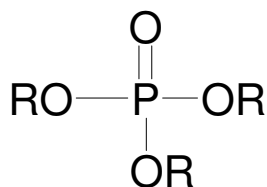




## TSCA Work Plan Chemical Problem Formulation and Initial Assessment

### Chlorinated Phosphate Ester Cluster Flame Retardants



| CASRN      | NAME                                                   | R =                                           |
|------------|--------------------------------------------------------|-----------------------------------------------|
| 115-96-8   | Ethanol, 2-chloro-, phosphate (3:1);<br>(TCEP)         | <b>-CH<sub>2</sub>-CH<sub>2</sub>-Cl</b>      |
| 13674-84-5 | 2-Propanol, 1-chloro-, 2,2',2''-phosphate;<br>(TCPP)   | <b>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-Cl*</b> |
| 13674-87-8 | 2-Propanol, 1,3-dichloro-, phosphate (3:1);<br>(TDCPP) | <b>-CH-(CH<sub>2</sub>-Cl)<sub>2</sub></b>    |

\* Major isomer

**August 2015**

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## AUTHORS / CONTRIBUTORS / ACKNOWLEDGEMENTS

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Please visit the public docket (Docket: EPA-HQ-OPPT-2015-0068) to view supporting information.

## ABBREVIATIONS

---

|                  |                                                       |
|------------------|-------------------------------------------------------|
| °C               | Degrees Celsius                                       |
| BAF              | Bioaccumulation factor                                |
| BCF              | Bioconcentration factor                               |
| BW               | Body weight                                           |
| CASRN            | Chemical Abstracts Service Registry Number            |
| CDC              | Center for Disease Control and Prevention             |
| CoC              | Concentration of Concern                              |
| CPE              | Chlorinated phosphate ester(s)                        |
| EC               | European Commission                                   |
| EFAST            | Exposure and Fate Assessment Screening Tool           |
| EFH              | Exposures Factors Handbook                            |
| EPA              | Environmental Protection Agency                       |
| EU               | European Union                                        |
| FR               | Flame retardant(s)                                    |
| GD               | Gestation day                                         |
| HHE              | Health hazard evaluation                              |
| HPV              | High production volume                                |
| hr               | Hour(s)                                               |
| IRIS             | Integrated Risk Information System                    |
| IURR             | Inventory Update Reporting Rule                       |
| kg               | kilogram(s)                                           |
| L                | Liter(s)                                              |
| Lb(s)            | Pound(s)                                              |
| LC <sub>50</sub> | Lethal concentration 50 percent                       |
| LD <sub>50</sub> | Lethal dose 50 percent                                |
| LOAEL            | Lowest-observed-adverse-effect level                  |
| m <sup>3</sup>   | Cubic meter(s)                                        |
| mg               | Milligram(s)                                          |
| mg/g             | Milligram(s) per gram                                 |
| mg/kg            | Milligram(s) per kilogram                             |
| mg/L             | Milligram(s) per liter                                |
| µg/L             | Microgram(s) per liter                                |
| MOE              | Margin of exposure                                    |
| ng/g             | Nanogram per gram                                     |
| NIH              | National Institutes of Health                         |
| NOAEC            | No-observed-adverse-effect concentration              |
| NOAEL            | No-observed-adverse-effect level                      |
| OCSPP            | Office of Chemical Safety and Pollution Prevention    |
| OECD             | Organisation for Economic Cooperation and Development |
| OPPT             | Office of Pollution Prevention and Toxics             |
| PBPK             | Physiologically based pharmacokinetic                 |
| pg               | picogram                                              |

|       |                                           |
|-------|-------------------------------------------|
| POTW  | Publicly Owned Treatment Works            |
| PPE   | Personal protection equipment             |
| PPRTV | Provisional Peer-Reviewed Toxicity Values |
| PU    | Polyurethane                              |
| PUF   | Polyurethane Foam(s)                      |
| SIDS  | Screening Information Data Set            |
| TCEP  | Tris(2-chloroethyl) phosphate             |
| TCPP  | 2-Propanol, 1-chloro-, phosphate          |
| TDCPP | 2-Propanol, 1,3-dichloro-, phosphate      |
| TRI   | Toxic Release Inventory                   |
| TSCA  | Toxic Substances Control Act              |
| US    | United States                             |
| WHO   | World Health Organization                 |
| WWTP  | Wastewater Treatment Plant                |

## EXECUTIVE SUMMARY

---

As a part of EPA/OPPT's comprehensive approach to enhance the Agency's management of existing chemicals, EPA/OPPT identified a work plan of chemicals for further assessment under the Toxic Substances Control Act (TSCA)<sup>1</sup> in March 2012. Chemical risk assessments will be conducted if, as a result of scoping and problem formulation, there are exposures of concern, identified hazards and sufficient data for quantitative analysis. If an assessment identifies unreasonable risks to humans or the environment, EPA will pursue risk reduction. This document presents the problem formulation and initial assessment of a cluster of chlorinated phosphate ester flame retardants (CPE FR), comprised of tris(2-chloroethyl) phosphate (TCEP), 2-Propanol, 1-chloro-, phosphate (TCPP) and 2-Propanol, 1,3-dichloro-, phosphate (TDCPP), as part of the TSCA Work Plan.

EPA/OPPT has identified a cluster of three CPE FR chemicals - TCEP, TCPP and TDCP - for risk assessment. These three chemicals have similar physical and chemical properties and environmental fate characteristics. All three chemicals are, or have been used as flame-retardants in polyurethane foams. In addition, they have similar toxicological properties. Given the common use, widespread exposure and potential health hazards, EPA/OPPT conducted a problem formulation based on the evaluation of readily available data and information to determine the feasibility of conducting a quantitative risk assessment.

The conclusions from this problem formulation and initial assessment are that EPA/OPPT will conduct additional analyses as follows:

- Assess potential risks to aquatic organisms from CPEs in the environment.
- Assess potential risks to human health from incidental ingestion of CPEs in inhaled dust or via hand-to-mouth transfer of settled dust released from consumer products.
- Assess potential risks to children from incidental ingestion of CPEs from mouthing of consumer products.
- Assess potential risks to human health from consumption of CPEs in drinking water, or fish (recreational and subsistence fishers).
- Evaluate potential risks to human health from aggregate oral exposure to CPEs.

EPA/OPPT has determined that several uses are not expected to result in significant releases to the environment and therefore will not be assessed:

- Releases from manufacturing and processing resulting in exposures to adjacent communities.
- The manufacture of printed circuit boards.
- The formulation of paints and coatings.
- The use of TDCPP in fabric, textiles and leather products.

EPA/OPPT has determined that a number of scenarios lack sufficient data to quantify risks and therefore will not be assessed at this time:

- Exposures of birds, terrestrial wildlife, or sediment-dwelling organisms (insufficient toxicity data).

---

<sup>1</sup> <http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html>

- Releases to the environment from non-industrial (e.g., office worker) and consumer uses of products containing CPEs (insufficient data to quantify releases).
- Industrial workers via inhalation of vapor and dermal exposure (no route-specific toxicity data).
- Consumer exposures via inhalation and dermal exposures (no route-specific toxicity data).

Exposures to CPE FRs in food (other than fish) will not be assessed, as this is the purview of other federal agencies.

During scoping and problem formulation, EPA/OPPT identified available fate, exposure and hazard data, and characterized potential exposures, receptors and effects. EPA/OPPT examined likely exposure and hazard scenarios based on current production, use, and fate information to identify scenarios amenable to risk analysis. The result of EPA/OPPT problem formulation was a conceptual models and an analysis plan.

Likely sources and pathways considered for analysis include:

- Releases of CPE FRs from chemical manufacturing and processing, resulting in exposures to aquatic organisms via contact with contaminated water.
- Releases of CPE FRs from consumer products, resulting in exposures via the incidental ingestion of air-suspended particulates or resuspended dust and hand-to-mouth transfer of settled dust.
- Mouthing of consumer and children's products containing CPE FRs by children, resulting in incidental oral exposures.
- Releases of CPE FRs from chemical manufacturing and processing, resulting in exposures via the ingestion of contaminated drinking water and fish.

Releases to water from chemical manufacturing, polyurethane foam manufacturing and textile processing are possible and could result in exposures to ecological receptors. EPA/OPPT anticipates that available toxicological data will support the evaluation of acute and chronic exposures in fish, daphnids (invertebrates) and algae.

The evaluation of human health risks will focus on general population and consumer oral exposures. For children and adults, exposures in the home and in other common microenvironments (e.g., schools, daycares, public and commercial buildings, vehicles) may be considered. Consumer exposures to CPE FRs are expected via multiple exposure pathways due to their migration from the polymer matrix into the environment where they are used, either via emission from the products and adsorption to particulates and settled dust or via matrix decomposition, aging or release. Because the predominant consumer uses of CPE-containing polymers, such as insulation and furniture, are in indoor environments, the potential for exposure via all exposure routes (i.e., inhalation of indoor air and dust, dermal contact with products and incidental ingestion of dust) is high.

Mouthing of consumer and children's products containing CPE FRs could result in the migration from the polymer matrix into a child's mouth, resulting in oral exposures. General population oral exposures will be evaluated based on assessed industrial releases and the presence of CPE FRs in fish and drinking water.

Human endpoints include cancer and non-cancer effects. Two CPEs (i.e., TCEP and TDCPP) are known animal carcinogens. Other non-cancer laboratory animal studies have shown effects on the kidney,

liver and the neurological system. Thyroid effects and developmental and reproductive toxicity were more variable across studies.

Inhalation exposures and dermal contact are expected to be significant exposure routes for industrial workers and consumers. However, as there are no toxicological data for inhalation or dermal exposure routes, therefore EPA/OPPT will not assess inhalation or dermal exposure. Inhalation and dermal toxicity studies have been identified as a critical data gap, necessary to evaluate these exposure pathways.

In summary, as a result of this problem formulation, EPA/OPPT proposes to conduct an assessment to evaluate potential risks to aquatic organisms and human health. This document describes the results of problem formulation and the proposed approach for the risk assessment under the TSCA Existing Chemicals Program using existing data and methods. EPA/OPPT plans to carefully review and evaluate the results of previous exposure assessments and health benchmarks. EPA will develop margins of exposure and cancer risk estimates to evaluate the potential risks from consumer and general population exposure to CPE FRs.

# 1 INTRODUCTION

---

As a part of EPA/OPPT's comprehensive approach to enhance the Agency's management of existing chemicals, in March 2012 EPA/OPPT identified a work plan of chemicals for further assessment under the Toxic Substances Control Act (TSCA)<sup>2</sup>. After gathering input from stakeholders, EPA/OPPT developed criteria used for identifying chemicals for further assessment<sup>3</sup>. The criteria focused on chemicals that meet one or more of the following factors: (1) potentially of concern to children's health (for example, because of reproductive or developmental effects); (2) neurotoxic effects; (3) persistent, bioaccumulative and toxic (PBT); (3) probable or known carcinogens; (4) used in children's products; or (5) detected in biomonitoring programs. Using this methodology, EPA/OPPT identified a TSCA Work Plan of chemicals as candidates for risk assessment in the next several years. In the prioritization process, a cluster of chlorinated phosphate ester flame retardant chemicals, including tris(2-chloroethyl) phosphate (TCEP2-propanol, 1-chloro-, phosphate (TCPP) and 2-propanol, 1,3-dichloro-, phosphate (TDCPP), was identified for assessment based on human health and ecotoxicity concerns, potential for human exposure, moderate releases to the environment and moderate environmental persistence.

EPA/OPPT is performing risk assessments on chemicals in the work plan. If an assessment identifies unacceptable risks to humans or the environment, EPA/OPPT will pursue risk reduction. The target audience for this risk assessment is primarily EPA risk managers; however, it may also be of interest to the broader risk assessment community as well as US stakeholders interested in TCEP, TCPP and TDCPP. The information presented in the risk assessment may be of assistance to other federal, state and local agencies as well as to members of the general public who are interested in the risks of TCEP, TCPP and TDCPP.

The initial steps in EPA/OPPT's risk assessment development process, which is distinct from the initial prioritization exercise, includes scoping and problem formulation. During these steps EPA/OPPT reviews currently available data and information, including but not limited to, assessments conducted by others (e.g., authorities in other countries), published or readily available reports and published scientific literature.

This document includes the results of scoping and problem formulation for the chlorinated phosphate ester cluster. In the initial prioritization and scoping stages, EPA/OPPT determined which chemicals would be included in the cluster and which uses would be considered in the assessment. During problem formulation, EPA/OPPT identified available exposure and hazard data, and characterized potential exposures, receptors and effects. EPA/OPPT developed the conceptual models (Figure 2-2 and Figure 2-3) and analysis plan (section 2.6.2) as a result of problem formulation.

---

<sup>2</sup> <http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html>

<sup>3</sup> <http://www.epa.gov/oppt/existingchemicals/pubs/wpmethods.pdf>

## 1.1 Scope of the Assessment

---

Chlorinated phosphate ester (CPE) flame retardants (FR) are high production volume chemicals (up to 50M lbs/yr, based on publicly available information) produced or imported into the United States (EPA, 2012). CPE FRs are widely used in applications for paints and coatings, textiles, insulation and polyurethane foam. Restrictions on the use of polybrominated diphenyl ethers (PBDEs) (EPA, 2012) have likely spurred the increased use of alternative flame retardants, such as CPE FRs, to meet flammability standards for many consumer products, such as mattress pads, furniture or automobile seating. The general US population may be exposed to these chemicals through multiple pathways (Wei et al., 2015).

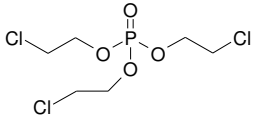
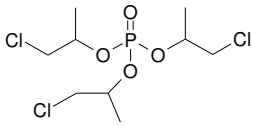
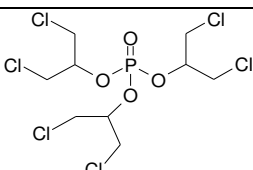
Animal toxicity studies indicate effects that may be suggestive of human health concerns. Two CPEs (i.e., TCEP and TDCPP) are known animal carcinogens. TCPP is currently under study<sup>4</sup>. Other animal studies have shown effects on the kidney, liver and the neurological system. Thyroid effects and developmental and reproductive toxicity were more variable across studies. Given the common use, widespread exposure and potential health hazards, EPA/OPPT conducted a problem formulation and evaluation of readily available data and information to determine the feasibility of conducting a quantitative risk assessment.

EPA/OPPT selected cluster members and uses for inclusion in this assessment based on available data, including chemical structure, physical chemical properties, toxicological information from existing assessments, production volume and reported uses. During the initial work plan chemical prioritization process described above, EPA/OPPT identified TCEP as a work plan chemical, although commercial uses of TCEP as a flame retardant were declining, since TCPP and TDCPP were structurally similar and increasing as substitutes for TCEP. As a result, EPA/OPPT grouped the three chemicals for evaluation (Table 1-1). The rationale for taking a “use cluster approach” is to evaluate chemicals that have a common pattern of use and may have similar fate, exposure and toxicity. Additionally, the cluster approach presents efficiencies in data evaluation and analysis.

---

<sup>4</sup> <http://ntp.niehs.nih.gov/testing/status/agents/ts-m20263.html>

**Table 1-1: CPE FR Cluster Members and Structures**

| CAS RN     | NAME                                                                                           | STRUCTURE                                                                                                        |
|------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| 115-96-8   | Ethanol, 2-chloro-, phosphate (3:1);<br>Tris(2-chloroethyl) phosphate<br>(TCEP)                |                                |
| 13674-84-5 | 2-Propanol, 1-chloro-, 2,2',2''-phosphate;<br>2-Propanol, 1-chloro-, phosphate<br>(TCPP)       | <br>(representative structure) |
| 13674-87-8 | 2-Propanol, 1,3-dichloro-, phosphate (3:1);<br>2-Propanol, 1,3-dichloro-, phosphate<br>(TDCPP) |                                |

EPA/OPPT considered additional CPE FR chemicals for inclusion in the cluster. This process began with the universe of chlorine- and phosphorus- containing chemicals on the TSCA Inventory. Selection criteria included chemical structure, physical chemical properties and data availability. Data availability requirements included sufficient exposure and toxicity data to permit a quantitative assessment. In addition to shared structural similarity, the three CPE FR cluster chemicals are most similar in terms of physical chemical properties and fate, in particular vapor pressure, water solubility and octanol water partition coefficient (Table 1-2). The three chemicals also have sufficient data for risk assessment (Appendix A).

**Table 1-2: Select Physical Chemical Properties Used For Selecting Cluster Members**

| Property                                                                                                                                         | TCEP<br>CAS RN<br>115-96-8   | TCPP<br>CAS RN<br>13674-84-5 | TDCPP<br>CAS RN<br>13674-87-8 |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------|-------------------------------|
| Physical State at Room Temperature                                                                                                               | Liquid                       | Liquid                       | Liquid                        |
| Boiling Point <sup>a</sup><br>°C                                                                                                                 | > 200° C [dec <sup>b</sup> ] | > 200° C [dec]               | > 200° C [dec]                |
| Vapor Pressure <sup>c</sup><br>Pa                                                                                                                | 1.14 E-3                     | 1.4 E-3 <sup>c</sup>         | 5.6 E-6                       |
| Water Solubility <sup>c</sup> mg/L                                                                                                               | 7820                         | 1080                         | 18                            |
| Octanol Water Partition Coeff.<br>Log K <sub>ow</sub> <sup>c</sup>                                                                               | 1.78                         | 2.68                         | 3.68                          |
| <b>Notes:</b><br><sup>a</sup> Stability of C-Cl bond loss HCl begins 200° C<br><sup>b</sup> dec = decomposition noted<br><sup>c</sup> EU (2008b) |                              |                              |                               |

## 1.2 Regulatory and Assessment History

---

EPA/OPPT reviewed the regulatory and assessment history of TCEP, TCPP, and TDCPP, to identify exposures, hazards and risks that have been previously documented.

### ***National***

TCEP, TDCPP and TCPP are existing chemicals on the TSCA Inventory and therefore were not subject to EPA's new chemicals review process and were grandfathered in with the passage of the Toxic Substances Control Act of 1976. EPA has established Provisional Peer-Reviewed Toxicity Values (PPRTVs) for TCEP<sup>5</sup>.

The ATSDR Toxicological Profile for Phosphate Ester Flame Retardants (2012) included TCEP, TDCPP and TCPP and provided detailed analyses of available hazard data. An earlier evaluation by the CPSC (2006) assessed the cancer risks associated with inhalation of TDCPP vapor released from furniture foam and cover fabrics. Estimated cancer risks from lifetime exposure in the home was 300 per million for adults and estimated cancer risk for children from inhalation exposure during the first two years of life was 20 per million. The Hazard Index (a comparison of exposure and critical effect level) was 2 for adults and 5 for children. CPSC estimated that 98-99% of exposure was via the inhalation route.

### ***State***

TCEP and TDCPP are both listed on California's proposition 65 list of chemicals known to the state of California to cause cancer<sup>6</sup>. In addition, California Department of Toxic Substances Control (DTSC) has proposed TDCPP and TCEP in Children's Foam Padded Sleeping Products for regulation under the Safer Consumer Products Regulations.<sup>7</sup>

These CPEs are subject to regulations by a number of states. Other states that have proposed legislation that could affect the use of TCEP, TDCPP and TCPP include Washington, Massachusetts and North Carolina.

### ***International***

The European Union (EU) has conducted risk assessments for TCEP, TCPP and TDCPP (EU, 2008a, 2008b, 2009). Occupational, general population, consumer and ecological exposures were included in these assessments and in some cases, unacceptable risks were identified. Specifically, risks to workers from inhalation and dermal exposure to TCEP were identified, as were risks to children from mouthing of objects made with TCEP (EU, 2009). For all scenarios, risk estimates were based on both carcinogenic and repeat dose effects. For children's risk, the assessment assumed high migration rates via mouthing of articles containing TCEP. The EU concluded that the use of TCEP in toys should be avoided (EU, 2012). TCEP is listed in the EU Authorisation List based on reproductive toxicity (category 1B) with a sunset date of August 21, 2015. No concerns were identified for ecological receptors.

---

<sup>5</sup> <http://hhpprtv.ornl.gov/quickview/pprtv.php>

<sup>6</sup> [http://oehha.ca.gov/prop65/prop65\\_list/Newlist.html](http://oehha.ca.gov/prop65/prop65_list/Newlist.html)

<sup>7</sup> <http://www.dtsc.ca.gov/SCP/index.cfm>

Based on a screening assessment of TCEP, Canada passed a Significant New Activity provision in January 2013 (Health Canada, 2014). As of April 2014, products made, in whole or in part, of polyurethane foam that contains TCEP and are intended for children under three years of age were added to Schedule 2 of the *Canada Consumer Product Safety Act* (CCPSA), based on concerns for carcinogenicity and impaired fertility. These products are prohibited from manufacture, import, advertising or sale.

Although the EU risk assessment for TDCPP also identified potential risks to workers, it concluded that current risk management measures should be effective (EU, 2008b). No risks were identified for consumers, general population, or ecological receptors. These conclusions took into account the EU determination that the cancer risks were below the threshold of concern.

The EU risk assessment for TCPP did not identify unacceptable risks for workers, consumers, general population, or ecological receptors (EU, 2008a).

Appendix B contains additional information on the assessment and regulatory history of these chemicals.

## 2 PROBLEM FORMULATION

---

Problem formulation aims to determine the major factors to be considered in an assessment, including exposure pathways, receptors and health endpoints (EPA, 1998, 2014b). Accordingly, this problem formulation summarized the exposure pathways, receptors and health endpoints EPA/OPPT considered to determine whether to conduct further risk analysis and what exposure/hazard scenarios to include in a potential risk assessment. To make this determination, EPA/OPPT conducted a preliminary data review to identify available fate, exposure and hazard data and determine its likely suitability for quantitative analysis and to identify exposure pathways, receptors and health endpoints for quantitative analysis.

EPA/OPPT summarized the outcome of this evaluation in conceptual models for ecological and human health that illustrate the exposure pathways, receptor populations and effects that will be considered in the risk assessment. EPA/OPPT also prepared analysis plans to demonstrate the proposed approach to answering the defined assessment questions for ecological and human health.

### **Data Needs**

This section summarizes data identified and considered during problem formulation and used to construct the conceptual models. The process by which use and exposure scenarios were selected for inclusion in the conceptual model was informed by the identification of high volume uses that are known or likely to be associated with exposures. The selection process was further aided by the identification of data quality objectives to establish study boundaries and determine the type of data needed to complete the assessment (EPA, 1994b, 1998). Following these established guidelines, EPA/OPPT identified the approach that will be used to assess risks, the data inputs needed and requirements for these inputs.

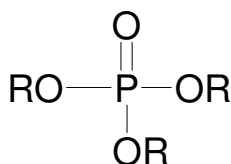
To determine if CPE FRs present a risk to human health, non-cancer risks will be assessed using the Margin of Exposure (MOE) approach. This approach requires the selection of a critical effect in a key study to determine the Point of Departure (POD). Cancer risks will be determined based on low-dose linear extrapolation, which requires the derivation of a cancer slope factor. To assess risks to ecological receptors, the Concentration of Concern (CoC) will be established. Both approaches require the comparison of estimated exposure with a critical effect level (e.g., the POD or the CoC). The types of data required for conducting this type of quantitative risk assessment are defined in Table 2-1.

**Table 2-1: Data Required for Risk Assessment**

|                           | <b>Workers</b>                                                                                                                                                                                                                     | <b>General Population</b>                                 | <b>Consumers</b>                                                                        | <b>Ecological Receptors</b>     |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------|
| <b>Exposure Scenarios</b> | Manufacture and processing.                                                                                                                                                                                                        | Releases to the environment (affecting water and edible). | Consumer product uses resulting in direct exposures or releases to indoor environments. | Releases to the environment.    |
| <b>Exposure</b>           | Measured or modeled concentrations in relevant media may be used. A combination of these approaches may be considered depending on the receptor and exposure scenario of interest.                                                 |                                                           |                                                                                         |                                 |
| <b>Hazard/Toxicity</b>    | Route-specific mammalian toxicity data [or physiologically based pharmacokinetic (PBPK) models to estimate internal doses]. Toxicological effects that are sensitive, adverse and relevant to the potentially exposed populations. |                                                           |                                                                                         | Acute and chronic effects data. |

## 2.1 Physical Chemistry

CPE FRs are formed via reaction derived from the addition of epoxide with  $O=P(Cl)_3$ . TCEP is formed using ethylene oxide. TDCPP is formed using epichlorohydrin. TCP is a chloropropyl phosphate, formed using propylene oxide. The common chemical structure is shown in Figure 2-1. The main substituents or “R” groups are shown in Table 2-2. TCP has a chiral center and is comprised of four isomers (EU, 2008a), as displayed in Table 2-3. All commercial mixtures contain varying amounts of the isomers and available toxicity data are based on the commercial mixture (NRC, 2000).



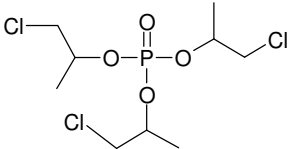
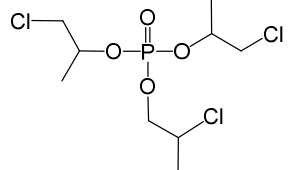
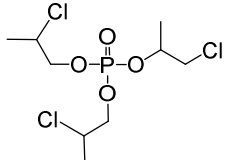
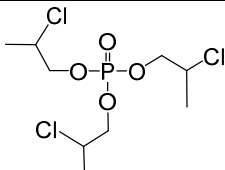
**Figure 2-1: CPE FR Structure**

**Table 2-2: CPE FR Substituents, "R" groups**

| CAS RN                      | Name                                                | R =                                           |
|-----------------------------|-----------------------------------------------------|-----------------------------------------------|
| 115-96-8                    | Ethanol, 2-chloro-, phosphate (3:1); (TCEP)         | <b>-CH<sub>2</sub>-CH<sub>2</sub>-Cl</b>      |
| 13674-84-5                  | 2-Propanol, 1-chloro-, 2,2',2''-phosphate; (TCPP)   | <b>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-Cl*</b> |
| 13674-87-8                  | 2-Propanol, 1,3-dichloro-, phosphate (3:1); (TDCPP) | <b>-CH-(CH<sub>2</sub>-Cl)<sub>2</sub></b>    |
| <b>Note:</b> * Major isomer |                                                     |                                               |

TCPP has chiral centers and is typically comprised of a mixture of four isomers (EU, 2008a), as displayed in Table 2-3. All commercial mixtures contain varying amounts of the isomers and available toxicity data is based on the commercial mixture (NRC, 2000).

**Table 2-3: TCPP in commercial products**

| CAS RN                                                                                  | Chemical Name                                        | Chemical Structure                                                                   | w/w % TCPP in commercial products |
|-----------------------------------------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------|
| 13674-84-5                                                                              | 2-Propanol, 1-chloro-, 2,2',2''-phosphate            |    | <b>50 – 85%*</b>                  |
| 76025-08-6                                                                              | Bis(2-chloro-1-methylethyl) 2-chloropropyl phosphate |  | <b>15 – 40%</b>                   |
| 76649-15-5                                                                              | 2-Chloro-1-methylethyl bis(2-chloropropyl) phosphate |  | <b>&lt; 15%</b>                   |
| 6145-73-9                                                                               | 1-Propanol, 2-chloro-, phosphate (3:1);              |  | <b>&lt; 1%</b>                    |
| <b>Note:</b><br>*Commercial manufacture produces TCPP as 70 – 85% CASRN = [13674-84-5]. |                                                      |                                                                                      |                                   |

The most abundant isomer in commercial products is the completely branched isomer, 2-Propanol, 1-chloro-, 2,2',2''-phosphate (CASRN = 13674-84-5) and the least abundant form is the completely linear isomer, 1-Propanol, 2-chloro-, phosphate (3:1) (CASRN = 6145-73-9) (NRC, 2000). Variations in manufacturing methods result in commercial formulations that contain different proportions of the four isomers. The different isomers may produce differential toxicity and EPA/OPPT will consider this potential variability when evaluating data for use in the risk assessment.

Select physical and chemical properties are displayed in Table 1-2 of section 1.1. A more complete listing of physical and chemical properties is presented in Table 2-4 below.

**Table 2-4: Physical Chemical Properties**

| Property                                                                                                                                         | TCEP<br>CAS RN<br>115-96-8   | TCPP<br>CAS RN<br>13674-84-5 | TDCPP<br>CAS RN<br>13674-87-8 |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------|-------------------------------|
| <b>Molecular Weight (grams/mol)</b>                                                                                                              | <b>285.50</b>                | <b>327.57</b>                | <b>430.88</b>                 |
| <b>Physical State at Room Temperature</b>                                                                                                        | Liquid                       | Liquid                       | Liquid                        |
| <b>Odor</b>                                                                                                                                      | Slight Odor                  | Mild Odor                    | Mild Odor                     |
| <b>Density at 25° C</b>                                                                                                                          | 1.425 g/cm <sup>3</sup>      | 1.29 g/cm <sup>3</sup>       | 1.48 g/cm <sup>3</sup>        |
| <b>Melting Point</b>                                                                                                                             | -55° C                       | -40° C                       | 27° C                         |
| <b>Boiling Point<sup>a</sup><br/>°C</b>                                                                                                          | > 200° C [dec <sup>b</sup> ] | > 200° C [dec]               | > 200° C [dec]                |
| <b>Vapor Pressure<sup>c</sup><br/>Pa</b>                                                                                                         | 1.14 E-3                     | 1.4 E-3 <sup>c</sup>         | 5.6 E-6                       |
| <b>Water Solubility<sup>c</sup> mg/L</b>                                                                                                         | 7820                         | 1080                         | 18                            |
| <b>Octanol Water Partition Coeff.<br/>Log K<sub>ow</sub><sup>c</sup></b>                                                                         | 1.78                         | 2.68                         | 3.68                          |
| <b>Notes:</b><br><sup>a</sup> Stability of C-Cl bond loss HCl begins 200° C<br><sup>b</sup> dec = decomposition noted<br><sup>c</sup> EU (2008b) |                              |                              |                               |

## 2.2 Production Volume and Use

EPA/OPPT searched the 2012 Chemical Data Reporting (CDR) database and market reports, to identify the uses and associated production volumes of each chemical, summarized in Table 2-5. Some information claimed as confidential business information cannot be included in this report. Additionally, primary literature and the Washington State’s Children’s Safe Product Act Database<sup>8</sup> were searched for other potential uses. Additional information is provided in Appendix B.

TCEP’s only CDR reported use is under the “paints and coatings” sector for both the industrial and consumer/commercial categories. Although not reported to the CDR, TCEP has also been reported to be used as a flame retardant in children’s car seats (Washington State, 2014) and has been detected in changing table pads, sleep positioners, portable mattresses, nursing pillows, baby carriers and infant bath mats (Stapleton et al., 2011).

TCPP is reported to the CDR in a variety of industrial use categories such as “furniture and related products” for the manufacture of flexible polyurethane foam and under “textiles, apparel and leather” for fabric finishing processing. Other industrial uses are given in Table 2-5. TCPP is reported to be used

<sup>8</sup> <https://fortress.wa.gov/ecy/cspareporting/Default.aspx>

in a variety of commercial and consumer use categories as well. Potential end-uses within the reported commercial and consumer products include household upholstered furniture and foam baby products, printed circuit boards in automotive electronics, fire stop sealants and panels and laminates for insulation and roofing applications. TCPP has been detected in household furniture including footstools, ottomans and chairs (Stapleton et al., 2009). TCPP has also been detected in polyurethane foam in certain baby products including car seats, changing table pads, sleep positioners, portable mattresses, nursing pillows and rocking chairs (Stapleton et al., 2011).

TDCPP is listed in the CDR's industrial use category under the construction sector and in the commercial and consumer use category under "building/construction materials." These sectors may refer to TDCPP's use in the manufacture of rigid polyurethane foam, which is used in laminates, pipes and ducts. Although not reported as a use in the CDR, TDCPP has been detected in furniture such as sofas, chairs and futons and in baby products including rocking chairs, baby strollers, car seats, changing pads, sleep positioners, portable mattresses, nursing pillows and infant bathmats (Stapleton et al., 2009; Stapleton et al., 2011). TDCPP has also been reported to the Washington State Children's Safe Product Act database (2014) for its use as a flame retardant in "arts/crafts variety pack" and also as a contaminant in footwear for children<sup>9</sup>.

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<sup>9</sup> Arts/Crafts Variety Pack" includes any products that may be described/observed as two or more distinct Arts and Crafts products sold together, which exist within the schema but belong to different classes; that is, two or more products contained within the same pack, which cross classes within the Arts and Crafts Family (GS1, 2014).

**Table 2-5: 2012 CDR Reported Use and Production Volumes**

| Industrial Use Reported to the 2012 CDR                                                                                           | Description of Industrial Use (Based on the Industrial Use Reported to the 2012 CDR) | Commercial or Consumer Use Reported to the 2012 CDR                          | Potential End-Uses Within CDR Category                                                                                                                                                                                                                                                             | 2012 CDR Production Volume |                            |                                     |
|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|----------------------------|-------------------------------------|
|                                                                                                                                   |                                                                                      |                                                                              |                                                                                                                                                                                                                                                                                                    | Industrial (lbs)           | Consumer/ Commercial (lbs) | Approximate % of National PV by Use |
| TCEP, (Ethanol, 2-chloro-, phosphate (3:1); Tris(2-chloroethyl) phosphate); 115-96-8<br>2012 CDR National Production Volume = CBI |                                                                                      |                                                                              |                                                                                                                                                                                                                                                                                                    |                            |                            |                                     |
| Processing: Paints and Coating                                                                                                    | Formulation of Paints and Coatings                                                   | Paints and coatings (not known if intended for consumer/ commercial or both) | Paints and Coatings                                                                                                                                                                                                                                                                                | CBI                        | CBI                        | CBI                                 |
| TCPP (2-Propanol, 1-chloro-, phosphate); 13674-84-5<br>2012 National Production Volume = 54,673,933                               |                                                                                      |                                                                              |                                                                                                                                                                                                                                                                                                    |                            |                            |                                     |
| Processing: Furniture and Related Products (337)                                                                                  | Manufacture of flexible PU Foam for the manufacture of upholstered furniture         | No Data Reported                                                             | <ul style="list-style-type: none"><li>• Polyurethane foam in household furniture (e.g., footstools, ottomans and chairs)</li><li>• Polyurethane foam in baby products (e.g., car seats, changing table pads, sleep positioners, portable mattresses, nursing pillows and rocking chairs)</li></ul> | 43,312,813                 | 17,325,125                 | 32                                  |
| Processing: Textiles, apparel and leather (313-316)                                                                               | Fabric finishing process                                                             | Foam Seating and Bedding Products (commercial and consumer use)              |                                                                                                                                                                                                                                                                                                    |                            | 12,993,844                 | 24                                  |
| Processing: Plastics Material and Resins (325211)                                                                                 | Material Fabrication Process for the Manufacture of Printed Circuit Boards           | Electrical and Electronic Products (commercial and consumer use)             |                                                                                                                                                                                                                                                                                                    |                            | 12,993,844                 | 24                                  |
| Construction                                                                                                                      | Formulation of Adhesives and Sealants ( <i>Not reported as a flame retardant</i> )   | Adhesives and Sealants (Commercial)                                          | - fire stop sealants                                                                                                                                                                                                                                                                               | 780, 604                   | 780, 604                   | 1.4                                 |

| Industrial Use Reported to the 2012 CDR                                                                                 | Description of Industrial Use (Based on the Industrial Use Reported to the 2012 CDR) | Commercial or Consumer Use Reported to the 2012 CDR                                      | Potential End-Uses Within CDR Category                                                                                        | 2012 CDR Production Volume |                            |                                     |
|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------|----------------------------|-------------------------------------|
|                                                                                                                         |                                                                                      |                                                                                          |                                                                                                                               | Industrial (lbs)           | Consumer/ Commercial (lbs) | Approximate % of National PV by Use |
| Construction*                                                                                                           | Manufacture of Rigid PU Foam (boardstock/ laminate, pour-in-place, or spray applied) | Construction Products                                                                    | <ul style="list-style-type: none"><li>• Panels and laminates for insulation applications</li><li>• Roofing laminate</li></ul> | 1,896,664                  | CBI                        | <20%                                |
| Processing: Paints and Coatings                                                                                         | Formulation of Paints and Coatings                                                   | Building/ Construction Materials Not Covered Elsewhere (commercial and consumer use)     |                                                                                                                               | CBI                        | CBI                        |                                     |
| All Other Basic Organic Chemical Processing                                                                             | Unknown                                                                              | N/A                                                                                      |                                                                                                                               | N/A                        | CBI                        |                                     |
| TDCPP, (2-Propanol, 1,3-dichloro-, phosphate); 13674-87-8<br>2012 CDR National Production Volume = 10-50 million pounds |                                                                                      |                                                                                          |                                                                                                                               |                            |                            |                                     |
| Construction                                                                                                            | Manufacture of Rigid PU Foam (boardstock/ laminate, pour-in-place, or spray applied) | Building/Construction Materials, e.g. Laminates, pipes, & ducts. (Consumer & commercial) | <ul style="list-style-type: none"><li>- Laminates</li><li>- Pipes</li><li>- Ducts</li></ul>                                   | CBI                        | CBI                        |                                     |

| Industrial Use Reported to the 2012 CDR    | Description of Industrial Use (Based on the Industrial Use Reported to the 2012 CDR) | Commercial or Consumer Use Reported to the 2012 CDR                     | Potential End-Uses Within CDR Category                                                                                                                                                                                                                                                                            | 2012 CDR Production Volume |                           |                                     |
|--------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------------|-------------------------------------|
|                                            |                                                                                      |                                                                         |                                                                                                                                                                                                                                                                                                                   | Industrial (lbs)           | Consumer/Commercial (lbs) | Approximate % of National PV by Use |
| Processing: Furniture and Related Products | Manufacture of flexible PU Foam for the manufacture of upholstered furniture         | Foam Seating and Bedding Products (Consumer & commercial)               | <ul style="list-style-type: none"> <li>Furniture (e.g., sofas, chairs, futons, rocking chairs)</li> <li>Automotive seating (i.e., cushions and headrests)</li> <li>Baby products (e.g., strollers, car seats, changing pads, sleep positioners, portable mattresses, nursing pillows, infant bathmats)</li> </ul> | CBI                        | CBI                       | CBI                                 |
|                                            |                                                                                      | Fabric, Textile and Leather Products Not Covered Elsewhere (Commercial) | <ul style="list-style-type: none"> <li>Automotive fabric lining</li> <li>Car roofing</li> <li>Textile back coating (specific textiles are not known)</li> </ul>                                                                                                                                                   | CBI                        | CBI                       | CBI                                 |

## **2.3 Fate and Transport**

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The EPA Design for the Environment Branch (DfE) recently published draft hazard profiles for TCEP, TCPP and TDCPP (EPA, 2014a) and included in these hazard profiles are assessments of fate, persistence and bioaccumulation. The summary below is based on information included in the DfE Report.

Although Level III fugacity models incorporating available physical and chemical property data indicate that at steady state TCEP and TCPP are expected to be found primarily in soil and to a lesser extent, water, available data from environmental monitoring indicates that TCEP and TCPP are routinely found in water. TCEP and TCPP are expected to have high mobility in soil, based on measured or estimated  $K_{oc}$  values. Leaching through soil to groundwater may occur. In the atmosphere, TCEP is expected to exist in the vapor phase based on its vapor pressure (EPA, 2014a).

Level III fugacity models indicate that at steady state TDCPP will likely be found primarily in soil and to a lesser extent, sediment and water. Leaching through soil to groundwater may occur. Monitoring data suggests TDCPP is bound to particulates in the atmosphere (EPA, 2014a; Moeller et al., 2011).

TCEP persistence is anticipated to be moderate, whereas TCPP and TDCPP are generally highly persistent. TCEP is expected to hydrolyze slowly; although hydrolysis rates will be dependent on temperature and pH conditions according to experimental studies. TDCPP will undergo hydrolysis under alkaline conditions, with half-lives of 15 days measured at pH 9 and 50°C. TDCPP is relatively stable to hydrolysis under neutral and acidic conditions, a half-life of >1 year was found under pH 4 and pH 7 conditions. None of the chemicals are expected to be susceptible to direct photolysis by sunlight, since they do not absorb light at wavelengths >290 nm. TCEP is not susceptible to significant degradation by ozone or hydroxyl radicals in experimental studies of water samples. The atmospheric half-lives of vapor-phase TCEP and TCPP are estimated to be less than one day, although TCPP is not expected to partition significantly to the atmosphere (EPA, 2014a).

Monitoring studies have reported the detection of TCEP in aquatic species, mammalian species, herring gull eggs and pine needles. Available toxicokinetic studies indicate that in some species, metabolites of TCEP are rapidly formed and eliminated. This demonstrates that these materials are likely bioavailable and could be observed in a biological matrix. However, the rate of metabolism and elimination may be successfully competing with that of uptake, which is also consistent with the experimental BCF results (EPA, 2014a).

## **2.4 Exposures**

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This section provides an overview of available exposure data and the receptors identified for quantitative risk assessment. Data availability tables are available in Appendix A. More detailed exposure summaries, including additional references, are presented in Appendix D. This appendix also includes literature references for the data that is related to releases of CPE FRs to the environment from industrial sites and that EPA took into account in preparing this document.

### **2.4.1 Releases to the Environment**

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EPA/OPPT reviewed readily available sources for information related to the release of flame-retardants in general from industrial sources. EPA/OPPT also searched the scientific literature for data related to releases to the environment from industrial sites, but did not find any chemical-specific data. US Toxic Release Inventory (TRI) data are not available for these chemicals. Releases to water from industrial operations are possible and may have localized impacts on ecological receptors. CPEs are present in WWTPs, sludge and biosolids, although in most cases, the source or sources are not known. Additional information is available in Appendix D.

### **2.4.2 Presence in the Environment**

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Several studies throughout the US and abroad have reported levels of the CPEs in the effluent and influent of wastewater. Measurements in sludge have been made in the EU. However, no US data were identified. Several studies throughout the US and abroad have reported levels of the CPEs in surface water. CPEs have been detected in several studies of US drinking water. Collectively, these data indicate high potential for exposures to ecological receptors, and in particular, aquatic organisms. Additional information is available in Appendix D.

### **2.4.3 Occupational Exposures**

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EPA/OPPT considers inhalation of vapor and dermal exposure to be the most important CPE FR exposure pathways for industrial workers based on (EU (2008a), (2008b)). Occupational inhalation exposure monitoring data for industrial workers in the US are not available, but monitoring data for inhalation exposure of European workers to TCPP or TDCPP vapors at industrial facilities are reported (EU, 2008a, 2008b). Worker exposure to PU foam dust that contains TCPP or TDCPP due to cutting of PU foam has been reported to be possible but was not assessed (EU, 2008a, 2008b). Use of engineering controls (dust extractors) that limit the possibility of dust exposure were reported in Europe (EU, 2008a, 2008b).

#### **2.4.4 General Population Exposures**

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General population exposures include exposures through food and drinking water. Several European studies (from Spain, Sweden and Norway) and one Canadian study have identified CPE FRs in fish. Several studies show that the levels of contaminants varied in relation to their proximity to sewage treatment plants. EPA/OPPT is not aware of data indicating presence of CPE FRs in fish from the US. However, as noted above, CPE FRs have been detected in US drinking water. Data summaries and additional references are available in Appendix D. EPA/OPPT considers it possible that presence in fish and drinking water may contribute to aggregate oral exposures.

#### **2.4.5 Consumer Exposures**

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Consumer exposures to CPE FRs may include:

- Inhalation of vapor,
- Dermal exposure to vapor,
- Direct skin contact with CPE FRs on the surface of objects or articles,
- Incidental ingestion of air-suspended particulates or resuspended dust that is subsequently trapped in mucous and moved from the respiratory system to the gastrointestinal tract (referred to here as incidental ingestion of inhaled dust), and
- Incidental ingestion of indoor settled dust via hand-to-mouth behaviors.

In addition, children may experience incidental ingestion via object-to-mouth behaviors.

A number of published studies have reported levels of CPEs in indoor air and dust. For children and adults, exposures in the home and in other common microenvironments (e.g., schools, daycares, public and commercial buildings, vehicles) may be considered. EPA/OPPT considers exposures to CPE FRs in indoor environments to be possible through inhalation of vapor, incidental ingestion of inhaled dust and hand-to-mouth transfer of settled dust (Cao et al., 2014; EPA, 2011; Makinen et al., 2009; Staaf and Ostman, 2005a; Yang et al., 2014). Additional details and summary data are available in Appendix D.

Numerous studies have measured concentrations of CPE FRs in infant products such as high chairs, bath mats, car seats, nursing pillows, carriers (Fang et al., 2013; Stapleton et al., 2011) sofas (Stapleton et al., 2009; Stapleton et al., 2012) and camping tents (Keller et al., 2014). Because many of these products are used in indoor environments, such as homes, consumer and children are likely to be exposed on a continuing basis using these products. CPE FRs are present in air and dust within the home. Exposures may be through inhalation of vapor or dust, dermal contact and incidental ingestion of inhaled dust. Small children may have additional exposures through contact with baby products containing CPEs and via mouthing behaviors. Data summaries are presented in Appendix D.

## **2.5 Hazard Endpoints**

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EPA's Integrated Risk Information System (IRIS) program has not developed a toxicological review for any of the CPE FRs in this cluster. In the absence of an IRIS assessment, EPA/OPPT's preliminary hazard

evaluation for CPE FRs was based on several existing assessments. In particular, the following studies were deemed helpful, as they were peer reviewed, widely distributed and largely concordant:

- Toxicological Profile for Phosphate Ester Flame Retardants (human health hazards only) (ATSDR, 2012)
- EU Risk Assessment Report: Tris (2-Chloroethyl) Phosphate, (TCEP) CAS No: 115-96-8 (EU, 2009)
- EU Risk Assessment Report: Tris(2-Chloro-1-Methylethyl) Phosphate (TCPP) CAS No: 13674-84-5 (EU, 2008a)
- EU Risk Assessment Report: Tris[2-Chloro-1-(Chloromethyl)Ethyl] Phosphate (TDCP) CAS No: 13674-87-8 (EU, 2008b)

### **2.5.1 Ecological Hazard**

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Data availability tables are presented in Appendix A. Available hazard information for ecological receptors, summarized in Appendix E, is limited to aquatic organisms. There is a robust data set for acute aquatic toxicity, including fish, invertebrate and algal toxicity data for all three chemicals. Chronic aquatic toxicity data is available for daphnids, but not fish. There are no sediment toxicity data or terrestrial toxicity data.

Sublethal effects were observed in acute tests with fish that included loss of coordination that culminated in overturned fish, edema, darkened pigmentation and hyperventilation. These effects suggest potential for long-term population level concerns in fish. In the absence of studies that characterize fish life stages to address population level concerns, EPA/OPPT will consider alternative approaches for evaluating chronic toxicity concerns in fish that may include use of acute-to-chronic ratios derived from halogenated phosphate esters with pesticidal use and non-halogenated phosphate esters with a comparison of sub-lethal effects observed in acute studies.

### **2.5.2 Human Health Hazard**

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#### ***Bioavailability and Metabolism***

Animal studies show that TDCPP, TCEP and TCPP are rapidly and extensively absorbed following oral dosing. Dermal absorption was significant for rats exposed to TDCPP and for *in vitro* studies of human skin exposed to TCPP. Exposure to nebulized TCEP also found extensive absorption (Yoshida et al., 1997), suggestive of the potential for absorption via inhalation although no toxicokinetic data are available for quantifying inhalation absorption. Absorbed TDCPP, TCEP and TCPP distribute throughout the body without preferential accumulation in specific tissues or organs. Transfer to human breast milk is indicated by biomonitoring studies that have found TCEP, TCPP and TDCPP in human breast milk. TDCPP, TCEP and TCPP are rapidly metabolized by extensive Phase I and Phase II metabolism. TDCPP is likely metabolized by a combination of MFO, hydrolase and GST reactions producing glutathione conjugates. TCEP and TCPP are likely metabolized by a similar pathway of hydroxylation possibly by MFO and CYP 450 enzymes then conjugated with glucuronic acid. Some of the metabolism of TCEP may occur extrahepatically, possibly via B-esterases. The metabolic products of TDCP, TCEP and TCPP are rapidly excreted, primarily in the urine. The biliary/fecal excretion ratios for TCEP and TCPP indicate

enterohepatic re-circulation occurs. PBPK models have not been developed for any of the phosphate ester flame retardants.

### ***Toxicological Effects***

A review of existing assessments and other readily accessible information during scoping and problem formulation reveals a number of well-characterized toxicological effects. The ATSDR Toxicological Profile provides a detailed summary of available toxicological data for these chemicals (ATSDR, 2012). Data availability tables are available in Appendix A. Key endpoints are summarized below, but additional detail, including complete references, can also be found in Appendix F.

Animal studies show that TDCPP, TCEP and TCPP are rapidly and extensively absorbed following oral dosing. Dermal absorption was significant for rats exposed to TDCPP and for *in vitro* studies of human skin exposed to TCPP. Exposure to nebulized TCEP also found extensive absorption (Yoshida et al., 1997), suggestive of the potential for absorption via inhalation although no toxicokinetic data are available for quantifying inhalation absorption. Absorbed TDCPP, TCEP and TCPP distribute throughout the body without preferential accumulation in specific tissues or organs. Transfer to human breast milk is indicated by biomonitoring studies that have found TCEP, TCPP and TDCPP in human breast milk. TDCPP, TCEP and TCPP are rapidly metabolized by extensive Phase I and Phase II metabolism. TDCPP is likely metabolized by a combination of MFO, hydrolase and GST reactions producing glutathione conjugates. TCEP and TCPP are likely metabolized by a similar pathway of hydroxylation possibly by MFO and CYP 450 enzymes then conjugated with glucuronic acid. Some of the metabolism of TCEP may occur extrahepatically, possibly via B-esterases. The metabolic products of TDCP, TCEP and TCPP are rapidly excreted, primarily in the urine. The biliary/fecal excretion ratios for TCEP and TCPP indicate enterohepatic re-circulation occurs. PBPK models have not been developed for any of the phosphate ester flame-retardants.

Repeat dose studies indicate that the kidney is a key target organ. In subchronic toxicity tests, kidney effects were noted with all three chemicals. In chronic studies with TCEP (NTP, 1991) and TDCPP (Freudenthal and Henrich, 2000), precancerous and cancerous lesions were observed in the kidneys. Mild liver toxicity (increased liver weights) was also observed in two studies, one on TCDPP (Stauffer Chemical Company, 1981) and another with TCEP (NTP, 1991). Thyroidal effects were seen in TCPP and TDCPP (Freudenthal and Henrich, 1999, 2000).

As noted previously, TCEP and TDCPP are considered animal carcinogens. For example, TCEP exposure was associated with renal tubule adenomas and carcinomas (rats, mice) and follicular cell adenoma or carcinoma of the thyroid (female, high dose rats). A two-year study of TDCPP in rats identified kidney tumors (males, females, testicular tumors (males) and adrenocortical tumors (females) (Freudenthal and Henrich, 1999).

The chemicals in this cluster are considered weak inhibitors of acetylcholinesterase. The toxicological impact of such inhibition continues to be debated. Blood and plasma cholinesterase studies are often conflicting. A number of studies testing TCEP identified neurological effects, such as seizures or convulsions (NTP, 1991; Tilson et al., 1990). A 16-week study in rats found hippocampal lesions, with females more impacted (NTP, 1991). Degenerative brain lesions were also found in female rats in a 2-

year study (NTP, 1991). A similar 2-year study on TDCPP did not identify brain lesions or clinical signs (Freudenthal and Henrich, 1999).

Two studies are available that assess CPEs effect on fertility; high doses of TCEP ( $\geq 350$  mg/kg/day) reduced the number of litters in a continuous breeding study and sperm parameters were reduced. In contrast, there were no effects on reproductive toxicity caused by TDCPP in rabbits (Anonymous, 1977), although in a two-year study with rodents, testicular lesions were noted (Freudenthal and Henrich, 1999).

Two studies are available to assess the developmental toxicity of TCEP; high doses of TCEP ( $\geq 350$  mg/kg/day) reduced the number of live pups per litter in a continuous breeding study and the number of male pups born to the treated F1 generation were reduced at concentrations  $\geq 175$  mg/kg. No fetal or developmental effects were observed in a study of rats administered TCEP on GD 7-15 (Kawashima et al., 1983).

A study of rats administered TDCPP on GD 6-15 resulted in increased resorptions, reduced fetal viability, decreased skeletal development and decreased mean fetal weight at 400 mg/kg/day and a developmental NOAEL of 100 mg/kg was identified (Stauffer Chemical Company, 1981). In this same study, maternal weight gain was also reduced.

EPA/OPPT considers the most significant hazards from exposure to CPEs to be cancer, kidney and liver effects, neurotoxicity and developmental toxicity.

## **2.6 Results of Problem Formulation**

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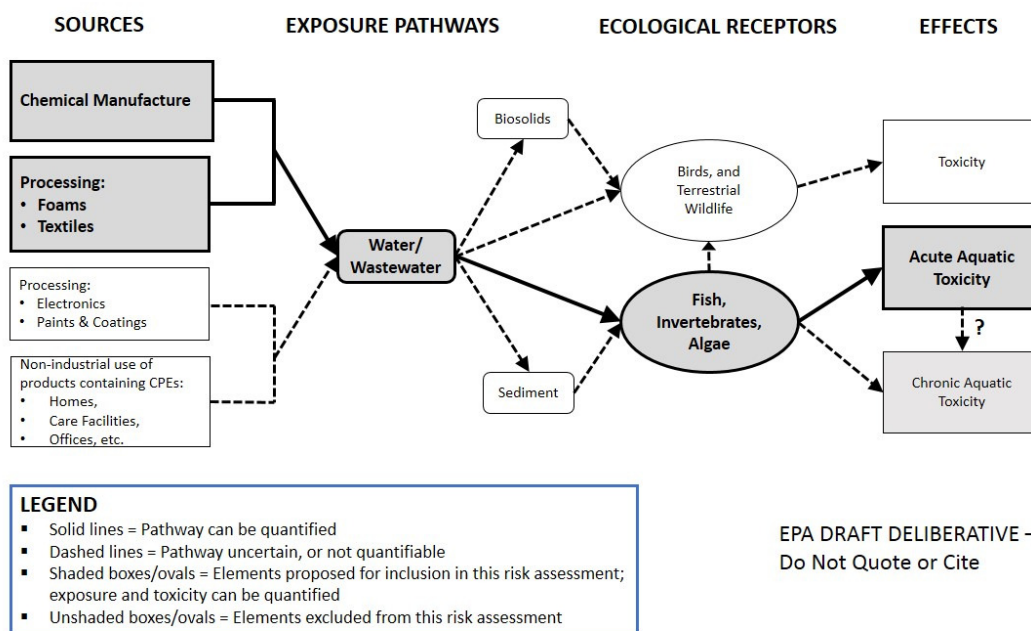
### **2.6.1 Conceptual Models**

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#### ***Conceptual Model for Ecological Receptors***

There is a potential for releases to water from chemical manufacturing, polyurethane foam manufacture and textile processing, which could result in exposures to ecological receptors. Available toxicological data will support the evaluation of acute and chronic exposures in fish, daphnids (invertebrates) and algae.

The following conceptual model (Figure 2-2) illustrates the flow (arrows) of the CPE FRs from chemical manufacture and processing, releases to the environment and potential exposure pathways for ecological receptors. Down the drain releases to water from consumer uses are plausible, as described in Schreder and La Guardia (2014), yet there are insufficient data to quantify these inputs.



**Figure 2-2: Conceptual Model for Ecological Receptors**

The key assessment question for ecological receptors is:

- Do levels of CPEs in the environment pose risk to aquatic organisms?

Based on the identified presence of the CPEs in multiple environmental media, many ecological receptors are potentially exposed. Fish and other wildlife are exposed to these chemicals via ambient air, surface water, sediment, or soil. EPA/OPPTs has limited ability to quantify risks for sediment, soil, sludge and ambient air because very little monitoring data and no hazard endpoints exist for these media. The focus of the environmental risk assessment will therefore be on assessing risks to aquatic organisms from CPE FRs in surface water.

**Table 2-6: Assessment of Environmental Exposures**

| Use Scenario And Applicable Chemicals                                                  | Rationale                                                                                                                                                                                                                         | Limitations                                               |
|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Manufacture:<br>TCPP<br>TDCPP<br>(TCEP is not present at the single import site (CDR)) | There is a potential for large releases to water at ICL-IP America's Gallipolis Ferry, WV site. 79% of the national TCPP production volume is produced at this location and this is the only site at which TDCPP is manufactured. | Releases must be estimated, which introduces uncertainty. |
| PU Foam and Textile finishing:<br>TCPP<br>TDCPP (PU foam only)                         | Releases to water of TCPP or TDCPP are expected.                                                                                                                                                                                  | Releases must be estimated, which introduces uncertainty. |
| TCEP, TCPP and TDCPP in water                                                          | Limited US monitoring data available.                                                                                                                                                                                             | Representativeness must be evaluated.                     |

Risks from acute exposures will be evaluated for fish, invertebrates (daphnids) and algae (Table 2-7). Data for acute aquatic toxicity are available for fish, daphnid and algae; there is only one chronic daphnid study, limiting EPA/OPPT's ability to assess chronic aquatic toxicity. It is possible that sublethal effects observed in fish in the acute study may be informative for a qualitative evaluation of chronic toxicity based on the use of acute-to-chronic ratios from similar halogenated phosphate esters with pesticide uses, and non-halogenated phosphate esters.

**Table 2-7: Assessment of Toxicity in Aquatic Organisms**

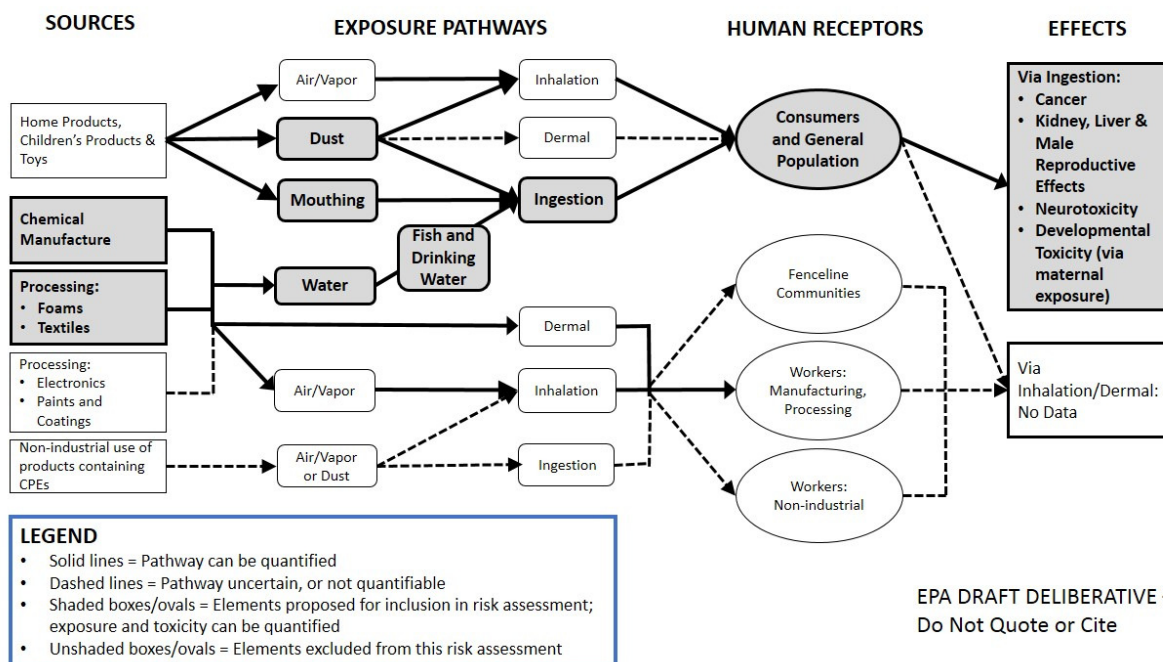
| Scenario<br>And Applicable<br>Chemicals    | Rationale                                                                                                                                                           | Limitations                                                                                                                                                                                                                           |
|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aquatic Organisms<br>TCEP<br>TCPP<br>TDCPP | Known or likely presence of CPEs in aquatic environments. Available acute toxicity for fish, daphnids and algae. Chronic toxicity data available for daphnids only. | Absence of chronic data for fish is a major limitation. It may be possible to do a qualitative assessment, based on sublethal effects in acute studies with a quantitative screening level assessment using predictive methodologies. |

### ***Conceptual Model for Human Receptors***

EPA/OPPT expects industrial worker exposures to be primarily via inhalation of vapor and dermal contact; given the lack of toxicity data for inhalation and dermal routes of exposure, these exposure pathways cannot be quantified in a risk assessment. Workers cutting PU foam at industrial sites may inhale dust containing CPEs, but EPA/OPPT does not have the necessary data to evaluate this potential exposure.

The potential sources of consumer exposure to CPE FRs include a number of consumer products in the home. The CPE FRs in this cluster are chemicals added to polyurethane foam and other matrices and are not chemically bonded to the polymers. Thus, CPE FRs in products are expected to migrate from the matrix into the environment where they are used, either via emission from the products and adsorption deposition to particulates or via matrix decomposition, aging or release. Because the predominant consumer uses of CPE-containing polymers, such as insulation and furniture, are in indoor environments, the potential for consumer exposure via inhalation of indoor air and dust, dermal contact with products and incidental ingestion of dust is high. As described above, neither inhalation nor dermal contact will be considered in this assessment due to absence of route-relevant toxicological data.

The following conceptual model (Figure 2-3) illustrates the flow (arrows) of the CPE FRs from chemical manufacture and processing, releases to the environment and potential exposure pathways for human (consumer and general population) receptors.



**Figure 2-3: Conceptual Model for Human Receptors**

There are four assessment questions associated with the conceptual model for human receptors:

- Does incidental ingestion of CPEs in particulates or dust derived from consumer products pose a risk to human health?
- Does incidental ingestion of CPEs from mouthing of consumer products pose a risk to children?
- Does consumption of CPEs in drinking water, or fish (recreational and subsistence fishers) result in risks to human health?
- Does aggregate oral exposure to CPEs pose a risk to human health?

## Consumers

Ingestion of particulates and dust may occur through the incidental swallowing of inhaled particulates and hand-to-mouth contact, and is likely to be greater for small children due to their activity patterns and increased proximity to areas where dust may gather. Children may also be exposed via ingestion during direct mouthing of toys made with FR-impregnated PU foam if the chemical migrates from the foam and is sufficiently soluble (Table 2-8). For children and adults, exposures in the home and in other common microenvironments (e.g., schools, daycares, public and commercial buildings, vehicles) are likely.

**Table 2-8: Assessment of Exposure to Consumers**

| Exposure Scenario<br>And Applicable<br>Chemicals                                                                                                                                                                                                                                             | Rationale                                                                                                               | Limitations                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Exposure of children in the home via hand-to-mouth transfer of dust, incidental ingestion of inhaled dust and mouthing of products.</p> <p>Exposure of adults in the home via hand-to-mouth transfer of dust and incidental ingestion of inhaled dust.</p> <p>TCEP<br/>TCPP<br/>TDCPP</p> | <p>Exposures are expected to be highest in children.</p> <p>Sufficient data to quantify oral exposure and toxicity.</p> | <p>Although there are data on occurrence of CPE FRs in air-suspended particulates, settled dust and on (children's) hands, these data are not informative as to the source; hence, these metrics will be considered as integrative surrogate exposures.</p> <p>EPA is considering the possibility of quantifying potential incidental ingestion of inhaled dust.</p> |

Much less is known about consumer exposures to textiles or printed circuit boards containing CPE FRs. It is expected that the FRs can migrate out of the textiles and printed circuit boards, but it is not possible at this time to quantify migration rates that may result in exposures. Dust can be considered an integrative metric that combines exposures from multiple sources.

### ***General Population***

Consumption of drinking water and fish are pathways by which humans may be exposed (Table 2-9). EPA/OPPT can estimate exposure to CPE FRs via drinking water and fish ingestion based on releases from industrial sources. These estimates can then be compared to measures of CPE FRs in water and fish samples collected and analyzed in the US and abroad.

For those whose diet relies more heavily upon locally sourced fish consumption, such as recreational and subsistence fishers and their children, exposures from this pathway may be an important contribution to aggregate exposure. A recent Canadian study evaluated the presence of organophosphate FRs, including several CPEs, in fish collected from the Great Lakes and other regions (McGoldrick et al., 2014). Low concentrations (ng/g wet weight) were frequently detected in a Lake Trout and Walleye. From a study in Sweden (Sundkvist et al., 2010), fish collected at points downstream from wastewater treatment plants (WWTPs) had markedly higher concentrations of CPEs when compared to fish collected upstream of the WWTP.

While there are not similar data available from the US for fish, the CPEs have been detected in urban rivers receiving wastewater effluent during low flow conditions (Sengupta et al., 2014). Although it is unknown if concentrations in fish in Sweden would be similar to the US, the samples taken from the Canadian side of the Great Lakes may be broadly representative of that environment. Though exposure factors may exist for fish consumption, there would be uncertainty in determining the concentration of phosphate esters in edible fish.

**Table 2-9: Assessment of Exposure to General Population**

| Scenario And Applicable Chemicals                                                                                                               | Rationale                                                                                      | Limitations                                                                                                                                                                                                                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| General population, including high-end fish consumption (recreational and subsistence fishers) by children and adults:<br>TCEP<br>TCPP<br>TDCPP | Based on stakeholder interest, this exposure pathway will be considered, based on feasibility. | Modeling will be needed to generate estimates of water ingestion and fish consumption. Fish ingestion rates will need to be modified to account for high-end consumption. There are uncertainties that could limit the reliability of these estimates. |

A number of hazard endpoints have been identified for consideration in the risk assessment, including cancer, target organ effects, reproductive and developmental effects and neurotoxicity (Table 2-10). More detailed data summaries are available in Appendix F. Each of these effects has been observed in at least two of the three chemicals.

**Table 2-10: Relevant Endpoints for Human Receptors**

| Receptor       | Acute Exposure (Transient)             | Subchronic Exposure (Short-term)                        | Chronic Exposure (Lifetime)                                              |
|----------------|----------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------|
| Children       | Not applicable                         | Kidney, Liver, Male Reproductive Effects, Neurotoxicity | Not applicable                                                           |
| Adults         | Not applicable                         | Kidney, Liver, Male Reproductive Effects, Neurotoxicity | Kidney Cancer<br>Kidney, Liver, Male Reproductive Effects, Neurotoxicity |
| Pregnant Women | Developmental toxicity (fetal effects) | Developmental toxicity (fetal effects)                  | Not applicable                                                           |

## 2.6.2 Analysis Plan

The analysis plans summarize EPA/OPPT's proposed approach and methods, based on available data as described above (see Data Needs description under section 2, Problem Formulation).

### ***Analysis Plan for Ecological Receptors***

Based on Problem Formulation, EPA/OPPT plans to use available data to evaluate:

- Potential risks to aquatic organisms from acute and chronic exposures to CPE releases to, and presence in the water.

To assess potential ecological risks, releases of TCPP and TDCPP from manufacturing and processing to water must be quantified. EPA/OPPT can consider environmental exposures in two ways. In the risk assessment, EPA/OPPT will assess releases of TCPP and TDCPP to wastewater from manufacturing and processing; and subsequent release to surface water resulting in exposures to aquatic organisms. Current industrial uses of TCEP are not expected to be significant (Table 2-11). Second, EPA/OPPT will

evaluate TCEP, TCPP and TDCPP exposures based on measured concentrations in surface water (Table 2-6). Note that TCEP is no longer manufactured or imported into the US, hence releases from manufacturing and processing will not be quantified. Due to past uses, as well as presence in articles, TCEP continues to be measured in the environment and, risks can be evaluated based on measured concentrations.

**Table 2-11: Analysis Plan for Releases to Water**

| Use Scenario                                                               | Scope                | Assessment Approach                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Releases to water from chemical manufacture                                | TCPP and TDCPP       | Releases will be assessed based on CDR site-specific production volumes. Releases due to cleaning of equipment in batch operation will be assessed in accordance with OPPT's method for assessing releases of New Chemicals from equipment cleaning. The literature will be searched for data that is useful for estimating releases from the washing and dehydration unit operations, including process water consumption rate or emission factor data for analogous processes and releases will be assessed based on the results of this literature search.                                        |
| Releases to water due to processing for the manufacture and use of PU foam | TCPP and TDCPP       | Releases from the following processes will be assessed: blending with polyols (applicable to TCPP only), the slabstock and molded foam processes for the manufacture of flexible PU foam (processing in the molded foam process is applicable to TDCPP only), processing for the manufacture of rigid PU foam and use in the manufacture of upholstered furniture. Releases will be estimated based on a number of sources, including emission factors reported in (EU (2008a), (2008b)), generic scenarios or other New Chemicals Program methods (refer to Appendix D for additional information.) |
| Releases to water due to processing for the finishing of textiles          | TCPP                 | Release from the pad/dry/cure process for textile finishing will be assessed in accordance with the assessment approach described in EPA (1994a) and OECD (2004b).                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Presence of CPE FRs in water                                               | TCEP, TCPP and TDCPP | Appendix D includes summaries of available data on CPE FR concentrations in water. Conduct a literature search to identify additional measured data and evaluate for use in risk assessment.                                                                                                                                                                                                                                                                                                                                                                                                         |

The analysis of risks to aquatic organisms will include effects from both acute and chronic exposures (Table 2-12).

**Table 2-12: Analysis Plan for Assessing Risks to Aquatic Organisms**

| Exposure Scenario                                 | Scope                | Assessment Approach                                                                                                                                                                                                                                                                                                      |
|---------------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Industrial releases and presence in surface water | TCEP, TCPP and TDCPP | A literature search will be conducted to identify any additional, relevant ecotoxicity data for fish, daphnids and algae. Concentrations of Concern (CoCs) will be derived based on results of acute toxicity data. A qualitative assessment will consider the potential effects of chronic exposure on aquatic species. |

## ***Analysis Plan for Human Receptors***

Based on Problem Formulation, EPA/OPPT plans to use available data to evaluate:

- Potential risks from incidental ingestion of CPEs in inhaled dust or via hand-to-mouth transfer of CPEs in settled dust released from consumer products.
- Potential risks from incidental ingestion of CPEs from mouthing of consumer products.
- Potential risks from consumption of CPEs in drinking water, or fish (recreational and subsistence fishers).
- Potential risks from aggregate oral exposure to CPEs.

During problem formulation, EPA/OPPT identified a subset of toxicological endpoints (Table 2-10) as relevant and sensitive, based on a review of existing hazard and risk assessments, as described in section 2.5.2. For the risk assessment, EPA/OPPT will perform a literature search to determine if new data exist and collect the studies identified during problem formulation, to refine the hazard identification and complete the dose-response analysis. To select studies for inclusion, available data will be reviewed to determine test species, test conditions, toxicity endpoints, statistical significance and strengths/limitations of the study, then summarized and evaluated for data quality. Data quality criteria will include use of appropriate analytical and test controls, identification of test substance and test organism, stated exposure duration time and administration route, a clear description of the effect endpoints and transparent reporting of effect concentrations. Guideline studies as well as studies using other protocols will be included if they meet data quality criteria. Studies that meet the criteria for inclusion will then be evaluated in the dose response assessment. The evaluation of TCPP will need to incorporate the potential differential toxicity of isomers.

## ***General Population and Consumers***

Table 2-13 describes the analysis plan for investigating general population and consumer risks. The evaluation of risks to the general population includes risks to adults and children from consumption of CPEs in drinking water and risks to recreational and subsistence fishers from high-end consumption of fish contaminated with CPEs. Consideration of ingestion by pregnant women will be included in this analysis.

Consumer exposures to CPE FRs will be evaluated based on incidental ingestion of inhaled dust (as described above), and incidental ingestion of indoor settled dust via hand-to-mouth behaviors. In addition, exposures to children from incidental ingestion via object-to-mouth behaviors will also be quantified.

Oral exposure by incidental ingestion of house dust via inhalation and hand-to-mouth transfer can be quantified based on US values of monitored house dust. Several recent studies of house dust are available which are expected to be representative of US households. The EPA Exposure Factors Handbook can be utilized to determine typical quantities of dust ingested and time-activity patterns.

The evaluation of risks to general population and consumers will begin with an evaluation of published assessments, including the risk assessment reports produced by the EU and CPSC and the ATSDR toxicological review. The evaluation will determine if components of these published reports are consistent with OPPT methodology, or if additional efforts are needed to supplement or supplant the

existing assessments. If we identify the need to review primary data that is not available in the US, EPA/OPPT will work to negotiate access to these studies. The analysis of primary data will be conducted in accordance with OPPT data adequacy guidelines. The evaluation of cancer and non-cancer risks will be conducted in accordance with EPA guidelines (Table 2-13) (EPA, 2005a, 2005b, 2013).

**Table 2-13: Analysis Plan for General Population and Consumer Risks**

| Exposure Scenario                                                                                                              | Scope                | Assessment Approach                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High-end fish consumption                                                                                                      | TCEP, TCPP and TDCPP | Appendix D includes summaries of available data on CPE FR concentrations in fish. Conduct additional literature search to identify additional US data. Search for and review literature on high-end fish consumption by recreational and subsistence fishers. Use EFAST modeling with comparison to European fish data and US data. Age specific activity patterns and exposure factors will be considered. Fish ingestion rates will be higher for subsistence fishers. Risks will be assessed based on MOE (non-cancer), or by low dose linear extrapolation (cancer). EPA/OPPT will systematically review the existing human health data and select the relevant benchmarks according to the relevant route of exposure. The exposure estimates will be adjusted for expected duration and frequency in agreement with the hazard assessment. |
| Drinking Water consumption                                                                                                     | TCEP, TCPP and TDCPP | Appendix D includes summaries of available data on CPE FR concentrations in drinking water. Conduct additional literature search to identify additional US data. Use EFAST modeling with comparison to US water data. Age specific activity patterns and exposure factors will be considered. Risks will be assessed based on MOE (non-cancer), or by low dose linear extrapolation (cancer). EPA/OPPT will systematically review the existing human health data and will select the relevant benchmarks according to the relevant route of exposure. The exposure estimates will be adjusted for expected duration and frequency in agreement with the hazard assessment.                                                                                                                                                                       |
| Exposure of adults and children via incidental ingestion air-suspended particulates and hand-to-mouth transfer of settled dust | TCEP, TCPP and TDCPP | Appendix D includes summaries of available data on CPE FR concentrations in dust. Conduct additional literature search to identify any US data. Select for inclusion dust monitoring data, based on a range of different indoor environments. Consider both hand-to-mouth and ingestion of inhaled dust particles. Exposure factors (e.g. time and activity patterns or ingestion values) will be based on US EPA Exposure Factors Handbook where available. Risks will be assessed based on MOE (non-cancer), or by low dose linear extrapolation (cancer). EPA/OPPT will systematically review the existing human health data and will select the relevant benchmarks according to the relevant route of exposure. The exposure estimates will be adjusted for expected duration and frequency in agreement with the hazard assessment.        |
| Mouthing of products by children                                                                                               | TCEP, TCPP and TDCPP | Migration rates will be based on assessment of available data, as well as estimates used in other assessments. Consult with CPSC and conduct additional literature search to identify if extraction data are available. Age specific activity patterns and exposure factors will be considered. Younger children are expected to have higher rates of dust ingestion and longer duration of mouthing activity when compared to older children and adults. Risks will be assessed based on MOE (non-cancer), or by low dose linear extrapolation (cancer). EPA/OPPT will systematically review the existing human health data and will select the relevant benchmarks according to the relevant route of exposure. The exposure estimates will be adjusted for expected duration and frequency in agreement with the hazard assessment.           |

## ***Aggregate Exposures and Risk***

Aggregate oral exposures will be assessed considering hand-to-mouth dust ingestion, incidental ingestion of inhaled dust, water ingestion, mouthing of objects (children) and high end fish consumption (Table 2-14).

**Table 2-14: Analysis Plan for Risks from Aggregate Oral Exposures**

| <b>Exposure Scenario</b> | <b>Scope</b>         | <b>Assessment Approach</b>                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aggregate oral exposures | TCEP, TCPP and TDCPP | Conduct additional literature search on averaging times and sensitive life stages for various endpoints. Age-specific activity patterns and exposure factors will be identified. Exposures over time will be aggregated for the pathways described and averaged over periods relevant for younger children, older children and adults. Risks will be assessed based on MOE (non-cancer), or by low dose linear extrapolation (cancer). |

### **2.6.3 Sources and Pathways Excluded From Further Assessment**

The following sources, uses or exposure pathways are excluded from further assessment:

- EPA/OPPT has determined that several uses are not expected to result in significant releases to the environment:
  - Releases from manufacturing and processing resulting in exposures to adjacent communities.
  - The manufacture of printed circuit boards.
  - The formulation of paints and coatings.
  - The use of TDCPP in fabric, textiles and leather products.
- EPA/OPPT has determined that a number of scenarios lack sufficient data to quantify risks:
  - Exposures of birds, terrestrial wildlife, or sediment-dwelling organisms (insufficient toxicity data).
  - Releases to the environment from non-industrial (e.g., office worker) and consumer uses of products containing CPEs (insufficient data to quantify releases).
  - Industrial workers via inhalation of vapor and dermal exposure (no route-specific toxicity data).
  - Consumer exposures via inhalation and dermal exposures (no route-specific toxicity data).
- Exposures to CPE FRs in food (other than fish) will not be assessed.

### **2.6.4 Uncertainties and Data Gaps**

There are a number of important uncertainties and data gaps that must be considered when characterizing risks associated with CPE FRs. Uncertainties and data gaps limit the scope of the assessment and can contribute to both the over- and under-estimation of risk.

### **2.6.4.1 Release and Exposure Uncertainties**

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#### **Industrial Releases**

The processing volumes and number of sites for the following particular processing steps are unknown or uncertain: TCPP blending with polyol, processing of TDCPP in the molded foam process for the manufacture of flexible PU, processing of TCPP and TDCPP for the manufacture of rigid PU foam.

#### **Data Representativeness**

Some exposure data are only available from other countries. There is uncertainty regarding its relevance to US exposure scenarios. Some of the available measurements were made outside the US and it is not clear how well the exposure scenarios derived from them are representative of similar exposure scenarios within the US. Available US monitoring data may not be representative of concentrations in the environment across all areas of the US. Uncertainties may exist in a quantitative evaluation. Mathematical modeling approaches can be used to yield exposure estimates. EPA/OPPT will consider the use of sensitivity analyses to determine key elements of uncertainty.

#### **Fish Consumption**

There are no reported US data of CPEs in fish that are representative of the US and it is unknown if concentrations in fish in Canada and Sweden would be similar to concentrations of fish in the US. Fish ingestion exposures will need to be modeled based on releases to the environment from manufacturing/processing/use. Though exposure factors may exist for fish consumption, there would be uncertainty in determining the concentration of phosphate esters in edible fish. If specific receiving waters are not identified, there will be uncertainty in the amount of dilution that may occur. EPA/OPPT will document the uncertainty and limitations associated with the fish consumption analyses.

#### **Exposure Route Extrapolation**

There is no PBPK model readily available for route-to-route extrapolation. EPA/OPPT has identified this as a critical data gap since the exclusion of dermal and inhalation exposure routes will result in the underestimation of risks. EPA/OPPT will acknowledge this in the risk characterization.

#### **Child Mouthing Exposures**

Data limitations may result in the under- or over-estimation of exposure from mouthing of toys and other consumer products. Oral exposure by direct mouthing of foam-based toys may yield tentative values, as empirical values for migration of FRs out of foam into saliva are not available, nor is there definitive data detailing concentrations of FRs in toys that children may mouth. Expert judgment and assumptions may need to be employed, which will increase the uncertainty of the assessment of this particular scenario. EPA/OPPT will specify all assumptions used in the estimation of exposure to children via mouthing.

### **Microenvironment Variability**

The concentration of CPE FRs in indoor air or dust in different microenvironments are expected to vary; concentrations in offices or workplaces may be greater than in homes. There are uncertainties using existing methodologies to estimate exposure for these different microenvironments. In general, incidental ingestion of dust by adults is expected to be low. EPA/OPPT will derive estimates of exposure via incidental ingestion of dust based on data that represents a variety of different microenvironments.

### **Source to Dose Models**

Source-to-dose models are absent or limited for most of the identified exposure scenarios, therefore the exposure cannot be linked to specific products or the use patterns of any one product. It is not possible to develop source-to-dose exposure models with currently available information. EPA/OPPT will consider the presence of CPE FRs in dust, fish, drinking water and food to be integrative measures of exposure from a number of sources.

### **Model Uncertainties**

Modeled releases to water from industrial facilities may result in the over- or under-estimation of concentrations in the aquatic environment. Modeling will be needed to generate estimates of fish ingestion. Modeling default values will need to be modified (e.g., fish consumption frequency) to account for high-end consumption. In all cases, model assumptions will be clearly articulated. EPA/OPPT will consider the use of sensitivity analyses to determine key elements of uncertainty.

## **2.6.4.2 Hazard Data Uncertainties**

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### **Aquatic Toxicity**

Chronic aquatic toxicity data are needed to better quantify risks to aquatic organisms. In general, availability of information for many of the aquatic toxicity studies are limited to secondary sources; to establish study validity, often a full study report is needed. Sufficient experimental data are not available to characterize chronic population level effects to fish and population level effects towards birds. EPA/OPPT will acknowledge these limitations in the risk characterization.

### **Toxicity Associated With Inhalation and Dermal Exposure**

There are no toxicity data via the inhalation exposure route that would permit a robust assessment of inhalation exposure risks. This problem applies to inhalation exposure to dust and particulates. In addition, there are no toxicity data via the dermal route that would permit a robust assessment of dermal exposure risks. The absence of data to inform health effects that may be associated with inhalation and dermal exposure significantly limits the scope of this assessment and may lead to the underestimation of risk. Although it is possible to estimate exposures via route-to-route extrapolation, these calculations would be highly speculative and potentially misleading. EPA/OPPT has identified this as a critical data gap since the exclusion of dermal and inhalation exposure routes will result in the underestimation of risks.

A chemical specific PBPK model would necessary to develop robust estimates of exposures via multiple routes. EPA/OPPT has identified this as a critical data gap since the exclusion of dermal and inhalation

exposure routes will result in the underestimation of risks. EPA/OPPT will acknowledge this in the risk characterization.

### **Neurotoxicity and Developmental Neurotoxicity**

There is uncertainty regarding the neurotoxic potency of CPE FRs with regard to cholinesterase inhibition. The structural similarity of the chemicals in the CPE cluster make it possible to perform read-across; however, the uncertainty that comes with read-across also must be considered in characterizing the risks associated with the identified exposure scenarios. The majority of available toxicological data are for TCEP and TDCPP. The National Toxicology Program is in the process of collecting toxicological data on TCPP (see <http://ntp.niehs.nih.gov/testing/status/agents/ts-m20263.html>). EPA Office of Research and Development is expected to publish the results of additional studies, as well. These data will help clarify biological similarity and differences among the three structurally similar chemicals.

There are limited data on developmental neurotoxicity. CPE FRs are considered to be weak inhibitors of cholinesterase; there is uncertainty regarding the relationship between weak cholinesterase inhibition and brain development and if this can result in adverse impacts. EPA/OPPT will acknowledge these limitations in the risk characterization.

### **Inter-individual Variability**

Co-morbidities, genetics, lifestyle and other chemical exposures that influence underlying toxic processes could also modulate risk (NRC, 2009). Currently there are no data to inform an analysis of these factors in the proposed risk assessment. EPA/OPPT will acknowledge these limitations in the risk characterization.

## **2.7 Critical Data Needs**

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EPA/OPPT has identified the absence of inhalation and dermal route-specific toxicity data as a critical data need because EPA/OPPT expects that these may be important exposure pathways that cannot be assessed due to data gaps. Inhalation and/or dermal exposures are possible in a number of occupational and consumer settings. The absence of sufficient route-specific toxicity data effectively prohibits the assessment of risks to workers in the occupational setting and to consumers in a residential setting. This data gap may result in the underestimation of aggregate risks associated with exposure to the CPE FR cluster chemicals.

The physical form of the chemical during its use is likely to influence the exposure pathway of interest. Similar to many other semi-volatile organic chemicals, CPE FR cluster chemicals are likely to be present in vapor phase air, total suspended particulates in air and in settled particles on the floor or other indoor surfaces in dust. Sub-chronic and chronic toxicity rather than acute toxicity may be of interest for multiple exposure routes. Air concentrations, dust concentrations, or surface loadings on articles, for example, need to be averaged over some duration (months, years) relevant to toxicity. Examples of exposure scenarios of potential interest, should adequate toxicity and exposure information become available, include:

- Industrial workers who routinely spend the majority of their day in close contact with CPE FR cluster chemicals or materials containing these chemicals;
- Consumers and non-industrial workers in indoor environments who routinely contact or spray apply products containing CPE FRs;
- Pregnant women who meet any of the above scenarios;
- Young children who may routinely spend time exercising in gymnasiums, as the children likely have elevated breathing rates in these environments.

The magnitude of the exposures for these scenarios is highly dependent on individual activity patterns and exposure factors, which are highly variable across the population.

The development of a PBPK model for oral, inhalation (vapor and dust) and dermal routes of exposure would provide the ability to perform route-to-route extrapolation. Route-to-route extrapolation would allow internal doses to be calculated from the oral route toxicity studies and compared with internal doses calculated from exposure scenarios for any of the routes as well as aggregate exposures to multiple routes. To construct a PBPK model, adequate toxicokinetic data would be needed for each route of exposure and these data are lacking for inhalation and dermal exposures.

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## APPENDICES

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## Appendix A Data Availability Tables

The following data availability tables provide a high-level overview of available data through December 2014. They do not reflect study or data quality; nor do they represent suitability for use in risk assessment, which will be determined during the assessment process.

**Table\_Apx A-1: Available Occupational Exposure and Release Data**

| CAS RN                                                       | 115-96-8                                                                  | 13674-84-5                              | 13674-87-8                                   |
|--------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------|----------------------------------------------|
| NAME                                                         | Ethanol, 2-chloro-, phosphate (3:1); Tris(2-chloroethyl) phosphate (TCEP) | 2-Propanol, 1-chloro-, phosphate (TCPF) | 2-Propanol, 1,3-dichloro-, phosphate (TDCPP) |
| Production Volume                                            | ●                                                                         | ●                                       | ●                                            |
| Number of Manufacturing and Processing Sites / Workers       | ●                                                                         | ●                                       | ●                                            |
| Occupational Exposure Limits                                 |                                                                           |                                         |                                              |
| Exposure Monitoring Data                                     |                                                                           | ●                                       | ●                                            |
| Engineering Controls or PPE                                  |                                                                           |                                         |                                              |
| Emission Factors Manufacture                                 | N/A                                                                       |                                         |                                              |
| Processing or Use                                            | ●                                                                         |                                         | ●                                            |
| Release Frequency                                            |                                                                           |                                         |                                              |
| <b>Note:</b><br>● = some data available, US or international |                                                                           |                                         |                                              |

Table\_Apx A-2: Available General Population and Environmental Exposure Data

| CAS NUMBER            | 115-96-8                               | 13674-84-5<br>(6145-73-9)                                                                        | 13674-87-8                                                                                            |
|-----------------------|----------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Chemical Name         | Tris(2-chloro-ethyl)<br>phosphate      | Tris(2-chloro-1-<br>methylethyl)<br>phosphate                                                    | 2-Propanol, 1,3-<br>dichloro-,<br>phosphate                                                           |
|                       | Ethanol, 2-chloro-,<br>phosphate (3:1) | 2-Propanol, 1-chloro-,<br>2,2',2''-phosphate, (1-<br>Propanol, 2-chloro-,<br>1,1',1''-phosphate) | 2-Propanol, 1,3-dichloro-,<br>phosphate (3:1), (1-<br>Propanol, 2,3-dichloro-,<br>1,1',1''-phosphate) |
| Abbreviation          | TCEP                                   | TCPP                                                                                             | TDCPP                                                                                                 |
| BIOMONITORING (HUMAN) |                                        |                                                                                                  |                                                                                                       |
| Blood                 |                                        |                                                                                                  |                                                                                                       |
| Breast Milk           | ●                                      | ●                                                                                                | ●                                                                                                     |
| Adipose Tissue        |                                        |                                                                                                  |                                                                                                       |
| Placenta              |                                        |                                                                                                  |                                                                                                       |
| Urine*                | △                                      | △                                                                                                | △                                                                                                     |
| HUMAN EXPOSURE        |                                        |                                                                                                  |                                                                                                       |
| Dust ingestion        | ●                                      | ●                                                                                                | ●                                                                                                     |
| USGS NWIS Data        |                                        |                                                                                                  |                                                                                                       |
| Water                 | ●                                      |                                                                                                  | ●                                                                                                     |
| Suspended sediment    |                                        |                                                                                                  |                                                                                                       |
| Solids                |                                        |                                                                                                  |                                                                                                       |
| Biota                 |                                        |                                                                                                  |                                                                                                       |
| AIR                   |                                        |                                                                                                  |                                                                                                       |
| Ambient Air           | ●                                      | ●                                                                                                | ●                                                                                                     |
| Indoor Air            | ●                                      | ●                                                                                                | ●                                                                                                     |
| SOIL                  | ●                                      | ●                                                                                                | ●                                                                                                     |
| INDOOR DUST           | ●                                      | ●                                                                                                | ●                                                                                                     |
| SEDIMENT              |                                        |                                                                                                  |                                                                                                       |
| Freshwater            | ●                                      | ●                                                                                                | ●                                                                                                     |
| Marine                | ●                                      | ●                                                                                                | ●                                                                                                     |
| SLUDGE                |                                        |                                                                                                  |                                                                                                       |
| amended soil          |                                        |                                                                                                  |                                                                                                       |
| biosolids             |                                        |                                                                                                  |                                                                                                       |
| landfill              | ●                                      | ●                                                                                                | ●                                                                                                     |
| sewage                | ●                                      | ●                                                                                                | ●                                                                                                     |
| WATER                 |                                        |                                                                                                  |                                                                                                       |
| drinking water        | ●                                      | ●                                                                                                | ●                                                                                                     |
| groundwater           | ●                                      | ●                                                                                                | ●                                                                                                     |
| leachate              |                                        |                                                                                                  |                                                                                                       |
| precipitation         | ●                                      | ●                                                                                                | ●                                                                                                     |
| surface water         | ●                                      | ●                                                                                                | ●                                                                                                     |

| CAS NUMBER                                                                                  | 115-96-8                               | 13674-84-5<br>(6145-73-9)                                                                        | 13674-87-8                                                                                            |
|---------------------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Chemical Name                                                                               | Tris(2-chloro-ethyl)<br>phosphate      | Tris(2-chloro-1-<br>methylethyl)<br>phosphate                                                    | 2-Propanol, 1,3-<br>dichloro-,<br>phosphate                                                           |
|                                                                                             | Ethanol, 2-chloro-,<br>phosphate (3:1) | 2-Propanol, 1-chloro-,<br>2,2',2''-phosphate, (1-<br>Propanol, 2-chloro-,<br>1,1',1''-phosphate) | 2-Propanol, 1,3-dichloro-,<br>phosphate (3:1), (1-<br>Propanol, 2,3-dichloro-,<br>1,1',1''-phosphate) |
| wastewater                                                                                  | ●                                      | ●                                                                                                | ●                                                                                                     |
| AIR + WATER                                                                                 |                                        |                                                                                                  |                                                                                                       |
| deposition                                                                                  | ●                                      | ●                                                                                                | ●                                                                                                     |
| BIOTA                                                                                       |                                        |                                                                                                  |                                                                                                       |
| avian                                                                                       | ●                                      | ●                                                                                                | ●                                                                                                     |
| fish                                                                                        | ●                                      | ●                                                                                                | ●                                                                                                     |
| aquatic animals                                                                             | ●                                      | ●                                                                                                | ●                                                                                                     |
| terrestrial animals                                                                         |                                        |                                                                                                  |                                                                                                       |
| vegetation                                                                                  |                                        |                                                                                                  |                                                                                                       |
| <b>Notes:</b><br>△ = presence of metabolite<br>● = some data available, US or international |                                        |                                                                                                  |                                                                                                       |

Table\_Apx A-3: Available Mammalian and Aquatic Toxicity Data

| CASRN                               | 115-96-8                                                                  | 13674-84-5                                   | 13674-87-8                                   |
|-------------------------------------|---------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------|
| NAME                                | Ethanol, 2-chloro-, phosphate (3:1); Tris(2-chloroethyl) phosphate (TCEP) | 2-Propanol, 1-chloro-, phosphate (TCP) (TCP) | 2-Propanol, 1,3-dichloro-, phosphate (TDCPP) |
| HUMAN HEALTH                        |                                                                           |                                              |                                              |
| Acute Oral Toxicity                 | ●                                                                         | ●                                            | ●                                            |
| Acute Dermal Toxicity               | ●                                                                         | ●                                            | ---                                          |
| Acute Inhalation Toxicity           | ●                                                                         | ●                                            | ---                                          |
| Repeated-Dose Toxicity              | ●                                                                         | ●                                            | ●                                            |
| Reproductive Toxicity               | ●                                                                         | ●                                            | ●                                            |
| Developmental Toxicity              | ●                                                                         | ●                                            | ○                                            |
| Neurotoxicity                       | ●                                                                         | ○                                            | ○                                            |
| Cholinesterase inhibition           | ●                                                                         | ○                                            |                                              |
| Developmental Neurotoxicity         | ○                                                                         |                                              | ○                                            |
| Endocrine Activity                  | ○                                                                         | ○                                            | ○                                            |
| Carcinogenicity                     | ●                                                                         |                                              | ●                                            |
| Genetic Toxicity Mutations in vitro | ●                                                                         | ●                                            | ●                                            |
| Chromosomal Aberrations in vitro    | ●                                                                         |                                              | ●                                            |
| Chromosomal Aberrations in vivo     | ●                                                                         | ●                                            | ●                                            |
| Skin Irritation                     | ●                                                                         | ●                                            | ●                                            |
| Eye Irritation                      | ●                                                                         | ●                                            | ●                                            |
| Sensitization                       | ○                                                                         | ●                                            | ●                                            |
| ECOLOGICAL RECEPTORS                |                                                                           |                                              |                                              |
| Log Kow (P)                         | ●                                                                         | ●                                            | ●                                            |
| Fish 96-h LC50                      | ●                                                                         |                                              | ●                                            |
| Daphnid 48-h LC50                   | ●                                                                         |                                              | ●                                            |

| CASRN                                                                                                                                                                         | 115-96-8                                                                  | 13674-84-5                             | 13674-87-8                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------|----------------------------------------------|
| NAME                                                                                                                                                                          | Ethanol, 2-chloro-, phosphate (3:1); Tris(2-chloroethyl) phosphate (TCEP) | 2-Propanol, 1-chloro-, phosphate (TCP) | 2-Propanol, 1,3-dichloro-, phosphate (TDCPP) |
| Green algae 96-h EC50                                                                                                                                                         | ●                                                                         | ●                                      | ●                                            |
| Fish ChV                                                                                                                                                                      |                                                                           |                                        |                                              |
| Daphnid ChV                                                                                                                                                                   | ●                                                                         |                                        | ●                                            |
| Green algae ChV                                                                                                                                                               | ●                                                                         | ●                                      |                                              |
| Notes:<br>● = data available, likely to be useful for quantitative analysis<br>--- = no data available<br>○ = data available, but may not be useful for quantitative analysis |                                                                           |                                        |                                              |

## Appendix B Regulatory and Assessment History

### B-1 Domestic

TCEP, TDCPP and TCPP are existing chemicals on the TSCA Inventory and therefore were not subject to EPA's new chemicals review process and were grandfathered in with the passage of the Toxic Substances Control Act of 1976.

No occupational exposure limits have been developed by the Occupational Safety and Health Administration, the National Institute for Occupational Safety and Health, or the American Conference of Government Industrial Hygienists. The EPA IRIS program has not determined reference doses and the EPA Office of Water has not set limits or goals for drinking water.

These CPEs are subject to regulations by a number of states, summarized in Table\_Apx B-1. Other states that have proposed legislation that could affect the use of TCEP, TDCPP and TCPP include Washington, Massachusetts and North Carolina.

**Table\_Apx B-1: Existing State Regulations**

| State       | Chemical(s)          | Regulation                                                                                                                                                                                                                                                                                  | Hazard Basis                                 |
|-------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| California  | TCEP and TDCPP       | Proposition 65 ( <a href="http://oehha.ca.gov/prop65/prop65_list/newlist.html">http://oehha.ca.gov/prop65/prop65_list/newlist.html</a> )                                                                                                                                                    | Cancer                                       |
| California  | TCEP, TCPP and TDCPP | Identified as candidate chemicals under the Safer Consumer Product Regulations ( <a href="https://dtsc.ca.gov/SCP/ChemList.cfm">https://dtsc.ca.gov/SCP/ChemList.cfm</a> )                                                                                                                  | Cancer, reproductive toxicity                |
| California  | TDCPP                | Identified as a priority chemical product combination (foam padded children's sleeping products) under the Safer Consumer Products Regulations ( <a href="https://dtsc.ca.gov/SCP/PriorityProducts.cfm">https://dtsc.ca.gov/SCP/PriorityProducts.cfm</a> )                                  | Cancer                                       |
| Connecticut | TCEP, TCPP and TDCPP | Regulates the use in children's products. ( <a href="http://www.cga.ct.gov/2013/FC/pdf/2013HB-06332-R000040-FC.pdf">http://www.cga.ct.gov/2013/FC/pdf/2013HB-06332-R000040-FC.pdf</a> )                                                                                                     | Cancer, reproductive toxicity                |
| Maine       | TCEP                 | Identified as a Chemical of High Concern ( <a href="http://www.maine.gov/dep/safechem/highconcern/">http://www.maine.gov/dep/safechem/highconcern/</a> )                                                                                                                                    | Prioritized by Canada                        |
| Maryland    | TCEP                 | Prohibits sale of certain children's products made with TCEP ( <a href="http://mgaleg.maryland.gov/webmg/frmLegislation.aspx?pid=legisnpage&amp;tab=subject3">http://mgaleg.maryland.gov/webmg/frmLegislation.aspx?pid=legisnpage&amp;tab=subject3</a> ; see 2013, either HB0099 or CH0349) | Cancer                                       |
| Minnesota   | TCEP and TDCPP       | Identified as a Chemicals of High Concern ( <a href="http://www.health.state.mn.us/divs/eh/hazardous/topics/toxfr ee kids/highconcern.html">http://www.health.state.mn.us/divs/eh/hazardous/topics/toxfr ee kids/highconcern.html</a> )                                                     | Cancer, reproductive toxicity                |
| New York    | TCEP                 | Prohibits sale of certain children's products made with TCEP ( <a href="http://assembly.state.ny.us/leg/">http://assembly.state.ny.us/leg/</a> ; see 2003-2004, S 7621)                                                                                                                     | Cancer, reproductive toxicity, neurotoxicity |
| Vermont     | TCEP and TDCPP       | Banned from use in children's products and residential upholstered furniture ( <a href="http://www.atg.state.vt.us/issues/consumer-protection/product-safety/flame-retardants.php">http://www.atg.state.vt.us/issues/consumer-protection/product-safety/flame-retardants.php</a> )          | Cancer                                       |

| State      | Chemical(s)    | Regulation                                                                                                                                                                                                                                                                                                                                                                                        | Hazard Basis                  |
|------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Washington | TCEP and TDCPP | Identified as a Chemicals of High Concern ( <a href="http://www.ecy.wa.gov/programs/swfa/cspa/chcc.html">http://www.ecy.wa.gov/programs/swfa/cspa/chcc.html</a> ) and the Children's Safe Products Act requires manufacturers to report on chemicals of high concern in children's products ( <a href="http://www.ecy.wa.gov/programs/swfa/cspa/">http://www.ecy.wa.gov/programs/swfa/cspa/</a> ) | Cancer, reproductive toxicity |

There are several domestic assessments for chlorinated phosphate ester flame retardants:

- The ATSDR Toxicological Profile for Phosphate Ester Flame Retardants (2012) included TCEP, TDCPP and TCPP and provided detailed analyses of available hazard data.
- EPA derived Provisional Peer-Reviewed Toxicity Values (PPRTVs) for TCEP: an oral subchronic RfD of 0.02 mg/kg-day (kidney effects); an oral chronic RfD of 0.007 mg/kg-day (kidney effects). EPA also identified oral exposures of  $5 \times 10^{-3}$  –  $5 \times 10^{-5}$  mg/kg-day as associated with cancer risks (renal tubular cell adenomas and carcinomas) ranging from  $1 \times 10^{-4}$  –  $1 \times 10^{-6}$ . EPA determined that there was not sufficient data to derive PPRTVs for two TCPP isomers.
- The US Consumer Product Safety Commission (2006) assessed the cancer risks associated with inhalation of TDCPP vapor released from furniture foam and cover fabrics. Estimated cancer risks from lifetime exposure in the home was 300 per million for adults and estimated cancer risk for children from inhalation exposure during the first two years of life was 20 per million. The Hazard Index (Average Daily Dose ÷ Acceptable Daily Intake) was 2 for adults and 5 for children. CPSC estimated that 98-99% of exposure was via the inhalation route.
- The California Environmental Protection Agency, Department of Toxic Substances Control (2014) released a draft document supporting the selection TDCPP in children's foam-padded sleeping products as a candidate priority chemical-product combination requiring an analysis of alternatives, per the California Safer Consumer Products Regulations (<https://dtsc.ca.gov/LawsRegsPolicies/Regs/SCPA.cfm>).
- The National Toxicology Program is in the process of evaluating TCPP in a 90 day toxicity study, a 2-year cancer bioassay and a developmental toxicity study (<http://ntp.niehs.nih.gov/testing/status/agents/ts-m20263.html>). At the time of writing, the results these studies have not yet been made available.

## B-2 International

There are numerous international activities relevant to the chemicals in this cluster. In 2009, Canada conducted a screening assessment of TCEP and concluded that TCEP is harmful to human health. In addition, Canada proposed a risk management approach for TCEP and recommended a prohibition relating to the presence of TCEP in products and materials. To that end, a Significant New Activity provision was concluded in January 2013. In April 2014, products made, in whole or in part, of polyurethane foam that contains TCEP and intended for children under three years of age were added to Schedule 2 of the *Canada Consumer Product Safety Act* (CCPSA), based on concerns for carcinogenicity and impaired fertility. Products listed in Schedule 2 are prohibited from manufacture, import, advertising or sale under section 5 of the CCPSA. Canada has also prepared a draft risk assessment of TDCPP and TCPP, but as of this date has not released the document to the public.

The EU conducted a Risk Assessment of TCEP, TCPP and TDCPP (EU, 2008a, 2008b, 2009):

- TCEP: The EU considered three occupational exposure scenarios: production, product formulation and paints and coatings. Worker risks from inhalation and dermal exposure associated with all scenarios were identified. Risks to children from mouthing of objects were also identified. For all scenarios, risk estimates were based on both carcinogenic and repeat dose effects and potential doses were estimated using probabilistic models. For children's risk, the assessment assumed very high migration rates via mouthing of articles containing TCEP.
- TCEP: Listed in the EU Authorisation List based on reproductive toxicity (category 1B), with a sunset date of August 21, 2015. No concerns were identified for ecological receptors.
- TCPP: The risk assessment identified concerns for workers in chemical manufacturing due to potential effects on fertility and developmental toxicity from dermal exposure. The EU noted that there is need for further information and/or testing for female reproductive effects, but that the LOAEL of 5 mg/kg from the chronic study will likely be protective for female reproductive effects. There were no risk concerns identified for consumer exposure based on the evaluation of exposure to TCPP in three kinds of foam products. The European Commission Scientific Committee on Health and Environmental Risks (SCHER) noted in review of the TCPP RAR that at least 40% of the CPE could volatilize from the PUF product.
- TDCPP: The EU concluded that there is a need for further information and/or testing regarding the effects on female fertility for all worker exposure scenarios, all consumer exposures and both regional and local exposures. Occupational exposure scenarios were considered and dermal and inhalation exposures were modeled using limited available input data. Consumer exposure data considered releases from flexible polyurethane foam. The EU concluded cancer risks were of low concern, but cancer risks were evaluated assuming a threshold mode of action, an approach that is not used by EPA. The EU assumed that the LOAEL of 5 mg/kg from the chronic study would likely be protective for female reproductive effects.
- Based on a screening assessment of TCEP, Canada passed a Significant New Activity provision in January 2013. As of April 2014, products made, in whole or in part, of polyurethane foam that contains TCEP and intended for children under three years of age were added to Schedule 2 of the *Canada Consumer Product Safety Act* (CCPSA), based on concerns for carcinogenicity and impaired fertility, meaning that they are prohibited from manufacture, import, advertising or sale
- Canada provided EPA/OPPT/RAD with a draft copy (not released to public) risk assessment for TDCPP and TCPP, based on intake from air, water, food, beverages and dust (general population) and from dermal and oral exposure to consumer products (consumer) for review and comment.
- Australia conducted a preliminary assessment of TCEP, TCPP and TDCPP as part of the NICNAS Priority Existing Chemical (PEC) assessment process in June 2001. Based on these assessments, the need for occupational exposure data was identified. Australia also recommends additional labeling and training for risk mitigation.

## Appendix C      Uses Supplemental Information

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### ***TCEP***

The Aceto Corporation was the only company that reported manufacturing TCEP during the 2012 CDR reporting cycle. The company's reported industrial, commercial and consumer uses of TCEP during this period are summarized in Table 2-5. Although use of TCEP in polyurethane foam was not reported in 2012, this use has occurred in the past. This has been confirmed with the detection of TCEP in baby products including car seats, changing table pads, sleep positioners, portable mattresses, nursing pillows, baby carriers and infant bath mats at loading levels ranging from 1.08-5.95 mg/g (Stapleton et al., 2011). Additionally, TCEP has been reported to the Washington States Children's Safe Product Act Database for its use in children's products. The database includes supporting evidence for its use in car seats for its flame retardant properties. Non flame-retardant uses reported to the database include as a manufacturing additive in textiles for children's clothing and as a contaminant in footwear, sleepwear and bedding (Washington State 2014). TCEP is included in the EPA's Design for the Environment Program's Furniture Flame Retardancy Report Update (see <http://www.epa.gov/dfe/pubs/projects/flameret/about.htm> for more information) which evaluates the hazards associated with flame retardants used in upholstered items for consumer use.

Additional flame retardant uses which have been identified for TCEP that do not overlap with the CDR reported use include: cast acrylic sheets, carpet backing, building insulation, electronics, rubber and plastics, furniture, adhesives and wood-resin composites (e.g. particle board) (ECHA, 2010; Health Canada, 2012; Joseph and Ebdon, 2010). Additionally, TCEP reportedly can be applied to polyester resins in thermosets, bathtubs and shower stalls (Weil and Levchik, 2009).

### ***TCP***

In addition to the industrial, commercial and use categories reported in 2012 CDR (see Table 2-5), secondary sources identified specific products in which TCP may be used. With respect to the "building and construction not covered elsewhere" category, TCP is known to be an additive flame retardant in rigid polyurethane foam in panels and laminates for insulation applications (EU, 2008a). Additionally, TCP is typically added to pentane-blown foam (15 parts by weight), which is used in applications such as roofing laminate (Weil and Levchik, 2009). ICL-IP's website confirms that Fyrol™ PFC, their commercial TCP product, is widely used for laminate roofing (ICL Industrial Products, No Date-a).

Further, regarding the foam seating and bedding products category, TCP has been used in polyurethane elastomers and in flexible polyurethane foams when combined with melamine (Kirk-Othmer, 1993; Weil and Levchik, 2009). TCP has been detected in household furniture including footstools, ottomans and chairs at loading levels ranging from 0.5 percent to 1.5 percent by foam weight. TCP has also been detected in the polyurethane foam from certain baby products including car seats, changing table pads, sleep positioners, portable mattresses, nursing pillows and rocking chairs in concentrations ranging from 1.11-14.4 mg/g. TCP is included in the EPA's Design for the Environment Program's Furniture Flame Retardancy Report Update (see <http://www.epa.gov/dfe/pubs/projects/flameret/about.htm> for more information) which evaluates the hazards associated with flame retardants used in upholstered items for consumer use.

As for the uses in the electrical and electronic products category reported in the 2012 CDR, the only company who reported this use for TCPP is ICL-IP. Their commercial product of TCPP is Fyrol™ PCF, which is advertised on their website as used in the automotive, bedding and seating and construction industries. Given that, electrical and electronic products would only fall under the automotive category it is reasonable to assume that this is the category of use that TCPP is used in electronics. Further, Fyrol™ PCF is advertised on ICL-IP's website as a flame retardant in phenolics in printed circuit boards (ICL Industrial Products, No Date-a). Based on these two data sources EPA concluded that TCPP is likely used in the circuit boards of automobiles.

Lastly, use of TCPP in the adhesives and sealants category was reported by Hilti, Inc., a construction service company which provides both firestop sealants and other construction chemicals where TCPP may be used (Hilti, 2013).

### ***TDCPP***

The industrial, commercial and consumer uses of TDCPP reported in 2012 CDR are summarized in Table 2-5. Since reporting use of TDCPP in the building/construction materials not covered elsewhere category in 2012 CDR, Albemarle – the only company to report this use – has since discontinued their production of phosphorous-based flame-retardants. Additional searches on company websites, government sources and academic publications on flame retardant uses did not specify where TDCPP has been used in building and construction. However, ICL-IP's website states that its Fyrol™ FR-2, their commercial TDCPP product, can be used phenolics and unsaturated polyester resins (ICL Industrial Products, No Date-b) which can be used in the construction industry in applications such as laminates, pipes and ducts (ICL Industrial Products, No Date-c, No Date-d; The Dow Chemical Company, No Date).

The other commercial/consumer uses reported to 2012 appear to be in the automotive and furniture sectors. For example, ICL-IP's website promotes Fyrol™ FR-2, which can be used in flexible polyurethane foam, as a chemical to assist in meeting automotive flammability tests. Additionally, the European Union Risk Assessment for TDCPP (EU, 2008b) states that TDCPP may be used in molded automotive seating foam (seat cushions, headrests) and slabstock foam in automotive fabric lining and car roofing .

TDCPP has been detected in furniture such as sofas, chairs and futons at loading levels of 1-5 percent by weight and in baby products including rocking chairs, baby strollers, car seats, changing pads, sleep positioners, portable mattresses, nursing pillows and infant bathmats at concentrations ranging from 2.4 to 124 mg/g (Stapleton et al., 2009; Stapleton et al., 2011). TDCPP reportedly can also be used in styrene-butadiene and acrylic lattices for textile back coatings and binding of nonwovens (Joseph and Ebdon, 2010; Weil and Levchik, 2009). TDCPP has also been reported to the Washington State Children's Safe Product Act database (2014) for its use as a flame retardant in "Arts/Crafts Variety Pack" and also as a contaminant in footwear for children.<sup>10</sup> Additionally, TDCPP is included in the EPA's

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<sup>10</sup> The product categories used by Washington State are defined by GS1 Global Product Classification Standards. They define "Arts/Crafts Variety Pack" as "Includes any products that may be described/observed as two or more distinct Arts and Crafts products sold together, which exist within the schema but belong to different classes , that is, two or more products contained within the same pack, which cross classes within the Arts and Crafts Family... Includes products such as Needlework Supplies sold with Beads. *Excludes products such as Printmaking equipment sold with Airbrushing Supplies and Artists Supplies sold with Stationery.*"(GS1, 2014)

Design for the Environment Program's Furniture Flame Retardancy Report Update (see <http://www.epa.gov/dfe/pubs/projects/flameret/about.htm> for more information) which is evaluating the hazards associated with flame retardants used in upholstered items for consumer use.

## Appendix D Exposure Data Summaries

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The following summaries reflect information identified through December 2014.

**Products** – Numerous studies have shown measured concentrations of these FRs in infant products such as high chairs, bath mats, car seats, nursing pillows, carriers (Stapleton et al., 2011; Stapleton et al., 2012), sofas (Stapleton et al., 2009; Stapleton et al., 2012) and camping tents (Keller et al., 2014). Because many of these products are used in indoor environments, such as homes, the general population and children are likely to be exposed on a continuing basis through the use of these products. Small children may have additional exposures through contact with baby products containing CPEs and via mouthing behaviors.

**Dust** – TDCPP has been detected in household, office, automobile and commercial airplane dust in the US and abroad (Ali, Dirtu, et al., 2012; Ali, Van den Eede, et al., 2012; Allen et al., 2013; Bergh et al., 2011; Brommer et al., 2012; Carignan et al., 2013; Dodson et al., 2012; Marklund et al., 2003; Meeker and Stapleton, 2010; Stapleton et al., 2009; Takigami et al., 2009). All three CPE FRs were identified in particulates in indoor air and settled dust collected from four different microenvironments (office, hotel, kindergarten and student dormitory) (Cao et al., 2014). There are several US studies which have quantified concentrations of CPEs in house dust (Dodson et al., 2012; Keller et al., 2014; Stapleton et al., 2009; Stapleton et al., 2012), with a most recent study finding CPEs in 100% of house dust samples and 47-96% of handwipe samples (Stapleton et al., 2014).

**Indoor Air** – Monitoring of indoor air concentrations is limited to studies outside the US, primarily from the EU (Bergh et al., 2011; Bjorklund et al., 2004; Green et al., 2008; Hartmann et al., 2004; Ingerowski et al., 2001; Makinen et al., 2009; Marklund et al., 2005c; Sanchez et al., 2003; Staaf and Ostman, 2005a, 2005b; Tollback et al., 2006) and Japan (Kanazawa et al., 2010; Ohura et al., 2006; Otake et al., 2004; Otake et al., 2001; Saito et al., 2007). Several of these studies also included air sampling in vehicles with many NDs (Hartmann et al., 2004; Sanchez et al., 2003; Staaf and Ostman, 2005a, 2005b), homes, commercial spaces, daycare/school (Bergh et al., 2011; Marklund et al., 2005c; Tollback et al., 2006), offices and public spaces (Hartmann et al., 2004).

**Industrial Releases to Water** – The TCPP manufacturing process is batch or continuous (OECD, 2000). The TCPP and TDCPP manufacturing processes involve washing and then dehydration and result in releases of these chemicals to water (EU, 2008a, 2008b). TCPP may be blended with polyols prior to processing for the manufacture of flexible or rigid polyurethane foam (EU, 2008a). There are two processes for the manufacture of flexible polyurethane foam: the slabstock and the molded foam processes (EPA, 2004a, 2004b); TCPP or TDCPP are processed in the slabstock process (EU, 2008a, 2008b) and EPA believes TDCPP is also processed in the molded foam process based on the use of TDCPP in automobile and airplane seats. Sources of release to water and the associated emission factors or loss factors that pertain to the aforementioned processing steps and, additionally, the use of TCPP and TDCPP in upholstered furniture, are reported in EU (2008b), EU (2008a), EPA (U.S. Environmental Protection Agency) (2004), EPA (U.S. Environmental Protection Agency) (2004), and OECD (2004a).

**Ambient Air** – The concentrations of phosphate esters in air are several orders of magnitude higher indoors than outdoors, indicating that the major sources of these indoor air pollutants are located in the indoor environment (Bergh et al., 2011). One study of ambient air in the Great Lakes region has shown concentrations in  $<<1 \text{ ng/m}^3$  range (Shoeib et al., 2014). Other studies from the EU, Asia and Scandinavia have shown ambient air concentrations in the range of  $\text{pg/m}^3$  to  $\text{ng/m}^3$  range with the highest level of  $58 \text{ ng/m}^3$  reported for a location outside a residence in Japan (Ohura et al., 2006). One study has identified TCEP, TCPP and TDCPP in the ambient air of the Antarctic Peninsula (Cheng et al., 2013), but the authors attribute these concentrations to human activities from a research station rather than global transport. Other studies such as one with measurements of ambient air in a remote area of Finland conclude that the observed concentrations are the result of long-range global transport (Marklund et al., 2005).

**Wastewater** – Several studies throughout the US (Gerrity et al., 2012; Glassmeyer et al., 2005; Jackson and Sutton, 2008; Vidal-Dorsch et al., 2012) and abroad have reported levels of the CPEs in the effluent and influent of wastewater: the highest reported effluent concentration was  $>6000 \text{ }\mu\text{g/L}$  (EU, 2008a). In a recently published study (Sengupta et al., 2014), water samples were collected during 2 low-flow events at locations above and below the discharge points of water reclamation plants in Southern California. Concentrations of chlorinated phosphate flame-retardants were highest among the chemicals of emerging concern tested, with mean total aggregate concentrations of TCEP, TCPP, TDCPP of  $3.4 \text{ }\mu\text{g/L}$  and  $2.4 \text{ }\mu\text{g/L}$  for the 2 rivers.

**Sludge** – Measurements in sludge have been made in the EU (Bester, 2005; Green et al., 2008; Marklund et al., 2005a; Olofsson et al., 2012; Olofsson et al., 2013), however there are no data for the US.

**Soil** – Studies of soil with measured US values are not readily available. The only measured concentrations of CPE in soil are from Germany at the  $\text{ng/g}$  level (Mihajlović and Fries, 2012; Mihajlovic et al., 2011).

**Sediment** – CPEs have been detected in sediment in China, Taiwan and Norway (Cao et al., 2012; Green et al., 2008; Leonards, 2011), however no US studies in the open literature were found. There may be some measurements performed by the USGS through their National Information Water System.

**Surface Water** – Several studies throughout the US (Alvarez et al., 2013; Hoppe-Jones et al., 2010; Kolpin et al., 2002; Oros et al., 2003; Vanderford et al., 2003; Vidal-Dorsch et al., 2012) and abroad (Andresen and Bester, 2006; Andresen et al., 2004; Andresen et al., 2007; Bacaloni et al., 2008; Bendz et al., 2005; Bollmann et al., 2012; Clara et al., 2010; Cristale et al., 2013a; Cristale et al., 2013b; Fries and Puttmann, 2003; Garcia-Lopez et al., 2010; Kim et al., 2007; Martinez-Carballo et al., 2007; Matamoros et al., 2012; Quednow and Puttmann, 2009; Quednow and Puttmann, 2008; Regnery and Puttmann, 2010; Rodil et al., 2012; Schwarzbauer and Heim, 2005; Stepien et al., 2013; Weigel et al., 2005; Yoon et al., 2010) have reported levels of the CPEs in surface water: the highest reported water concentration was  $8.9 \text{ }\mu\text{g/L}$  TCPP (Alvarez et al., 2013). Additional data may be available from the USGS NWIS.

**Drinking Water** – CPEs have been detected in several studies of US drinking water (Benotti et al., 2009; Snyder et al., 2007; Stackelberg et al., 2007). One study of 19 water utilities across the US examining

source water, finished water and tap water (Benotti et al., 2009) showed maximum concentrations of up to 720 ng/L with CPEs detected in up to 50% of the samples.

***Edible Fish*** – See description of biota, below.

***Biota*** – Fish and other wildlife may be exposed to the cluster via surface water, sediment or soil. Measurable levels of the CPEs in fish and other marine species from Canada, Spain, Sweden, Norway have been detected (Evenset, 2009; Green et al., 2008; Jakimska et al., 2013; Leonards, 2011; McGoldrick et al., 2014; Sundkvist et al., 2010). In a study from Sweden (Sundkvist et al., 2010), there were marked differences in CPE concentrations and profiles in fish from sample locations near known sources when compared to background locations. For example, TDCPP was detected (36-140 ng/g lipid weight) in fish collected at points downstream of sewage treatment plants, whereas fish upstream of the sewage treatment plant had a similar profile to other background samples. In the screening study from the Norwegian Arctic (Evenset, 2009), TCEP, TCPP and TDDCP were detected in the fish samples (< 0.6 – 26 ng/g ww), while only TCEP and TCPP were detected in the seabird samples (< 0.5 – 4.7 ng/g ww). TCEP, TCPP and TDCPP in herring gull eggs from the Lake Huron area in the US have been measured (Chen et al., 2012).

Chlorinated phosphate esters have been detected in the breast milk of women from Sweden (Sundkvist et al., 2010) and Asia (Kim et al., 2014). Breast milk was collected from women in four Swedish towns and obtained from the Swedish National Food Administration. The milk was pooled with samples from up to 90 women. TCEP, TDCPP and TCPP were detected with TCPP having the highest reported concentration (median 45 ng/g lipid wt) and TCEP (4.9 ng/g lipid wt) and TDCPP (4.3 ng/g lipid wt) detected at lower levels. TCPP was one of the most frequently occurring FRs in this study.

A study of organophosphorus flame-retardants in human breast milk from Japan, Philippines and Vietnam found that TCEP was one of the most predominant compounds, detected in more than 60% of samples from all three countries. Samples were collected from women living in urban settings including near a municipal waste dumping site in the Philippines and near an e-recycling site in Vietnam. The highest concentration of TCEP from these samples was found in breast milk from the Philippines (median 42 ng/g lipid wt). TDCPP was not detected in the samples from Vietnam and the Philippines and was detected in only 2% of the samples from Japan with the highest value 162 ng/g lipid wt (median ND).

Metabolites of this cluster have been detected in human urine from men and women and children in the US (Carignan et al., 2013; Cooper et al., 2011; Hoffman et al., 2014; Meeker et al., 2013; Stapleton et al., 2014; Van den Eede et al., 2013); and Germany (Schindler et al., 2009).

## Appendix E Ecological Hazard Studies

The following summaries reflect information identified through December 2014.

**Aquatic Toxicity** – Experimental acute aquatic toxicity data are available to characterize fish and aquatic invertebrates for all the CPE members; these data were largely obtained from secondary sources and study reports will need to be located for further evaluation of acceptability. The acute 96-hour LC<sub>50</sub> values ranges from 1.1 mg/L to 249 mg/L for fish and the acute 48-hour EC<sub>50</sub> values ranges from 4.2 mg/L to 170 mg/L for aquatic invertebrates. Available algae toxicity data suggest 72-hour EC<sub>50</sub> value ranges from 2.3 mg/L to 278 mg/L and chronic effects ranges from 4.3 mg/L to 25 mg/L for aquatic plants. In addition, chronic duration studies are available to characterize aquatic invertebrate population level effects.

**Sediment Toxicity** – No data were available to characterize the toxicity of sediment dwelling organisms.

**Terrestrial Toxicity** – Limited data were available to characterize the toxicity of terrestrial organisms. A single in ovo study suggests potential for sub-lethal effects in TDCPP and TCPP.

**Table\_Apx E-1: Ecological Toxicity Data**

| Endpoint                                                                             | Tris(2-chloroethyl) phosphate (TCEP)<br>(CAS RN 115-96-8) | Tris(2-chloro-1-methylethyl) phosphate (TCPP)<br>(CAS RN 13674-84-5) | Tris(1,3-dichloro-2-propyl)phosphate (TDCPP)<br>(CAS RN 13674-87-8) |
|--------------------------------------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------|
| Aquatic Plants Toxicity<br>72 to 96-h EC <sub>50</sub> (mg/L)<br>Growth rate biomass | 278 (m)                                                   | 73 (m)<br>47 (m)                                                     | 2.3 (m)                                                             |
| Aquatic Invertebrates Acute<br>48-h EC <sub>50</sub> (mg/L)                          | 170 (m)                                                   | 97 (m)                                                               | 4.2 (m)                                                             |
| Fish Acute<br>96-h LC <sub>50</sub> (mg/L)                                           | 6.3 – 249 (m)                                             | 55.3 (m)                                                             | 1.1 (m)                                                             |
| Fish Chronic                                                                         | ND                                                        | ND                                                                   | ND                                                                  |
| Aquatic Plants (NOEC/LOEC/GMAT)                                                      | 25 (m)                                                    | 10.4 (m)                                                             | 4.3 (m)                                                             |
| Sediment/Soil                                                                        | ND                                                        | ND                                                                   | ND                                                                  |
| Avian Toxicity                                                                       | ND                                                        | ND                                                                   | ND                                                                  |
| <b>Notes:</b><br>ND = no data<br>(m) = measured data                                 |                                                           |                                                                      |                                                                     |

## Appendix F Human Health Hazard Study Summaries

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Based on a review of existing literature identified through December 2014, we propose the following endpoints for inclusion in the quantitative evaluation of risk:

**Acute Toxicity** – Oral LD50s range from 430 – 3160 mg/kg BW. TCEP has the lowest reported LD50s, ranging from 430-794 mg/kg BW, while TDCPP has the highest LD50 (3160 mg/kg BW). LD50s for TCPP are more variable (ATSDR, 2012).

**Repeated Dose Toxicity** - In addition to kidney tumors, there is evidence of non-cancer kidney and liver effects associated with repeated oral dosing, including renal tubular hyperplasia and altered liver weights (Freudenthal and Henrich, 1999, 2000; Matthews et al., 1993). Thyroid follicular cell hyperplasia was associated with TCPP (OECD SIDS) and TCEP (Matthews et al., 1993). In addition an epidemiological study identified a correlation between decreased thyroid hormone levels in men with TDCPP levels in dust (Meeker and Stapleton, 2010).

**Male Reproductive Toxicity** - One study in rats has noted effects on male reproductive organs. Freudenthal and Henrich (2000) observed a higher incidence of atrophy in seminal vesicles, decreased secretory product and testicular enlargement in a two-year bioassay. Two studies in rabbits yielded no adverse effects, however the duration of these studies were shorter. The European Union determined that the weight of evidence yielded no concern for male reproductive. Given the uncertainty surrounding the impact of long-term exposures and male reproductive toxicity, it is not possible to quantify risks at this time.

**Developmental Toxicity** - Two studies are available to assess the developmental toxicity of TCEP; high doses of TCEP ( $\geq 350$  mg/kg/day) reduced the number of live pups per litter in a continuous breeding study and the number of male pups born to the treated F1 generation were reduced at concentrations  $\geq 175$  mg/kg (Chapin et al., 1997). No fetal or developmental effects were observed in a study of rats administered TCEP on GD 7-15 (Kawashima et al., 1983).

A study of rats administered TDCPP on GD 6-15 resulted in increased resorptions, reduced fetal viability, decreased skeletal development and decreased mean fetal weight at 400 mg/kg/day and a developmental NOAEL of 100 mg/kg was identified (Stauffer Chemical Company, 1981). In this same study, maternal weight gain was also reduced.

**Endocrine Activity** - There is some evidence for modulation of endocrine activity. In a small human population study, gynecomastia was noted in workers at a TDCPP manufacturing plant (Stauffer Chemical Company, 1981). Several studies evaluated the association between TDCPP and thyroid activity. Decreased whole body changes in T3 and T4 and genes related to thyroid hormone synthesis, metabolism and gland development were noted in a zebrafish model (Wang et al., 2013). Decreased plasma T4 was observed in chick embryos treated with TDCPP (Farhat et al., 2013). In a human exposure study there was an association between TDCPP in house dust and decreased T4 levels in men (Meeker and Stapleton, 2010). But in a recent study evaluating the relationship between TDCPP exposure in rats and thyroid weight or serum T3/T4, no changes were observed (Moser et al., 2014).

## Chlorinated Alkyl Phosphate Flame Retardants

The conflicting data and lack of consistent adverse endpoints makes it difficult to evaluate quantitatively.

**Genetic Toxicity in vitro and in vivo** - Mutagenicity data on chemicals in this cluster yield mixed results. In general, Ames assays were negative, while several chromosomal aberration assays were positive (ATSDR, 2012). Therefore, the putative mechanism of carcinogenicity is not clear.

**Carcinogenicity** - Animal studies have demonstrated that TCEP and TDCPP are carcinogenic in rodents. Takada et al. (1989) showed that ddY mice given TCEP in the diet for 18 months had dose-related increases in the incidences of renal cell adenomas/carcinomas and hepatocellular adenomas/carcinomas in males and forestomach papillomas/squamous cell carcinomas and leukemia in females. NTP cancer bioassays (gavage studies) indicated that TCEP treatment was associated with increased kidney and thyroid tumors in rats and Harderian gland tumors in mice (NTP, 1991). In a 2-year oral study involving TDCPP exposure, rats of both sexes developed kidney and liver tumors and males also had higher incidences of testicular tumors (Freudenthal and Henrich, 1999). NTP is currently in the process of evaluating data from a cancer study on TCPP; we will track progress in this study and incorporate data as soon as it is available (<http://ntp.niehs.nih.gov/?objectid=BD724190-123F-7908-7BA185DA18C1EBB8>). Based on a comparison of the calculated doses causing 50% incidence of tumor (TD<sub>50</sub>), TDCPP (TD<sub>50</sub>= 46.4 mg/kg/day) appears to have a higher carcinogenic potency than that of TCEP (TD<sub>50</sub>= 86.7 mg/kg/day) in the rat by the **oral route** (<http://toxnet.nlm.nih.gov/cpdb/>). The chlorinated alcohol metabolite of TDCPP (i.e., 1,3-dichloro-2-propanol) has also been shown to be carcinogenic by the oral route (IARC, 2012; NTP, 2005). The corresponding metabolite of TCEP (2-chloroethanol) was considered not carcinogenic in a dermal study by (NTP, 1985).

**Neurotoxicity** - A number of studies present evidence that moderate to high exposure to TCEP can decrease plasma cholinesterase activity in rodents and birds. In rats, brain lesions were noted following short term high-dose exposure (Matthews et al., 1990). The same study found convulsions associated with high doses in rats and mice. The study authors noted that female rats appear to be more sensitive than male rats and rats appear to be more sensitive than mice. There is anecdotal evidence of acute poisoning in dogs, who consumed seat cushions when left in cars overnight (Lehner et al., 2010). All studies were based on oral exposure.

Additional endpoints are of interest, but will not be included in the quantitative assessment for reasons described below.

**Developmental Neurotoxicity** - Decreased plasma cholinesterase levels observed in female rats is considered representative of modulation of cholinesterase levels in the fetus of pregnant rats. Decreased fetal cholinesterase levels pose a risk to fetal neurological development, in particular, altering critical proliferation and differentiation events (e.g., see Rice and Barone 2000). Additional evidence lending weight to this hypothesis comes from in vitro studies using PC12 cells as a model for neurological development (Dishaw et al., 2011). When treated with TDCPP, TCEP, TCPP and chlorpyrifos (as a model OP), the cells exhibited decreased DNA content – a marker of development-induced cell proliferation, oxidative stress and altered neurodifferentiation. The concern for modulation of neurological development based on mechanistic data does not seem to manifest in

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available animal studies. As described by ATSDR (2012) TCEP oral exposure in pregnant rats did not induce abnormalities in functional behavioral tests (Kawashima et al., 1983). A more recent study by Moser et al. (2014) also did not identify alternations in behavioral effects, based on an examination of righting reflex and locomotor activities. Additional studies are underway and should be reported this year.