TDCPP are estrogenic or androgenic/anti-androgenic and which biomarkers have the strongest evidence?

The studies associated with each specific question are available in the interactive map by filtering on the specific KCC subtype and evidence stream. The study sets or EECO for each question are below for the identified KCC (Table 3-4).

Table 3-4. Final EECO for mechanistic studies of TCEP, TCPP, and TDCPP

Evidence type	Exposure	Outcome
Exposed humans (influential)	TCEP, TCPP, TDCPP exposure biomarkers (serum, adipose tissue)	Q1: Receptor-mediated effects: Thyroid hormone disruption; studies in exposed humans and in vivo animals
Experimental animals (influential)	TCEP, TCPP, TDCPP exposure	
<i>In vitro</i> (or cell-free) Streamlined data extraction	TCEP, TCPP, TDCPP exposure	

3.2. Study Overview and Study Informativeness

As mentioned above, our study informativeness evaluation applies to all studies being evaluated across all OFRs identified. The study informativeness assessment primarily focuses on OFR studies in exposed humans and animals.

We evaluate the informativeness of mechanistic studies using a domain-based approach consisting of questions and guidance appropriate for the evidence type. For each question, we evaluate the potential for, direction of, and magnitude of the bias by comparing the study to an “ideal” study element specific to that bias (e.g., selection of participants). “Ideal” is defined as a study design condition resulting in low concern for bias or sufficient sensitivity to detect an effect if present. Outcome specific judgements (e.g., a study reporting on multiple outcomes) will have multiple judgements of that domain.

Two reviewers assess the studies and resolve differences through mutual discussion and reference to the original data source. To facilitate the review process and reduce ambiguity, we conduct a pilot phase using a small set of studies before proceeding with the complete evaluation. If reporting of the studies is too incomplete to evaluate bias, we will contact the study authors for additional details.

While in vitro studies were not identified as influential literature initially, they will still be reviewed as part of the mechanistic evaluation. Should the strength of evidence for studies in exposed humans and exposed animals be weaker based on our assessment, we may determine in vitro studies to be of greatest influence. Findings and general limitations of these studies will be reviewed, and a comparison of the results will be made between the in vitro studies and the studies in exposed humans and animals.

3.2.1. Studies in Exposed Humans

Based on the scoping and mapping activities, OFR studies in exposed humans share similar study designs, populations, and strengths and limitations. Consistent with recommendations by Savitz et al. (2019), our approach is to identify the most influential factors (as opposed to using all questions) affecting informativeness (biases/sensitivity) and evaluate whether those factors impact the results. We apply this approach across study sets with similar designs rather than on individual studies. Table 3-5 shows the influential questions and issues for the informativeness domains in exposed humans.

Overall, most exposed human studies are OFR exposure biomarker-based studies of OFR metabolites. We evaluate the assessment method, study design, population characteristics, and co-exposures, in interactive evidence maps (e.g., [PBDE evidence map](#), [PHOPs evidence map](#)). Key considerations to examine patterns that could explain this complex database are below.

Key considerations for exposed human studies:

- a. Study design: Cross-sectional, cohort
- b. Study population: Occupational (e.g., OFR plant workers, firefighters, e-waste facility workers), general population, pregnant mother, mother/child dyads, children/adolescents

- c. Exposure assessment method: Household dust, blood, cord blood, urine, handwipes, silicone wristbands, adipose tissue, breast milk, placenta
- d. Exposure factors: Significant exposure contrast in study population, high exposure study populations
- e. Confounding: Co-exposure to other persistent organic pollutants, correction for biological measures in biomarker studies (e.g., lipids, urine dilution), iodine (thyroid hormone studies)

Table 3-5. Study informativeness of studies in exposed humans: Influential questions and issues

Type of bias/sensitivity issues	Questions	Comments
Exposure assessment	Does the exposure assessment (e.g., proxy, measurements) adequately distinguish exposure groups? Was temporality established either by study design or is there sufficient information on biopersistence to assume temporality?	Exposure levels should be high enough to detect the relevant effects. OFRs vary in half-lives of measured metabolites.
Potential confounding	Did the study design or statistical methods address the major potential confounders?	Confounders include age, race/ethnicity, SES, biomarker adjustment (e.g., lipids, specific gravity, creatinine), iodine, persistent organic pollutant co-exposures Biomarker studies of OFRs may require correction or adjustment based on media collected (e.g., urinary dilution, lipid correction)
Outcome assessment	Was the biomarker measured at a relevant time frame and is it informative for predicting cancer? See Appendix for information on relevant biomarkers.	Tissue: local more informative than systemic, especially in sites concordant with cancer sites. Informative biomarkers for each KCC relevant to exposed humans may include, but not limited to: Inflammation: cytokines, inflammation (histology) Receptor-mediated effects: • <i>Thyroid hormones</i> : T3 (total triiodothyroxine (T3), TT3), T4 (total thyroxine (T4), TT4), free T3 (FT3), free T4 (FT4), thyroid stimulating hormone (TSH), other (thyroid binding globulin (TBG), thyroid hormone receptor alpha (TR α) and beta (TR β)). Concentrations of these hormones, receptors, and proteins are all biological indicators of various

Type of bias/sensitivity issues	Questions	Comments
		steps involved in TH hormone disruption. The utility of multiple biomarkers of thyroid functioning within a study is preferred as it may allow for a broader understanding of the effect of the exposure on the thyroid system. • <i>Reproductive hormones</i>: Total testosterone, estrogens (estradiol, E2), progesterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), anti-Mullerian hormone (AMH), prolactin (PRL), sex hormone-binding globulin (SHBG). These hormones are indicators of estrogenic, androgenic, and/or anti-androgenic dysfunction. As with above, multiple complementary biomarkers for an intermediate endpoint of concern within a study could be more useful than individual biomarkers alone.
Sensitivity	Is exposure chronic or acute? Is the study sized adequately powered to detect biological effects?	Although most KCC biomarkers are short-lived, chronic exposure likely reflects the cumulative effects of repeat (acute) exposures. Long-term or repeated exposure studies are more informative for detecting persistent effects, which are more relevant for carcinogenicity.

3.2.2. Studies in Exposed Animals

Overview of studies

In exposed animal studies, both experimental studies (rodent, avian, or aquatic species) and observational studies (mammals, aquatic mammals) were identified (see Table 3-6 for an overview of study characteristics). A detailed discussion of external validity for each species is provided below (Section 3.3.1).

Table 3-6. Overview of OFR studies in exposed animals

Study design	Species	Exposure assessment method or route of administration
Experimental	Mammals: Rats, mice, hamsters, mink, pigs Avian: Chickens (streamlined) Aquatic: Fish, frogs (streamlined), mollusks (excluded)	Administered dose and route (oral, dermal)
Observational	Mammals: Cats, dogs, polar bears Aquatic mammals: Seals, whales	Measured concentrations (serum, dust, lipids)

Study Informativeness

Tables to guide the study informativeness of individual studies in experimental and observational animal studies are below. Table 3-7 provides the relevant study questions and guidance, organized by study domain, for evaluating mechanistic studies of OFRs in experimental animals. Table 3-8 provides relevant study questions and guidance, organized by study domain, for evaluating mechanistic studies of OFRs in observational studies of exposed animals.

Table 3-7. Study informativeness of experimental animal studies: Influential questions and issues

Type of bias/ sensitivity issues	Questions	Comments	Judgements
Study design	Is there concern that the concurrent control group/sample is not adequate for evaluating effects across treatment groups?	Concurrent controls are the most relevant comparison group for evaluating potential exposure-related biological effects. Ideally, the concurrent control group includes appropriate vehicle-matched, comparable treatment conditions and randomization at least as many animals as in each treatment group at study start.	Minor concern Adequate unexposed and/or vehicle concurrent controls were used for experimental studies. For studies in which a vehicle control is not applicable, the unexposed control group received the same experimental conditions as the exposed group. No evidence of relevant background exposure or systematic difference between groups. Some concern For experimental studies, controls may not be vehicle or may have background OFR exposure. There are minor differences in control and treatment conditions that are unlikely to substantially influence the outcome. Moderate to major concern For experimental studies, there is evidence suggesting that the animals are non-concurrent controls. There are concerns about the comparability of treatment and control groups that could introduce systematic bias, but the study still provides a meaningful concurrent comparison. Critical concern Critical concerns about any bias. The control condition is so fundamentally inappropriate or systematically different that the observed differences cannot reliably be attributed to the exposure.
Exposure conditions	Dose Selection Is there concern that the dose levels were too high to attribute specific effects to the substance?	Dose should be high but not cause excess toxicity, for the duration of the study.	Minor concern Administration of OFR compound in laboratory settings. No/minimal concern of excessive toxicity as indicated by significant body weight changes or decreased survival. Some concern

Type of bias/ sensitivity issues	Questions	Comments	Judgements
			Exposure collection following less than ideal methods resulting in some concern for bias. Some treatment related decreases in body weight or survival or other toxic effects unlikely to influence interpretation. Moderate to major concern Low confidence that the exposure contains OFRs. The study may still be informative, but caution should be taken in interpretation. Substantial treatment related decreases in body weight or survival or other severe systemic effects that make it difficult to distinguish a specific exposure-related effect from severe toxicity. Irrelevant route of exposure. Critical concern The dose regimen is extreme that the study cannot provide a reliable assessment of exposure-related effects because observed responses are dominated by severe toxicity and other non-specific effects.
Sensitivity: Model and exposure	Is there concern that the study design and exposure is sensitive enough to adequately detect a neoplastic effect if present? This question considers • Statistical power (number of animals/group) • Study duration • Exposure regimen: duration and dose	Sensitivity rating integrates statistical power, study design, and exposure conditions. In some cases, one factor may compensate for limitations in another (e.g., a sensitive animal model may offset a smaller sample size). Ideally, studies would include 5 animals of each sex. However, single sex studies may be acceptable if there are no sex-specific differences for the endpoint being measured. The exposure route should consider metabolism of the chemical (e.g., a route that bypasses metabolic activation may not be informative). Evaluation of dose response can contribute to confidence in the study findings and allow for evaluation of potential effects at lower doses.	Minor concern Animal strains/stocks of at least intermediate sensitivity using conditions close to the ideal conditions (defined in guidance), adequate numbers of animals with appropriate exposure dose and duration. Ideally, there should be data from positive controls confirming the dose is adequate. Some concern Studies may have less than ideal conditions for some aspects of the study design or exposure conditions (e.g., duration, dose, number of animals) but not all Moderate to major concern Insensitive model or inadequate conditions for the animal model, but still some utility for detecting an effect. Critical concern Model or conditions are so inadequate, or study is so small,

Type of bias/ sensitivity issues	Questions	Comments	Judgements
			that it does not have an ability to detect an effect.
Outcome	Is there concern that the endpoint proxy (e.g., biomarker) did not represent the effect of interest? Is there concern that the biomarker was not measured in a relevant tissue or cell type? Measurement methods Is there concern that measurement methods (e.g., timepoints, accuracy, precision) are not adequate to generate valid and reliable data? The measurement methods consider consistency, replication, and sampling (collection methods and timing).	Ideally studies should measure the most relevant biomarkers related to the biological effect or KCCs in tissue or cells. See Appendix B for information on assays and biomarkers. Biomarkers in local tissues are more informative than systematic biomarkers. Ideally, each study should use accurate and reliable methods for measuring each endpoint at the appropriate time point and should follow applicable protocols and guidelines. For some biological effects, there are OECD guidelines. The timing of sample collection is important to determine if an observed effect is transient or persistent. The length of the exposure period as well as the timing of sample collection should both be considered in the determination of chronic responses. The study should include enough replicates or repetitions to generate reliable results for the endpoint of interest and without any serious uncertainties or limitations in the sampling process. For effects related to each outcome, multiple complementary biomarkers and/or multiple assays may provide additional strength to assessing treatment-related effects. For example, effects related to thyroid hormone disruption may be strengthened by multiple complementary endpoints and/or assays. For thyroid hormone biomarkers in particular, see additional references which may serve as	Minor concern Appropriate biomarkers are relevant measures of the KCCs and are assessed using ideal methods in the appropriate target tissue(s) and using the most relevant assays. Some concern Less than ideal methods are used to assess the biomarker of interest. Assay not as sensitive for the biomarker of interest. Moderate/major concern Biomarkers assessed do not represent the effect of interest. Measurement methods are not blinded/randomized, are inappropriate for the biomarker being assessed, or are measured using an assay that is not specific or sensitive for the biomarker. Critical concern Strong evidence that the biomarker measurement methods do not represent the effect of interest, or that measurement cannot distinguish between treatment groups.

Type of bias/ sensitivity issues	Questions	Comments	Judgements
		guidance for this endpoint (Bianco et al. 2014). <i>See Appendix B for endpoint/KCC specific guidance</i>	
	Differential measurement error Is there concern for differential measurement error, e.g., the treated and control groups were assessed differently?	All treatment and control groups should follow the same protocols for endpoint assessment and should be clearly reported to properly interpret results.	
	Sensitivity questions Is there concern that the assay or methods were not sensitive enough to detect an effect?	Ideally, appropriate and sensitive assays (e.g., current state-of-the-science assays with sufficient counts, such as the number of cells) should be used to measure biological effects (e.g., KCCs) in the target tissue or tissue of interest.	
Confounding	Chemical Characterization Is there concern that the chemical characterization and dose formulations (e.g., source, homogeneity, purity, solubility, volatility, and stability) are not adequate to support attribution of any effects to the substance? Substance Administration Is there concern that the vehicle or stabilizers may have confounded the findings? Conduct Issues Is there concern about confounding from the conduct of the study or maintenance of the animals or cells?	Ideally, a non-toxic vehicle should be used, and the test agent should be soluble in the vehicle. Contaminants or vehicles associated with the endpoint of concern are potential confounders.	Minor concern Minimal concern for confounding in test vehicle, administration, and conduct of study. Some concern Moderate magnitude of confounding is present, but there is still an ability to distinguish exposure/outcome relationships. Moderate/major concern There is evidence that the effects of the exposure may not be able to be distinguished from the effects of potential confounders. Critical concern Strong evidence that effects from the exposure are confounded to the point of not being able to distinguish treatment-related effects from confounder(s).

Table 3-8. Study informativeness of observational studies of exposed animals: Influential questions and issues

Type of bias/ sensitivity issues	Questions	Comments	Judgements
Selection bias	Is there concern that the study design chosen may be an incorrect design for assessing effects? Is there concern that selection criteria differed by exposure and outcome?	Cross-sectional studies are sufficient to assess short-term effects	Minor concern A separate control group was used, or the animal served as its own control at a previous time point. Moderate to major concern Unexposed controls may differ from the exposed animals for factors other than exposures. Critical concern There is strong evidence that selection or attrition of animals was clearly related to both OFR exposure and the biomarker outcome.
Exposure misclassification/ mismeasurement	Exposure proxy Is there concern that the exposure proxy did not adequately represent the exposure of interest at an appropriate time window of exposure? Exposure measurement Is there concern about error in the measurement of the exposure of interest or exposure proxy?	OFRs are measured via environmental media (dust sampling) and biological media (biomarkers of exposure). OFR biomarkers are generally measured as metabolites (e.g., hydroxylated PBDEs). Biological measurements can include common matrices for OFR measurement, including blood and adipose tissue. Consideration for biomarker half-lives and an evaluation of temporality is critical to determine the potential for reverse causation. Biological half-lives of lower brominated PBDEs, which bioaccumulate into adipose tissue, can be years, whereas higher brominated PBDEs are more rapidly excreted over days-months.	Minor concern Valid exposure collection method and exposure proxy. Exposure likely preceded outcome. Some concern Exposure administration or collection method following less than ideal methods resulting in some concern for bias. Moderate to major concern Nonrandom missingness for exposure data, poor exposure proxy, or potential for reverse causation. Critical concern Exposure proxy does not approximate the exposure of interest, resulting in poor discrimination between exposed and unexposed and among exposure groups. High nonrandom missingness is large enough that the estimated effect of exposure on outcome is likely to be substantially different from an estimate generated from a complete dataset. Reverse causation is likely.
Study sensitivity	Is there concern that the numbers of exposed cases were not adequate for detection of an effect in the exposed		Minor concern Adequate exposed cases, good exposure contrast and relevant exposure metric(s) used. Some concern

Type of bias/ sensitivity issues	Questions	Comments	Judgements
	population or subgroups of the exposed population? Is there concern that the levels, duration, or range of exposure of the population at risk in observational studies was not sufficient or adequate for detection of an effect of exposure? Is there concern that the exposure assessment did not capture the relevant exposure metric, ideally to the outcome of interest (if biological understanding is known)?		Study was underpowered based on lower number of exposed cases. Study did not use additional metrics to sufficiently distinguish between levels of OFR exposure to detect an effect or used an incorrect metric for assessing OFR exposure. Moderate to major concern Study is insensitive to detect an effect based on poor statistical power, poor exposure contrast, or did not use a relevant exposure metric to assess relevant KCC outcomes. Critical concern The study was too small to meaningfully interpret, with few exposed subjects, and/or the exposure range was minimal.
Outcome Misclassification	Is there concern that the endpoint proxy (e.g., KCC biomarker) did not represent the effect of interest? Is there concern that the KCC biomarker was not measured accurately, precisely, or in a relevant time window? Or that a less relevant method was used to extract biomarkers of KCCs?	Ideally studies should measure the most relevant biomarkers related to the biological effect or KCCs in tissue or cells. See Appendix B for information on assays and biomarkers.	Minor concern Appropriate biomarkers are relevant measures of the KCCs and are assessed using ideal methods using the most relevant assays. Some concern Less than ideal methods are used to assess the biomarker of interest. Assay not as sensitive for the biomarker of interest. Moderate/major concern Biomarkers assessed do not represent the effect of interest, or substantial misclassification of KCC outcome exists. Critical concern Strong evidence that the outcome measurement methods do not represent the effect of interest, or that measurement cannot distinguish between outcome groups.
Confounding	Is there concern about the measurement of coexposures or personal behaviors in the study? If no data are provided about confounders, are surrogate data on potential confounders available.	Confounders include age and sex of animal, and persistent organic pollutant co-exposures Biomarker studies of OFRs may require correction or adjustment based on media collected	Minor concern The study measured key potential confounders and/or used appropriate analyses or designs to address them. Some concern Moderate magnitude of confounding is present, but there is still an ability to distinguish exposure/outcome relationships.

Type of bias/ sensitivity issues	Questions	Comments	Judgements
	Is there concern that the design or analysis did not adequately address important confounding through matching, stratification, multivariable analysis, or other approaches?	(e.g., urinary dilution, lipid correction)	Moderate/major concern There is evidence that the effects of the exposure cannot be distinguished from the effects of potential confounders, leading to a major confounding effect. Critical concern There is strong evidence that any effects of exposure cannot be distinguished from the effects of potential confounders.

3.3. Evidence Evaluation and Integration

In this section, we provide guidance for how we will evaluate evidence and integrate evidence for each identified compound to ultimately reach a level of evidence (LoE) conclusion on carcinogenicity from mechanistic studies. For sake of efficiency, this section applies to all compounds we are separately evaluating and making individual LoE conclusions on.

Individual LoE conclusions will be given for the following compounds:

- TBBPA (in the PBAF subclass)
- TetraBDE (in the PHDE subclass)
- PentaBDE (in the PHDE subclass)
- DecaBDE (in the PHDE subclass)
- TCEP (in the PHOP subclass)
- TCPP (in the PHOP subclass)
- TDCPP (in the PHOP subclass)

As mentioned in Section 3.1, the influential questions in our evaluation of OFRs relate to evaluating the confidence in the evidence for the following biological effects related to a subset of KCCs, as well as evaluate whether there is evidence for associations among the KCCs. In addition, we will evaluate proposed MOAs for TBBPA and for multiple PBDE compounds (i.e., tetraBDE, pentaBDE, and decaBDE).

The KCCs and MOAs of interest by compound are:

Compound	KCCs	MOA
TBBPA	Induces oxidative stress, induces chronic inflammation, is immunosuppressive, modulates receptor mediated effects	Estrogen hormone disruption leading to uterine tumors
TetraBDE, pentaBDE, decaBDE	Induces oxidative stress, induces chronic inflammation, modulates receptor mediated effects	Thyroid hormone disruption leading to thyroid follicular cell tumors

Compound	KCCs	MOA
TCPP, TCEP, and TDCPP	Modulates receptor mediated effects	None.

3.3.1. Evidence Evaluation

Study findings are interpreted considering study sensitivity and the direction of any potential biases and external validity when relevant.

External Validity

External validity relates to the generalizability of a study to populations and situations other than those included in the original study. External validity includes the relevance of the chosen animal model and outcome endpoints to human exposures and responses. Studies using mammalian models have minimal concern of issues regarding external validity of exposure and mechanistic outcomes. Selection of non-mammalian animal models may have limited applicability to conclusions related to human health. The route of exposure can affect external validity.

- No/minor concern: Mammalian model is used for experiments and for observational studies.
 - For observational studies, larger aquatic mammals such as seals and whales are near the top of the aquatic food chain, making their toxic burden magnified compared to other aquatic organisms. Larger aquatic mammals contain a large percentage of blubber where lipophilic compounds such as PBDEs are stored. Further, these mammals share a similar endocrine system structure to humans, which makes them an adequate model to evaluate hormone disruption.
- Some concern: Fish, amphibian, and avian models are used for experiments, primarily to evaluate thyroid hormone disruption.
 - Nonmammalian species, including fish, frogs, and chickens, are also considered relevant sensitive models, primarily for experimental dosing studies evaluating TH disruption; however, given the tight regulation of the HPT axis for TH homeostasis, these nonmammalian species might be less relevant than mammalian models. Amphibians are valuable models for studying thyroid hormone disruption because their metamorphosis relies on THs. Structurally, fish share a comparable thyroid hormone system to humans and are considered valid models for evaluating TH effects. Chickens are considered more vulnerable than humans to TH disruption via chemical exposure. For experimental studies of avian, aquatic, and amphibian nonmammalian species, a streamlined approach of summarizing available evidence will be employed.
- Critical concern: Invertebrate model (mollusks) is used for experiments.
 - Mollusks are less relevant models for thyroid hormone functioning given differences in receptor activation, and will be excluded from our review.

To determine human relevance of an identified MOA, additional guidance may aid in the interpretation of experimental data (e.g., IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans, Boobis et al. 2006).

3.3.2. Evidence Integration

We use a three-step process for evaluating the evidence and reaching a conclusion regarding the level of evidence for carcinogenicity from mechanistic studies (Box 3-2).

Step 1 Assess the evidence from each study set for each biological effect

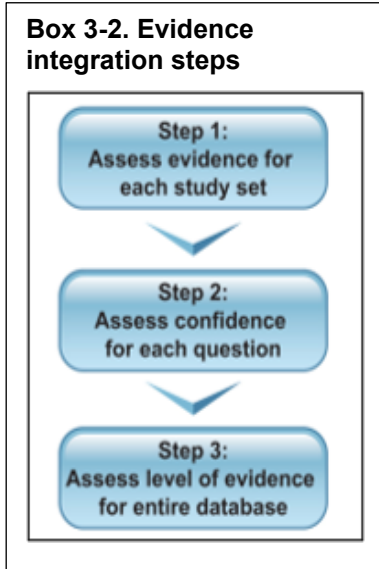
Step 2 a. Assess the confidence of the evidence for each biological effect
b. Integrate the evidence across each study/data set assessment

Step 3 Assess the level of evidence (convincing, supportive)

Step 1: Evaluating the Evidence of Each Study Set

For each study set, we plan to consider the following factors:

- Consistency of the evidence across studies for individual biomarkers and study level judgments (see below)
- Strength of the association, such as magnitude of the effect and exposure-response relationships
- Study informativeness (i.e., internal validity, sensitivity)
 - Relevance (e.g., exposure dose and duration, timing of sample collection) of the exposure and measurement of the biological effect
 - Tissue/sample (e.g., local, target tissue, or circulation). In general, evidence for KCC biomarkers in target tissues is more informative than circulating/systemic biomarkers, although it may depend on the KCC and cancer site of interest.
- The assessment uses a triangulation approach, which integrates evidence from different study designs and methods, as well as different sources of potential biases, to reach conclusions about consistency



Step 2a: Assess the Confidence of the Evidence: Biological Effects

For each influential question, we integrate the assessments across study sets, using triangulation approaches, to reach a confidence judgment based on the guidance outline in Table 3-9. The informativeness of the study set considers the quality of the study set as a whole, including the evidence type, the adequacy of the exposure proxy, and utility of the indicators or biomarkers for accurately measuring the biological effect. Key considerations are the consistency and coherence for both the effect and the biomarkers used to measure the effect/KCC, the overall quality of the collective evidence across study sets, and the informativeness of the biomarkers.

Table 3-9. Confidence judgment for biological effect

Descriptor	Biological Effect (Including Connection between Effects)
High	<i>Individual biological effect (KCC)</i> Consistent evidence of informative KCC biomarkers/indicators across studies of sufficient quality and ideally in more than one evidence type Coherence across individual KCC biomarkers/indicator <i>Relationships between KCCs or multi-omics data</i> Consistent evidence across studies for an association between two or more biological effect biomarkers/indicators
Moderate/Limited	Less than consistent evidence across studies, KCC biomarkers/indicators, and evidence types Consistent evidence for less relevant KCC biomarkers/indicators or less biological or human-relevant evidence types, or fewer number of studies
Inadequate	Negative or unexplained inconsistent findings Few data or limited study informativeness Evidence is mainly from evidence types with low biological or human relevance for the substance and specific biological effect under evaluation KCC biomarkers/indicators are of limited informativeness for the biological effect and cancer development

Note: Biological and human relevance are evaluated on a case-by-case basis, e.g., some non-mammalian *in vivo* assays may be relevant for some but not other KCCs, and some species may be more relevant than others.

Informativeness of study set

KCC-specific informativeness guidance for oxidative stress, chronic inflammation, immunosuppression, and receptor-mediated effects are presented in Table 3-10. Specifically, we provide guidance to reach high confidence for each of the relevant KCCs.

Table 3-10. KCC specific informativeness guidance

KCC	Ideal evidence for high confidence	Other evidence for high confidence: Combination of biomarkers
KCC5: Induces oxidative stress	Several oxidative stress biomarkers (pro- and anti-oxidative stress) • Integrative score • Pro-and anti-oxidative stress biomarkers in the same studies	One or more clinically relevant oxidative stress biomarker(s), such as F2-isoP and oxidative damage to DNA AND Link with other KCCs (e.g., KCC2, KCC6)

KCC	Ideal evidence for high confidence	Other evidence for high confidence: Combination of biomarkers
KCC6: Induces chronic inflammation (or immune activation)	Evidence of chronic inflammatory (e.g., autoimmune) diseases in exposed humans or animals Histological evidence of chronic cellular inflammation in target tissues (WBCs- e.g., lymphocytes) with local increases in proinflammatory biomarkers (e.g., specific cytokines or chemokines) in exposed humans or animals • Ideally, the biomarkers are associated with cancer and are identified in the context of evidence of chronic exposure (or repeated acute exposures)	Histological evidence of chronic cellular inflammation in nontarget tissues with local increases in proinflammatory biomarkers in exposed humans or animals Systemic increases in acute (with evidence of chronic exposure) or chronic inflammatory cells or proinflammatory biomarkers (e.g., cytokines, chemokines, or acute phase proteins) in circulation • Ideally, the biomarkers are associated with cancer and are identified in the context of evidence of chronic exposure (or repeated acute exposures) • Systemic inflammation may be more informative for blood cancers compared to solid tumors
KCC7: Is immunosuppressive	Evidence of increased viral infections in exposed humans or animals Impaired immune function, such as decreased antibody responses (e.g., vaccine-induced), NK, CTL, and T cell activation/activity in exposed humans or animals	Evidence of increased non-viral infections in exposed humans or animals and supporting evidence (e.g., alterations in immune components or organs) Severe decreases in WBC/leukocyte subsets and supporting evidence (e.g., decreased cytokines)
KCC8: Modulates receptor-mediated effects	Direct receptor-mediated binding and transactivation (with effects on gene expression)	Indirect modulation of receptor effects Increased levels of endogenous hormones Overexpression of receptors for hormone sensitivity

When assessing the relationship between KCCs, we consider consistency across studies and evidence types, dose/response, timing, or sequence of events. Assessing the confidence of biological effects may lead to new mechanistic hypotheses for the substance under evaluation. Proposed biological pathways or MoA (e.g., timing/steps) may be based on actual studies or general knowledge about carcinogenicity. However, the associations between the substance and specific biological changes could reflect the availability of studies and not the level of its contribution to carcinogenicity.

Step 2b: Assess the Confidence of the Evidence: Mode of Action

MoA/AOP (or other biological pathway)-related influential questions are identified after broad literature searches and are unlikely to be the only questions for an evaluation. Confidence judgment is reached by assessing (1) the confidence that the substance causes the predominant biological effects in the proposed MoA/AOP or pathway (e.g., molecular initiating event or

several key events) and (2) how well the data for the substance fit the proposed MoA (see Table 3-11). To illustrate the evaluation process, we discuss two exemplars of RoC-listed substances.

Table 3-11. Confidence judgment for mode of action

Descriptor	MoA
High	High/moderate confidence that the substance causes the key biological events in the proposed MoA The evidence is a “good fit” for the proposed MoA as demonstrated by: High confidence for the most critical biological events in the MoA The biomarker used to measure the specific biological event is the most relevant for the MoA The sequence/timing and dose/response of events (e.g., semiquantitative) relative to each other and tumor formation are consistent with the proposed MoA
Moderate/Limited	High confidence that the substance causes an event in the proposed MoA, but the evidence is a moderate fit for the proposed MoA Moderate confidence for several key events in the MoA and moderate confidence for a good fit to the MoA
Inadequate	Inadequate confidence for several key events in the MoA

Step 3: Assessing the Level of Evidence

The LoE conclusion of carcinogenicity from mechanistic evidence is reached by applying the RoC listing criteria to the body of literature. The final step integrates the confidence judgments across the influential mechanistic questions on oxidative stress, chronic inflammation, immunosuppression, and receptor-mediated effects. The review also summarizes the data that were not considered to be influential.

Information on connections, sequence, and timing between oxidative stress, chronic inflammation (or immune activation), and receptor-mediated effects may help identify substance-specific biological pathways and increase the confidence. See Table 3-12 below for applying RoC listing criteria to reach the level of evidence guidelines for mechanistic studies.

Table 3-12. Level-of-evidence guidelines

RoC Criterion	Convincing	Supporting
Q1. Plausibility: Biological effects KCC or other relevant effects, including metabolism Connectivity between KCCs	• Coherence in the database (including mechanistic data, toxicokinetics) • AND • High confidence for one or more informative biological effects considering the following^a: • Number, sequence, connections between KCCs leading to the development of a biological pathway • Specificity and informativeness of KCC biomarkers • Supporting cancer-related data • Biological effect measured in cancer studies (typically <i>in vivo</i>) exposed to the substance • Measured in target or cancer site of interest	High or moderate confidence for informative KCCs • If the confidence judgment for KCC is moderate confidence, a greater number and specificity of the KCC is needed • If the confidence judgment is high, a single specific KCC or several less specific KCCs would meet the requirement
Q1: Plausibility: Reported biological pathway/MoA	• High confidence for an MoA that is for one of the following: • Cancer site observed in humans or experimental animals • Established cancer pathway	Moderate confidence for an MoA
Q3. Not relevant to humans/MoA (Compelling)	High confidence for an MoA for a cancer site observed in animal studies Strong scientific consensus that the MoA is not relevant to humans Low confidence for KCCs in the target tissue Inadequate^c mechanistic data in exposed humans	Not relevant ^b

^aScientific judgment is used to integrate the issues in the bullet, and not all are required

^b“Supporting” is not relevant because these questions are for when there is not an adequate database from human or animal cancer studies, or the evidence is downgrading the studies in experimental animals.

^c“Inadequate” means that either no human data are available or no data in humans supporting biological plausibility are available.

LoE of carcinogenicity from mechanistic studies will be integrated with the LoE of carcinogenicity from cancer studies in exposed humans and animals to reach a cancer hazard conclusion (i.e., listing recommendation). This section will be forthcoming when a read-across approach is developed for each subclass. Class-Based Approach (Future)

As mentioned in both the NAS report on class-based approach to evaluating health effects of OFRs (NAS 2019) and within the RoC Handbook (2025), a goal of the RoC is to move toward evaluating not only individual OFRs, but subclasses of OFRs. Our RoC Handbook contains guidance on read-across approaches to evaluate data poor chemicals within a class.

Although we initiated our scoping with a search for chemicals within a subclass, this protocol addresses the evaluation of mechanism evidence for individual chemicals. In the future, our

intention is to develop a read-across approach to evaluating these chemical subclasses, in addition to individual chemicals. This approach would be captured in a future protocol.

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Appendix A: Search Terms and Evaluation Team Responsibilities Date: March 13, 2026

A.1. 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 A-1 is a general OFR search string that includes general terms for OFRs, subclasses, and selected chemicals. Table A-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](#).

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 A-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 A-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'-isopropylidene)bis(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) dipropionate" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, dipropionate" 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 "Benzene,

Database	Search String
	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-dichloropropan-2-yl) phosphate" OR "Phosphoric acid, 3-bromo-2-(bromomethyl)-2-(chloromethyl)propyl bis[2-chloro-1-(chloromethyl)ethyl] ester" OR

Database	Search String
	"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-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" [EC/RN Number]) OR "organophosphate 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" 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'-isopropylidene)bis(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-

Database	Search String
	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 "3,3',5,5'-Tetrabromobisphenol A bispropionate" OR "(Propane-2,2-diyl)bis(2,6-dibromo-4,1-phenylene) dipropionate" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, dipropionate" OR "37419-42-4" OR "TBBPA-BP" OR (Tetrabromobisphenol A dimethyl ether OR

Database	Search String
	"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-

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	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',P'-[2,2-bis(chloromethyl)-1,3-propanediyl] 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-3,9-diphosphaspiro[5.5]undecane-3,9-dione" 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-

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	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 "organophosphate 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'-isopropylidene)bis(2,6-dichlorophenol)" OR "Phenol, 4,4'-(1-methylethylidene)bis[2,6-dichloro-" OR "Tetrachlorobisphenol 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,

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	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',5,5',6,6'-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") 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

Database	Search String
	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 ("TCEP 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) biphosphate" 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 "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 "organophosphate ester"))

A.2. 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, Ruth M. Lunn, Whitney D. Arroyave, and Danila Cuomo

Information Specialists

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)
- Matthew L. Urich, PhD, NIEHS (toxicologist)
- Bevin Blake, PhD, NIEHS (toxicologist)
- Whitney D. Arroyave, PhD, ILS – an Inotiv Company (epidemiologist)
- Danila Cuomo, PhD, ILS – an Inotiv Company (toxicologist)
- Claire Heit, PhD, ILS – an Inotiv Company (toxicologist)
- Alton Peters, MS, ILS – an Inotiv Company (exposure assessment)

Data Visualization

Create data visualization in Tableau

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

Protocol Peer Reviewers

Reviewed draft protocol in April 2026 and their comments were used to produce October 2026 version:

- June Dunnick, PhD, NIEHS
- William Gwinn, PhD, NIEHS

Appendix B. Background information on Key Characteristics of Carcinogens (KCC) Biomarkers and Indicators

Tables in this appendix provide background information on the biomarkers and indicators for evaluating study informativeness (Table 3-4 and Table 3-6) and reaching a confidence of the evidence of selected KCCs for Halogenated Flame Retardant Studies.

B.1. Induces Oxidative Stress (KCC5)

Oxidative stress occurs when there is an imbalance in the redox status within target tissues that favors formation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) at the expense of their detoxification (Smith et al. 2020). This imbalance can lead to oxidative damage to DNA, proteins, and lipids and other effects that are directly related to several other KCCs. These include genotoxicity (KCC2), altered DNA repair (KCC3), chronic inflammation (KCC6), and altered cell proliferation, cell death, or nutrient supply (KCC10). Although oxidative stress is a KCC, it is not specific to carcinogens as many non-carcinogens can also induce oxidative stress. Table B-1 generally follows the steps in the biological process of oxidative stress. Within each subtype, biomarkers are generally organized alphabetically.

Table B-1. Background information on common biomarkers or indicators of oxidative stress (KCC5)

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence/	Subtype
Oxidants: ROS, RNS, ROM	ROS: H ₂ O ₂ , OH ⁻ , ROO ⁻ , or O ₂ ⁻	Cell-free Exposed humans or animals: WBC or other cells, cellular components <i>In vitro</i> (real/time live cells)	Very transient (nsec to sec) to longer lived ^a	Endpoint considerations: Urinary H ₂ O ₂ can be an indicator of whole-body oxidative stress but is confounded by diet Assay considerations: Measurement instrumentation: electron spin resonance, fluorescent probes, biosensors Fresh samples are needed; oxidants are unstable Not recommended for ex vivo tissue homogenates
	RNS: ONOO ⁻ , NO ₂			
	ROM: ROOH	Exposed humans or animals: Serum/plasma		Assay considerations: Criticisms of the reliability of the d-ROM test
ROS Modifications: lipid, DNA, protein	All			Endpoint considerations: Systemic or tissue-specific oxidative stress
Lipid peroxidation	All	Exposed humans or animals: Body fluid (e.g., urine,	Minutes to hours	Endpoint considerations: May directly affect the function of target molecules or

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence/	Subtype
		serum, plasma), exhaled breath cells, tissues		enzymes or indicate local degrees of oxidative stress
	F2-isoP		Minutes (serum), hours (urine)	Endpoint association with cancer: Conflicting findings found for breast cancer risk Assay considerations: IsoP in serum and urine correlate with in vivo oxidative stress in humans and animals (unaffected by diet). Preferred method and recognized by EFSA.
	MDA/TBARS			Endpoint or assay considerations: MDA/TBARS is a nonspecific biomarker and is susceptible to methodological bias, yet it may have clinical relevance (induces IL-7 producing cells). However, MDA/TBARS is not recommended as the only test of lipid peroxidation. MDA measured by MS is useful.
	Others: HNE, LOOH, oxLDL			Assay considerations: oxLDL recognized by EFSA
Oxidative damage to DNA/RNA	8-OHdG	Exposed humans or animals: Urine, plasma, serum, tissue	Minutes	Endpoint considerations: Rapidly repaired, usually measured in urine, may serve as an indicator of whole-body oxidative stress Endpoint association with cancer: Some evidence shows that pre-diagnosis frequencies are associated with increased breast cancer risk in postmenopausal

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence/	Subtype
	Comet assay modified with lesion-specific repair endonucleases (e.g., OGG1, FPG, Endonuclease III)	Cells (e.g., leukocytes), <i>ex vivo</i>		women and lung cancer in non-smokers. Often carries greater weight than other biomarkers
	Repair enzymes: hOGG APE			Assay considerations: Accepted by EFSA
	Oxidized guanine/guanosine (OxGua)	Exposed humans or animals: Urine		Endpoint considerations: OxGua molecules are derived from repair products of the oxidatively generated DNA/RNA lesions, 8-OH-dGuo from DNA, and 8-OHGuo from RNA. Endpoint association with cancer: Pre-diagnosed levels are associated with increased risks of all cancer in non-smokers and possibly men; colorectal cancer in women, non-smokers, and non-obese people; and prostate cancer in non-smokers.
Oxidative stress: Proteins	Carbonylated proteins (CPs), AOPP	Exposed humans or animals: Plasma/serum	Days	Endpoint considerations: CPs: irreversible; a hallmark of oxidative stress and is biologically significant and clinically relevant
	s-glutathionylation			Prone to methodological artifacts

RoC Protocol: Mechanistic Studies of Organohalogen Flame Retardants

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence/	Subtype
	3-nitrotyrosine			Circulating levels of the biomarkers (3-nitrotyrosine) are not equivalent to tissue levels
ROS generating enzymes	MPO, XO	Exposed humans or animals: serum, urine, tissues <i>Ex vivo</i> : neutrophils	Hours	Endpoint considerations: MPO released from neutrophils can also be an indicator of inflammation (KCC6). Endpoint association with cancer: MPO is associated with cancer progression.
Inflammation/oxidative stress biomarkers	COX-2	Exposed humans or animals: tissues, serum <i>In vitro</i>	Hours to days	Endpoint association with cancer: COX-2 inhibitors can prevent the carcinogenesis of colorectal cancer. Endpoint considerations: It can also be considered as a proinflammatory biomarker (KCC6).
Antioxidant status	Enzymes: SOD, catalase, GST, GPx	Exposed humans or animals: Serum, erythrocytes (catalase)	Minutes	
	GSH; Vitamin A, C, E		Minutes	Assay considerations: Unstable, difficult to analyze
	Nrf2-ARE response pathway	Exposed humans or animals: Leukocytes, tissue		Assay considerations: Difficult to analyze
	Total antioxidant capacity			
Indices	GSH/GSSG ratio Oxy score (damage – protection)			

RoC Protocol: Mechanistic Studies of Organohalogen Flame Retardants

Sources: Basu 1998; Loft et al. 2006; Harris et al. 2008; Dai et al. 2009; Ho et al. 2013; Lim and Thomas 2013; Loft et al. 2013; Brenner et al. 2014; Frijhoff et al. 2015; Gryszyńska et al. 2017; Ito et al. 2017; Lee et al. 2017; Marrocco et al. 2017; Tas and Erturk 2017; Gao et al. 2019; Katerji et al. 2019; Smith et al. 2020; Andries et al. 2021; Menzel et al. 2021; Murphy et al. 2022; Valadez-Cosmes et al. 2022.

8-OH-dG = 8-hydroxy-2'-deoxyguanosine, APE = apurinic/aprimidinic endonuclease, ARE = antioxidant responsive element, AOPP = advanced oxidation protein products, COX-2 = cyclooxygenase-2, FPG = formamidopyrimidine (fapy)-DNA glycosylase, GPx = glutathione peroxidase GSH = glutathione (reduced), GSSG = oxidized glutathione, GST = glutathione S-Transferase, H2O2 = hydrogen peroxide, HNE = 4-hydroxy-2-nonenal, hOGG = human 8-oxoguanine-DNA-glycosylase, Iso-P = isoprostanes, LOOH = lipid hydroperoxides, oxLDL = oxidized low density lipoproteins, MDA = malondialdehyde, MPO = myeloperoxidase, NO2 = nitrogen dioxide, O2- = superoxide, OH- = hydroxyl radical, OGG1 = 8-oxoguanine DNA glycosylase, ONOO- = peroxynitrite, RNS = reactive nitrogen species, ROM = reactive oxygen metabolites, ROO- = peroxy radicals, ROOH = hydroperoxides, ROS = reactive oxygen species, SOD = superoxide dismutase, TBARS = thiobarbituric acid reactive substances, XO = xanthine oxidase, WBC = white blood cells.

We used the term indicators for effects that are not biomarkers per se, such as outcomes.

^aRadical electrons/ionization charge species are very transient, others such as H2O2 are longer lived.

B.2. Induces Chronic Inflammation (KCC6) or Immune Activation

Many protein biomarkers (e.g., cytokines) can indicate chronic or acute inflammation depending on the exposure conditions. Thus, evidence of chronic or persistent/repeated exposure and/or the timing/duration of response is critical in determining whether the study is measuring chronic inflammation. The RoC review also considers immune activation (e.g., by B-cell antigens) which may be linked to chronic inflammation and both chronic inflammation and dysregulation/persistent immune activation can contribute to the development and progression of cancer. The concept of immunomodulation is part of the 2015 handbook, as recommended by the peer reviewers of that handbook. Table B-2 is organized inflammation-related diseases and pathology, with the remaining subtypes listed alphabetically. Within each subtype, biomarkers are organized alphabetically as well.

Table B-2. Background information on common biomarkers or indicators of chronic inflammation (KCC6) or immune activation

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence	Comments or Guidance
Chronic inflammatory diseases (e.g., autoimmune diseases)	Increased risk or incidence of autoimmune diseases that have been linked to cancer	Exposed humans Animal models of autoimmune disease	Months to years	
Chronic inflammation with WBC infiltration	Histology Local evidence of infiltration of acute (with evidence of acute exacerbations from repeated exposures) or chronic inflammatory cells	Exposed animals or (possibly) humans: tissue	Timing/ persistence can vary	Endpoint considerations: Specific cell types can indicate chronic inflammation. Granulocytes (including neutrophils) in tissue indicate acute inflammation. Lymphocytes, plasma cells, and monocytes/macrophages in tissue indicate chronic inflammation. Pathologists can diagnose acute vs. chronic. Histological evaluation is limited in exposed humans.
Cytokines and chemokines (some proinflammatory)	Chemokines: MCP-1, MIP-2 Interferon: IFN γ	Exposed humans or animals: serum/plasma, tissue, body fluids, exhaled breath	Minutes: IL-1 β , IL-8, TNF α Hours: IL-6	Endpoint considerations: IL-6 is involved in inflammation, autoimmunity, and B-cell malignancies.

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence	Comments or Guidance
Acute phase proteins	Interleukins ^a : IL-1 α , IL-1 β , IL-2, IL-6, IL-8, IL-12, IL-15, IL-23	<i>Ex vivo, in vitro</i>		The associated cytokine/chemokine receptors are also critical and ideally should be considered together with ligands.
	Transforming growth factor: TGF β			Endpoint association with cancer:
	Tumor necrosis factor: TNF α			Pre-diagnosed elevated circulating (systemic) levels of IL-6 and IL-8 are associated with increased lung cancer risk. Increased IL-6 levels are also associated with all cancers combined and CRC in several studies or meta-analyses. Experimental (rodent) models for the role of TNF α , TGF β , IL-1, IL-6, and IL-23 in cancer development or progression.
Acute phase proteins	Amyloid A (serum, SAA)	<i>Ex vivo, in vitro</i>	24 to 48 hr	Endpoint considerations: CRP is nonspecific and the most sensitive acute phase protein in humans.
	CRP	Exposed humans or animals: serum/plasma, tissue	Hours to days	Endpoint association with cancer: Pre-diagnosed elevated circulating CRP is associated with increased cancer incidence/mortality for all cancers combined, and several cancer types, such as lung, CRC, breast, and ovarian. SAA is associated with an increased risk of several cancers, such as lung and colon, and is correlated with CRP.
	ESR		Weeks	Endpoint considerations and association with cancer: ESR is the most widely used laboratory test for evaluating inflammation status in clinical

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence	Comments or Guidance
Prostaglandin endoperoxide synthase	COX-2	Exposed humans or animals: tissue, serum <i>In vitro</i>	Hours to days	practice, including infection, autoimmunity, and cancer. Endpoint association with cancer: COX-2 inhibitors can prevent the carcinogenesis of colorectal cancer. Endpoint considerations: It can also be considered as an oxidative stress biomarker (KCC5).
Transcription factors	JAK/STAT NF-kb	Exposed humans or animals: cells/tissue <i>Ex vivo, in vitro</i>	Minutes Hours	Endpoint considerations and association with cancer: NF-kb activation is essential for inflammation and is activated in several types of cancer.
WBC (circulating)	Increases in total WBC or leukocyte subsets: lymphocytes, monocytes, granulocytes Ratios (NLR, PLR, LMR) and SII Increased bone marrow hematopoiesis	Exposed humans or animals: blood	Days to weeks	Endpoint considerations: Decreased systemic WBC can also indicate increased inflammation via extravasation into tissue (local inflammation). In general, lymphocytes are chronic inflammation indicators, and granulocytes are acute inflammation indicators. NLR represents the imbalance between the innate and adaptive immune response. SII is based on peripheral lymphocyte, neutrophil, monocyte, and platelet counts. Endpoint association with cancer: Pre-diagnosed elevated lymphocytes, monocytes, neutrophils, basophils, and NLR are associated with increased lung cancer risk.

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence	Comments or Guidance
Immune cell activation	B cell stimulation/antigens (antibody production)	Exposed humans or animals: cells/tissue <i>Ex vivo</i>		Pre-diagnosed elevated leukocytes are associated with an increased risk of all cancers combined, lung cancer, or CRC. Endpoint association with cancer: B-cell stimulation (by the by itself due to autoimmunity or by foreign antigens due to immunosuppression) leads to DNA damage from genomic recombination and mutation during class/isotype switching and somatic hypermutation and possibly increased risk of B-cell lymphoma.
	Macrophage and granulocyte phagocytosis, ROS production	Exposed humans or animals: cells/tissue <i>Ex vivo, in vitro</i>		Endpoint considerations: ROS from immune cells contribute to oxidative stress (immune-regulated ROS can be considered under inflammation or oxidative stress- KCC5). Persistent immune cell activation can be a driver of chronic proinflammatory responses. It can be difficult to definitively determine if evidence/endpoints of immune activation are linked to chronic inflammation.

Sources: Germano et al. 2008; Van Hemelrijck et al. 2011; Zhou et al. 2012; Brenner et al. 2014; Zhou et al. 2014; Kakourou et al. 2015; Allin et al. 2016; Brenner et al. 2017; Puar et al. 2018; Kang et al. 2019; Qian et al. 2019; Chauhan and Trivedi 2020; Smith et al. 2020; Wong et al. 2020; Hirano 2021; Liu et al. 2021; Michels et al. 2021; He et al. 2022; Ji et al. 2022; Zhu et al. 2022.

COX-2 = cyclooxygenase-2, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, JAK/STAT = Janus kinase/signal transducers and activators of transcription, INF γ = interferon gamma, LMR = lymphocyte to monocyte ratio, MCP-1 = macrophage chemoattractant protein-1, MCP-2 = macrophage chemoattractant protein-2, NF-kb = nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kb), NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, ROS = reactive oxygen species, SAA = serum amyloid A, SII = systemic immune-inflammation index, TGF β = transforming growth factor beta, TNF α = tumor necrosis factor alpha, WBC = white blood cell.

We used the term indicators for effects that are not biomarkers per se, such as outcomes.

*Some interleukins (like IL-8) are considered to be chemokines.

B.3. Is Immunosuppressive (KCC7)

Immunosuppression is characterized by a reduction in the capacity of the immune system to respond effectively to foreign antigens, including surface antigens on tumor cells. Potentially neoplastic cells may escape immune surveillance which facilitates the survival of tumor cells. T cells and natural killer cells are critical components in anti-tumor immunity. Table B-3 prioritizes the most clinically relevant and direct measures of immunosuppression, followed by indirect measures (or subtypes). Biomarkers within each subtype are organized alphabetically.

Table B-3. Background information on common biomarkers or indicators of immunosuppression (KCC7)

Subtype or Assay	Biomarkers/Indicators	Evidence type: Biospecimen	Comments or Guidance
Increased infections	Increases in the incidence of opportunistic infections (especially viral)	Exposed humans (observational studies) or animals	Endpoint considerations: Strong evidence for immunosuppression
Immune function (challenge to foreign antigen)	Decreases in primary or secondary antibody response to vaccinations or natural antigens	Exposed humans (controlled clinical or observational studies) or animals	Endpoint considerations: Strong evidence for immunosuppression but indicator may not be relevant for immunosurveillance and cancer risk. Not usually conducted in humans because of ethical reasons. Observational studies may evaluate whether environmental exposure affects vaccination antibody response.
	Decreases in NK function, phagocytosis/bacterial killing by PMNLs, antigen presentation	Exposed humans or animals Ex vivo	
Immune function (humoral or cell-mediated immunity)	Decreases in antibody production (e.g., T cell dependent, antigen-specific) including specific	Exposed humans or animals Ex vivo	Endpoint association with cancer: Impact on CTL or NK activity and memory T cells may be most relevant for cancer (e.g., immunosurveillance)

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Subtype or Assay	Biomarkers/Indicators	Evidence type: Biospecimen	Comments or Guidance
	subclasses/isotypes, NK or CTL activity, T cell activity		with B cell/antibody production less relevant. Low CTL activity is associated with increased cancer risk.
Immune components	Cytokines: IL-10, TGF β	Exposed humans or animals	Endpoint considerations: Not sensitive or predictive alone to predict immunosuppression but may be used to support experimental animal data.
	Immunoglobulins (T cell-dependent or -independent)		
	Lymphocyte phenotyping (decreased NK, NKT, CD4+ T, CD8+ T; increased CTLA4+ T, Tregs)		
Immune components (hematology)	Altered WBC and leukocyte subsets	Exposed humans or animals	Endpoint considerations: Only severe changes are sufficient evidence of immunosuppression.
Immune organs (histopathology and organ weights)	Lymph node or splenic germinal centers, bone marrow suppression of hematopoiesis	Exposed humans or animals	Endpoint considerations: Reduced organ weight may be secondary to general toxicity or stress. Extensive histopathology may support the weight of evidence for immunosuppression. Evaluation is limited in exposed humans.

Source: Imai et al. 2000; IPCS 2012; Ponce et al. 2014; Lebrech et al. 2016; Sharma et al. 2017; Smith et al. 2020.

CTL = cytotoxic T lymphocyte, NK = natural killer cell, PMNL = polymorphonuclear leukocyte, TGF β = transforming growth factor beta, WBC = white blood cell.

We used the term indicators for effects that are not biomarkers per se, such as outcomes.

B.4. Modulates Receptor-mediated Effects (KCC8)

Some receptors promote cell proliferation (e.g., hormone nuclear receptors such as estrogen [ER], androgen [AR], and progesterone [PR]). Activation of the aryl hydrocarbon receptor (AhR) can lead to immunosuppression (KCC7), in addition to effects on cell proliferation and survival (KCC10) (Smith et al. 2020). Table B-4 prioritizes the most relevant and direct measures of receptor-mediated effects, followed by indirect measures (or subtypes). Biomarkers within each subtype are organized alphabetically.

Table B-4. Background information on common biomarkers or indicators of receptor-mediated effects (KCC8)

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence	Comments or Guidance
Receptor-mediated genomic action (NRs, AhR)	All			Endpoint considerations: Nuclear and cytosolic receptors are more relevant than peptide-regulated growth factor receptors.
	Activates or antagonizes receptors, e.g., ER, PR, AR, AhR	Cell-free Cell culture (in vitro): including non-cancerous and cancerous, endogenously expressing or transiently/stably transfected Exposed humans or animals	Months	Assay considerations: Commonly used assays: ER, AR, AhR transactivation assays (OECD TG-455, TG-458, US EPA METHOD 4435, JIS K 0463) Measures both receptor binding and function
	Interacts with receptors: ER and AR binding	Cell-free In vitro cells (usually human)	Months	Assay considerations: Recommended assay: OECD TG 493 Receptor binding-only assays do not indicate downstream effects

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence	Comments or Guidance
Alters hormone/ligand synthesis (levels), distribution, and transport	Binding to enzymes and transport proteins f h	Cell-free In vitro cells (human H295 cancer cells), human recombinant microsomes	Months	Recommended assays: Steroidogenesis with H295R (OECD TG-456), Aromatase assays (US EPA 890.1200/1550), Radioligand binding and displacement (e.g., displacement of 125I-T4)
	Endogenous hormone levels (e.g., E2, T, T4) Sex hormone-binding globulins levels and modulation	Exposed humans or animals: serum/plasma, urine, other fluids, tissue		Endpoint considerations: Agents that modulate ligand transport, distribution, and clearance can also indirectly modulate receptor-mediated effects. Recommended assays: Usually hormone immunoassays Endpoint association with cancer: Increased levels of endogenous estrogens and androgens with subsequent increase in receptor-mediated activation is associated with breast cancer risk in pre-and postmenopausal women. Estrogen (endometrial, ovary, and limited for breast cancer) and estrogen-progestogen menopausal therapy (breast and endometrial cancer), and estrogen-progestogen oral contraceptives (breast,

Subtype	Biomarkers/Indicators	Evidence Type: Biospecimen	Persistence	Comments or Guidance
				cervical, and liver cancer) are known human carcinogens. Pre-diagnosed circulating androgens and estrogens are associated with an increased risk of non-serous ovarian cancer in postmenopausal women. Thyrotropin levels that are suggestive of hyperthyroid function are associated with increased cancer risk, specifically, with an increased risk of lung and prostate cancer.
Alters nuclear receptor expression	ER, PR, AR	Exposed humans or animals: serum/plasma	Months	Recommended assays: Immunohistochemistry or western blotting with animal or human tissue Endpoint association with cancer: The overexpression of ER in benign breast epithelium is associated with estrogen sensitivity and breast cancer risk.

Sources: Khan et al. 1998; Diel et al. 2000; Meerts et al. 2000; Key et al. 2002; Hellevik et al. 2009; Endogenous Hormones Breast Cancer Collaborative Group et al. 2011; IARC 2012; Endogenous Hormones Breast Cancer Collaborative Group et al. 2013; Hogervorst et al. 2013; McIver et al. 2013; Baan et al. 2019; Trabert et al. 2019; Jacobs et al. 2020; Smith et al. 2020; NTP 2021.

NR = nuclear receptor, AR = androgen receptor, ER = estrogen receptor, PR = progesterone receptor, AhR = aryl hydrocarbon receptor, E2 = 17 β -estradiol, OECD = Organisation for Economic Co-operation and Development, T = testosterone, T4 = thyroxine.

We used the term indicators for effects that are not biomarkers per se, such as outcomes.