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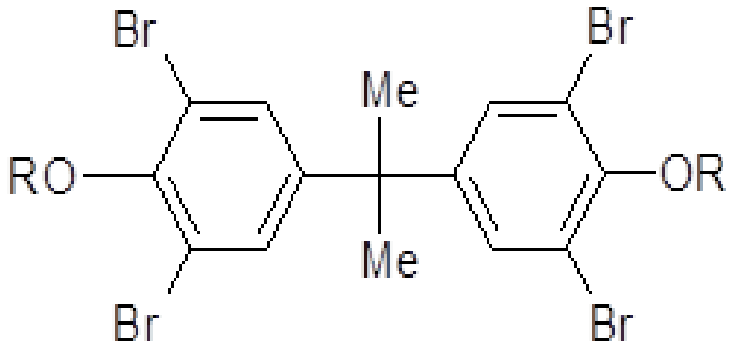
Office of Chemical Safety and
Pollution Prevention

United States
Environmental Protection Agency

TSCA Work Plan Chemical
Problem Formulation and Initial Assessment

Tetrabromobisphenol A and Related Chemicals Cluster
Flame Retardants



CASRN	NAME
79-94-7	Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo
21850-44-2	Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)-
25327-89-3	Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-
37853-61-5	Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-methoxy-

August 2015

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Docket

Please visit the public docket (Docket: EPA-HQ-OPPT-2014-0730) to view supporting information.

ABBREVIATIONS

ABS	Acrylonitrile butadiene styrene
ADEQ	Arkansas Department of Environmental Quality
AERMIC	AMS/EPA Regulatory Model Improvement Committee
AERMOD	AERMIC AMS/EPA Regulatory Model
AMS	American Meteorological Society
ASTM	American Society for Testing and Materials
B1, 2 or 3	Bioaccumulation level 1, 2 or 3
B6C3F1	Mouse strain
B6C3F1/N	Mouse strain
BA-59P	Trade name for TBBPA
BAEP	Brainstem auditory evoked potential
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BPA	Bisphenol A
BSEF	Brominated Science and Environmental Forum
CASRN	Chemical Abstract Service Registry Number
CBI	Confidential business information
CFR	Code of Federal Regulations
CDR	Chemical data reporting
COC	Concentration of concern
DL	Detection limit
Doverguard 59	Trade name for TBBPA
Doverguard 68	Trade name for TBBPA-bis(dibromopropyl ether)
dw	Dry weight
EC	European Commission
ECB	European Chemicals Bureau
EC/HC	Environment Canada and Health Canada
ECHA	European Chemicals Agency
ECOTOX	EPA database of ecotoxicity studies
EPA	United States Environmental Protection Agency
EPI	Estimation Programs Interface
ER	Estrogen receptor
EU	European Union
e-waste	electronic waste
F_0	Parental generation
F_1	First generation of offspring
F344/NTac	Rat strain
FR-720	Trade name for TBBPA-bis(dibromopropyl ether)
FR-1524	Trade name for TBBPA
GLCC	Great Lakes Chemical Corporation
GLP	Good laboratory practice

HPV	High production volume
ICL-IP	ICL Industrial Products America, Inc.
ISO/DIS	International Organization for Standardization/Draft International Standard
IUR	Inventory update reporting
kg	Kilogram
lb	Pound
LC_{50}	Lethal concentration at which 50% of test organisms die
LD_{50}	Lethal dose at which 50% of test organisms die
LOAEL	Lowest-observed-adverse-effect level
LOEC	Lowest-observed-effect concentration
LOQ	Limit of quantitation
Log K_{OC}	Logarithmic soil organic carbon partition coefficient
Log K_{OW}	Logarithmic octanol-water partition coefficient
lw	Lipid weight
MATC	Maximum acceptable toxicant concentration
mg/kg-bw/day	Milligrams (of a chemical) per kilogram of body weight per day
MITI	Ministry of International Trade and Industry (Japan)
MOA	Mode of action
MOE	Margin of exposure
MOS	Margin of safety
MSW	Municipal solid waste
NAICS	North American Industry Classification System
NMRI	Mouse strain
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
NTP	National Toxicology Program
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics
P1, 2 or 3	Persistence level 1, 2 or 3
PAHs	Polyaromatic hydrocarbons
PBDDs	Polybrominated dibenzodioxins
PBDFs	Polybrominated dibenzofurans
PND	Postnatal day
QSAR	Quantitative structure activity relationship
RCRA	Resource Conservation and Recovery Act
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SAYTEX® CP-2000	Trade name for TBBPA
T_3	Triiodothyronine
T_4	Thyroxine
TBBPA	Tetrabromobisphenol A
TOC	Total organic carbon
Tp53	Gene for tumor suppressor p53 protein
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act

TSH	Thyroid stimulating hormone
TTR	Transthyretin
UL	Underwriters Laboratories
US	United States
ww	Wet weight
WWTP	Wastewater treatment plant
yr	Year

EXECUTIVE SUMMARY

As part of EPA'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) 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 for TBBPA and related chemicals as part of the TSCA Work Plan.

EPA/OPPT included TBBPA-bis(dibromopropyl ether) (CASRN 21850-44-2) and TBBPA-bis(allyl ether) (CASRN 25327-89-3) in the TBBPA cluster as a result of an initial prioritization exercise because these compounds have additive flame retardant uses; EPA/OPPT assumes that additive uses will lead to higher potential for exposure. EPA/OPPT included a fourth chemical, TBBPA-bis(methyl ether) (CASRN 37853-61-5), because monitoring studies have routinely found this substance in the environment. Its presence is likely to be a result of microbial transformation of TBBPA.

Conclusions

As a conclusion of this problem formulation and initial assessment, EPA/OPPT will further assess the following risks to:

Environment

- Aquatic, sediment-dwelling or soil-dwelling organisms resulting from two manufacturing facilities that emitted the vast majority of TBBPA to air during a 13-year period (2000-2012) as indicated from Toxics Release Inventory (TRI) data.

Human Health

- Workers at manufacturing and processing facilities who may ingest TBBPA in dust from the air after further developing assessment methods.
- Aggregate oral exposure from the following oral exposure pathways:
    - Incidental ingestion of TBBPA in dust from outdoor sources
    - Incidental ingestion of TBBPA in dust from indoor sources
    - Incidental ingestion of TBBPA from mouthing of consumer products
    - Consumption of TBBPA in fish (recreational and subsistence fishers)

  These aggregate exposures will be assessed and compared for the following: 1) those who live near two manufacturing facilities, and 2) those who do not live near such facilities.

EPA/OPPT will not specifically assess the following risks:

- To the general population near processing sites, due to smaller releases from processors than from manufacturers.
- To the environment and human health from recycling plants given limited information regarding recycling of electronic products in the United States.
- From product disposal, due to required controls, limited data or low concerns.
- From drinking water due to lack of information as well as a likelihood of low risk concerns.
- From eating food other than fish because this is considered the purview of other agencies.
- For adults exposed directly (through mouthing) to consumer products, based on low concerns.

Exclusion of Three Cluster Members and Degradation Products

Some limited information is available for the cluster members other than TBBPA. However, EPA/OPPT concluded that no quantitative risk assessment is needed for these other cluster members for one or more of the following reasons: limited information, inability to use the more robust data for TBBPA to read across to other cluster members, low toxicity or likely low risk concerns.

EPA/OPPT also investigated the possibility of evaluating risks for degradation and combustion products of TBBPA. However, information is too limited on rates of degradation and the specificity of identified combustion products to incineration of TBBPA. Therefore, EPA/OPPT will not assess risks from exposure to these products in the proposed assessment.

TBBPA Data Evaluated During Problem Formulation

TBBPA (CASRN 79-94-7) is used as a flame retardant, is persistent and has been detected in the environment, in humans and in biota. Of the brominated flame retardants, TBBPA has the highest US and global production volume with a reported 2011 US volume of 120 million pounds. It is used as both an additive and reactive flame retardant[1] and is reacted to produce more than 70 compounds. It is used primarily in electronics but may be found in a variety of other products.

In 2012, reports to TRI indicated that 52 manufacturing and processing facilities released or disposed approximately 127,845 pounds of TBBPA. The compound may undergo direct photolysis and indirect photo-oxidation, but the amount of vapor in air is expected to be low. It is expected to be persistent in water, soil and sediment and has a low bioaccumulation potential.

TBBPA has been found in humans (blood, breast milk and adipose tissue) and in biota (aquatic and terrestrial animals and plants and in birds). Several studies have also found TBBPA in a variety of environmental media that includes sediment, soil, landfill leachates, sewage sludge, surface water, wastewater and indoor and outdoor air.

[1] A reactive use is one in which TBBPA is covalently bound with the substrate matrix. An additive use means that TBBPA is not reacted with the substrate.

Ecological toxicity studies include acute and chronic data for aquatic organisms (including sediment-dwelling organisms), terrestrial plants, soil invertebrates, birds and amphibians. Epidemiological studies and toxicity studies to inform human health hazard are also available. These include acute, repeated-dose, reproductive, developmental, carcinogenicity, genotoxicity, irritation and sensitization studies. Some information is also available on toxicokinetics.

EPA/OPPT followed Agency guidance during problem formulation and reviewed previous assessments, such as those by the EU and Canada, to help inform the proposed assessment for TBBPA (and TBBPA-bis(allyl ether)). Other published and unpublished data sources were also reviewed. During problem formulation, EPA/OPPT identified available fate, exposure and hazard data, and characterized potential exposures, receptors and effects.

To assist in targeting sources and exposure pathways of most concern, high-end exposure values from existing risk assessments or more recent data were compared with toxicity values. For the environmental scenarios, EPA/OPPT developed concentrations of concern (COCs) by applying routinely-used uncertainty factors. For human health scenarios, EPA/OPPT calculated a health-conservative toxicity value for developing uterine tumors using a recent carcinogenesis bioassay from the National Toxicology Program.

Results of Problem Formulation

The results of this problem formulation are illustrated in the conceptual models and described by the analysis plan that seeks to answer several assessment questions.

In summary, EPA/OPPT will conduct additional risk analysis of potential exposure to organisms surrounding manufacturing facilities using concentrations of concern to determine risk quotients. EPA/OPPT will also investigate potential exposure for workers and the general population/consumers under the TSCA Existing Chemicals Program using existing data and methods.

Occupational risks will focus on workers within manufacturing and various processing facilities. For the general population (with some exposure from consumer products), risks will be aggregated for multiple oral pathways (direct oral ingestion or indirect ingestion from inhaled dust) and will focus on individuals near manufacturing facilities and those farther away from such facilities. EPA/OPPT will compare these exposure estimates to cancer and developmental effects benchmark values to evaluate risk.

1 INTRODUCTION

As a part of EPA's comprehensive approach to enhance the Agency's management of existing chemicals, in March 2012 EPA identified a work plan of chemicals for further assessment under the Toxic Substances Control Act (TSCA)[2]. After gathering input from stakeholders, EPA developed criteria used for identifying chemicals for further assessment[3]. 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, tetrabromobisphenol A (TBBPA) was identified for assessment based on its use as a flame retardant in epoxy resin circuit boards and in electronic enclosures in consumer uses, acute aquatic toxicity and environmental persistence. Other chemicals were added to the cluster during this initial prioritization based on considerations described in Section 1.1.

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 TBBPA and related chemicals. 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 TBBPA and related chemicals.

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. During scoping and problem formulation the more robust review of the factors influencing initial prioritization may result in refinement – either addition/expansion or removal/contraction – of specific hazard or exposure concerns previously identified in the prioritization methodology.

This document includes the results of scoping and problem formulation for TBBPA and related chemicals. In the initial prioritization and scoping stages EPA/OPPT determined which chemical(s) would be included and what 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 two conceptual models, Figure 2-1 and Figure 2-2, and an analysis plan (Section 2.6.2) as a result of problem formulation.

[2] http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html
[3] http://www.epa.gov/oppt/existingchemicals/pubs/wpmethods.pdf

1.1 Scope of the Assessment

The four chemicals in the TBBPA and related chemicals assessment have the following general structure:

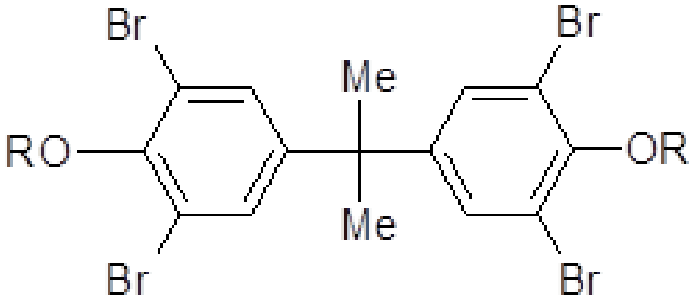


Figure 1-1: General Structure for TBBPA and Related Chemicals

Table 1-1 identifies the chemical names, Chemical Abstract Service Registry Numbers (CASRNs) and definitions of R groups that are shown in the above structure.

Table 1-1: Chemical Names and Structures

Chemical Name	CASRN	CAS Name	R =
TBBPA	79-94-7	Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo	H
TBBPA-bis(dibromopropyl ether)	21850-44-2	Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)-	CH2(CHBr)2H
TBBPA-bis(allyl ether)	25327-89-3	Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-	CH2CH=CH2
TBBPA-bis (methyl ether)	37853-61-5	Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-methoxy-	-CH3

Of all brominated flame retardants, TBBPA has the highest US and global production volume (BSEF, 2014; EPA, 2014b). It is used as both an additive and reactive flame retardant[4] and it is reacted to produce more than 70 compounds (EPA, 2015).

In the initial prioritization process, EPA/OPPT considered structurally similar non-polymeric compounds that could be assessed along with TBBPA. Two of the compounds, TBBPA-bis(dibromopropyl ether) and TBBPA-bis(allyl ether), have additive flame retardant uses in addition to reactive uses. EPA/OPPT chose these two compounds based on the assumption that additive uses lead to higher potential for exposure than compounds with only reactive uses. EPA/OPPT included a fourth chemical, TBBPA-bis(methyl ether), in the cluster based on studies that show it has routinely been found in the environment. Its presence is likely to be a result of microbial transformation of TBBPA (George and Haggblom, 2008).

[4] A reactive use is one in which TBBPA is covalently bound with the substrate matrix. An additive use means that TBBPA is not reacted with the substrate.

1.2 Regulatory and Assessment History

The United States government, individual states and foreign governments have regulated TBBPA or taken other actions with respect to TBBPA and some of the other cluster members. Primary risk assessments are the European Union's environmental and human health assessments (EC, 2006, 2008) and Canada's recent environmental and human health assessment (EC/HC, 2013).

1.2.1 Federal

At the federal level, companies report production volume and chemical use information for TBBPA, TBBPA-bis(dibromopropyl ether) and TBBPA-bis(allyl ether) under the Chemical Data Reporting rule (EPA, 2014b). TBBPA and TBBPA-bis(dibromopropyl ether) are produced in volumes greater than 1 million pounds per year and are thus considered high production volume (HPV) chemicals as defined by EPA and industry prepared a test plan that was submitted to EPA under the HPV Chemicals Challenge Program. TBBPA emissions are reported yearly to the Toxics Release Inventory (TRI) (EPA, 2012e).

1.2.2 State

The Oregon Department of Environmental Quality classifies TBBPA as a priority persistent pollutant as part of its water quality program based on concerns related to persistence and chronic toxicity to fish (Oregon_DEQ, 2010a, 2010c). Oregon also provides data on use, exposure pathways and releases for TBBPA under this program (Oregon_DEQ, 2010b).

Washington lists TBBPA as a chemical of high concern based on human health effects[5] and presence in humans and accordingly provides some toxicity and exposure information under the Children's Safe Products Act (WSDE, 2011, 2014b). Washington also lists information regarding the amount of TBBPA contained in children's products, as reported to the Washington State Department of Ecology (WSDE, 2014a).

California lists TBBPA and TBBPA-bis(dibromopropyl ether) as priority chemicals for biomonitoring identified by a scientific guidance panel (SGP) from a list of designated chemicals compiled using Centers for Disease Control National Biomonitoring Program and other SGP recommendations (California_Biomonitoring, 2014b, 2014c). No information is available regarding when biomonitoring might begin However, California is not yet biomonitoring for these chemicals (California_Biomonitoring, 2013, 2014a). In addition, TBBPA and TBBPA-bis(dibromopropyl ether) are listed as candidate chemicals under the state's Safer Consumer Products regulations. Presence on this list indicates that the chemical meets criteria for the initial priority products list specified in regulations. TBBPA is listed based on bioaccumulation, endocrine toxicity, environmental persistence, neurotoxicity, reproductive toxicity and other (undefined) toxicity. TBBPA would only be named as a chemical of concern if it was part of a product-chemical combination that is listed as a priority product (CalEPA, 2013).

[5] However, it should be noted that a primary reference is for a formulated product called Saytex 111, not for TBBPA as a monomer.

Maine uses a tiered system to classify chemicals (Maine_DEP, 2013c). The first level includes roughly 1400 chemicals of concern including both TBBPA and TBBPA-bis(dibromopropyl ether) (Maine_DEP, 2013c). This list uses tools such as the Washington state list and EPA TRI information (Maine_DEP, 2013a). The second tier is comprised of 49 chemicals of *high* concern; TBBPA is the only chemical from the TBBPA and Related Chemicals Cluster on this list (Maine_DEP, 2013b).

Minnesota lists TBBPA and TBBPA-bis(dibromopropyl ether) as chemicals of high concern based on persistence, bioaccumulation and toxicity and references other authoritative lists (MDH, 2013a, 2013b). Among these authoritative sources, Minnesota refers to Washington state and EPA's TRI information.

States do not appear to regulate or provide information on either TBBPA-bis(allyl ether) or TBBPA bis(methyl ether).

1.2.3 International

1.2.3.1 European Union

In the European Union (EU), TBBPA and TBBPA-bis(dibromopropyl ether) are registered chemicals under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation. This means that companies (registrants) provided the European Chemicals Agency with information on the uses, properties, hazards and potential risks for these substances (ECHA, 2015b). The EU has also conducted human health and environmental risk assessments of TBBPA (EC, 2006, 2008).

The other two cluster members are pre-registered in the EU, which means companies will be providing information on the properties and uses of these substances to the European Chemicals Agency by the extended registration deadline of May 2018. These two substances are pre-registered because the substances are manufactured or imported at 1 to 100 metric tons per year (ECHA, 2014).

On October, 2014, ECHA proposed to update the Community Rolling Action Plan (CoRAP) and identified TBBPA as a proposed substance for evaluation in 2015. Member states evaluate substances included in the CoRAP to determine if the measures in place are enough to manage the risks. If not, an evaluation of whether there is a need for further action is conducted. Such action could include restrictions, identification of substances of very high concern or other actions outside the scope of REACH. The final decision regarding the substances to be evaluated in 2015 will be adopted by ECHA at the end of March 2015 (ECHA, 2015a).

1.2.3.1.1 European Union Risk Assessment

Environmental Assessment

In their environmental risk assessment (EC, 2008), the European Union concluded that there is a need to limit risks to surface water, sediment and terrestrial organisms when TBBPA is used as an additive flame retardant in formulation (compounding) of acrylonitrile butadiene styrene (ABS). Risks for the terrestrial compartment were also identified at ABS *conversion* sites (which conduct final processing of semi-finished products with TBBPA as an additive flame retardant); the risks were found only when sewage sludge is applied to agricultural land. Risks to terrestrial organisms were also identified at sites where TBBPA is reacted into epoxy/polycarbonate resins. In addition, the European Union concluded there may be risks to organisms in the marine environment (EC, 2008).

The EU environmental assessment indicated TBBPA may degrade to bisphenol A (BPA) in anaerobic sediments (EC, 2008). Formation of BPA from TBBPA was assessed in the updated risk assessment of BPA; after testing in snails was conducted, no risks were reported for all environmental organisms evaluated (United_Kingdom, 2008).

Human Health Assessment

The human health assessment of TBBPA (EC, 2006) identified no health hazards of potential concern to adults. Therefore, no risk characterization was performed for workers. Also, because no health effects were identified for adults and because consumer exposures were found to be negligible, the European Union did not identify concerns for consumers. Similar conclusions were reached by the European Union when evaluating risks to humans via the environment (through food, air and drinking water).

For infants, non-cancer health hazards were identified and two exposure scenarios were analyzed. One exposure scenario was based on the environmental scenario used for adults (described above) and the second scenario was based on exposure of infants via breast milk. The European Union concluded that risks were low and that risk reduction measures were not needed (EC, 2006).

1.2.3.1 Canada

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999*, the Canadian government identified TBBPA and TBBPA-bis(dibromopropyl ether) in the categorization of the Domestic Substances List (DSL) as priorities for screening assessment because they met the criteria for persistence and inherent toxicity to non-human organisms. TBBPA was determined to present an intermediate potential for exposure of individuals in Canada.

On November 30, 2013, Canada published their final screening assessment of TBBPA and TBBPA-bis(allyl ether) along with another substance, TBBPA bis(2-hydroxyethyl ether) (CASR RN 4162-45-2), which is not included in the EPA cluster (EC/HC, 2013)Environment and Health Canada conducted both environmental and human health assessments for TBBPA and TBBPA-bis(allyl ether) (EC/HC, 2013). For environmental organisms, Canada concluded the quantity of TBBPA and TBBPA-bis(allyl ether) that may be released to the environment is below the level expected to cause harm to organisms.

For humans, conservative estimates of exposure suggested that breast-fed infants may be exposed to more TBBPA than older Canadians. Yet, recent studies have shown that TBBPA was virtually undetected in breast milk and blood samples from pregnant women in North America. Therefore, Canada concluded that TBBPA is not harmful to human health at current levels of exposure. TBBPA-bis(allyl ether) was also determined to not to be harmful for human health (EC/HC, 2013).

2 PROBLEM FORMULATION

The problem formulation stage is intended to determine the major factors to be considered in the assessment, including exposure pathways, receptors and health endpoints (EPA, 1998, 2014f). Accordingly, this problem formulation document summarizes the exposure pathways, receptors and health endpoints EPA/OPPT has recommended for inclusion in the 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. EPA/OPPT summarized the outcome of this evaluation in conceptual models that illustrate the exposure pathways, receptor populations and effects that will be considered in the risk assessment. EPA/OPPT also prepared an analysis plan to demonstrate the proposed approach to address remaining defined assessment questions that are possible based upon TSCA uses and best available data, tools and models.

TBBPA

Previous risk assessments identified several human health and some environmental scenarios that resulted in low risks for TBBPA. Some environmental scenarios evaluated in these previous assessments resulted in risks. Although EPA/OPPT referred to these previous risk assessments as much as possible to inform the current problem formulation process, there are several updates that were considered during the current effort that differ from the outcome of previous assessments.

Unlike Canada and the European Union, TBBPA is manufactured in the United States. Therefore EPT/OPPT identified exposure near manufacturers for further evaluation. Also, a recent cancer bioassay has been published (NTP, 2014a) and has been used to determine which human health scenarios to evaluate further. Finally, new information regarding the presence of TBBPA in children's products prompted EPA/OPPT to consider evaluating risks to children of certain ages as a result of exposure to consumer products.

To assist in determining pathways that may be of particular concern, EPA/OPPT calculated very preliminary estimates by comparing high-end exposure values from existing risk assessments or recent published and unpublished data with provisional toxicity values. For the environmental scenarios, EPA/OPPT developed preliminary concentrations of concern (COCs) by applying routinely-used uncertainty factors (EPA, 2012d, 2013b) to results of selected ecotoxicity studies. For human health scenarios, EPA/OPPT calculated a provisional health-conservative toxicity value for developing uterine tumors using the recent carcinogenesis bioassay from the National Toxicology Program (NTP, 2014a). Scenarios specific to young children were also compared with a no observed adverse effect level (NOAEL) from a developmental toxicity study (Fukuda et al., 2004). These preliminary calculations allowed EPA/OPPT to understand which pathways might be of highest concern for TBBPA.

Other Cluster Members

EPA/OPPT concluded that no quantitative risk assessment is needed for cluster members other than TBBPA for one or more of the following reasons: limited information, inability to use the more robust data for TBBPA to read across to other cluster members, low toxicity or likely low risk concerns. More information on these decisions and data for these chemicals are presented in Appendix A.

Appendix B presents information on literature searching and data adequacy, and Table 2-1 lists the type of information needed for each scenario, population and type of hazard. The literature search will be updated before conducting the risk assessment.

Table 2-1: Data Required for Risk Assessment

	Workers	**General Population**	**Consumers**	**Ecological Receptors**
Exposure Scenarios	Manufacture and processing	Releases to the environment from manufacturing	Consumer product uses resulting in direct exposures or releases to indoor environments.	Releases to the environment from manufacturing
Exposure	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			
Hazard/Toxicity	Hazard data, low dose extrapolation to obtain a cancer slope, bioavailability			Acute and chronic effects data

2.1 Physical and Chemical Properties

Table 2-2 identifies the physical-chemical properties for TBBPA, the only cluster member considered for further evaluation. Estimation program values (EPA, 2013a) for vapor pressure and water solubility were unrealistically low and log K_{OW} values were unrealistically high. Therefore, estimated values are not reported in Table 2-2.

Table 2-2: Physical-Chemical Properties

Chemical Name	CASRN	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg @ 25°C)	Water Solubility (mg/L)	Octanol-Water Partition Coefficient (log K_{OW})
TBBPA	79-94-7	178 [(a)]	> 200°C [(a)] (decomposes)	< 1 x 10^{-6} [(a)]	4.16 @ 25°C[(b,c)]	5.90 [(a)]

ND: no measured data
[(a)] EC (2006)
[(b)] Morf et al. (2003)
[(c)] Highest measured value (at neutral pH) from available literature

2.2 Production Volume and Uses

This section describes production and use information that informs EPA/OPPT's discussions on sources, pathways and receptors to be evaluated for TBBPA.

2.2.1.1 Production

The 2011 national production volume of TBBPA as reported to the CDR was approximately 120 million pounds (EPA, 2014b)[6]. Production volume data for TBBPA is presented in **Error! Reference source not found.**. Production volume by company is not available in the publically available CDR because either no data were reported or companies filed confidential business information (CBI) claims (as noted in **Error! Reference source not found.**). There is little or no public information on the production or import volumes of final products treated with TBBPA-based flame retardants.

According to the Brominated Science and Environmental Forum (BSEF), TBBPA has the highest global production volume of all brominated flame retardants (BSEF, 2014).

2.2.1.1.1 Manufacturers

The CDR data (EPA, 2014b) identifies five companies that manufacture and/or import TBBPA:

- Albemarle Corporation
- ICL Industrial Products (ICL-IP) America, Inc.
- LG Chemical America
- Sabic Innovative Plastics US, LLC
- A company that was claimed as CBI

[6] The 2012 release of the CDR database contains domestic manufacturing volumes, import volumes, export volumes, and industrial and consumer use data for reporting sites during the year 2011. In addition, it reports past production volume, which includes domestic manufacturing volumes (including imports) for the year 2010.

Table 2-3: CDR Production Volume Data

Company Site	Domestic Manu-facturing	Imported (lbs)	Exported (lbs)	Used on Site (lbs)[a]	2010 Past Production (Import/ Manufacture)	2011 National Production (lbs/yr)
Albemarle Corp South Plant 2270 Highway 79 South Magnolia, AR 71753-9129	CBI	ND	CBI	CBI	CBI	119,837,559
ICL-IP America, Inc. 622 Emerson Road, Suite 500 St. Louis, MO 63141-6742	ND	CBI	CBI	N/A	CBI	
LG Chemical America 910 Sylvan Avenue Englewood Cliffs, NJ 07632	ND	485,159	0	N/A	454,941	
Sabic Innovative Plastics US, LLC State Route 892 Washington, WV 26181-0068	ND	CBI	0	N/A	CBI	
CBI	CBI	ND	0	0	CBI	

[a] The total volume (domestically manufactured and imported) of the chemical used at the reporting site. This number represents the volume of the chemical that did not leave the manufacturing site.
CBI = Confidential business information
ND = No Data; the company did not provide the requested information.
N/A = Not Applicable; the imported chemical was never physically at the site

2.2.1.1.2 Trade Names

Albemarle Corporation and ICL-IP sell TBBPA as SAYTEX® CP-2000 and FR-1524, respectively (Albemarle, 1999; ICL-IP, 2013b). Trade literature does not indicate the trade name of Sabic Innovative Plastics US, LLC's or LG Chemical America's TBBPA products. Additionally, although not listed in the 2012 public CDR, company websites state that Chemtura[7] sells TBBPA as BA-59P and Dover Chemical Corporation sells the chemical as Doverguard 59 (Dover_Chemical, 2012; ICL-IP, 2013b). Chemtura reported manufacturing TBBPA to the 2006 Inventory Update Rule (IUR), but Dover Chemical Corporation did not (EPA, 2014h). For more detailed information on manufacturers of TBBPA who reported for the CDR collection period that reported the 2011 production volume data, see **Error! Reference source not found.**.

2.2.1.1.3 Import and Export

CDR data indicate that TBBPA is imported but do not indicate whether TBBPA is exported (EPA, 2014b). According to the CDR, LG Chemical America imported 485,159 pounds of TBBPA in 2011, while other companies either did not report import and export volumes or claimed them as CBI.

[7] The division of Chemtura that produces bromine-based products (including TBBPA) is called Great Lakes Solutions (Chemtura, 2014).

2.2.1.2 Uses

The CDR provides data on the industrial and consumer uses of TBBPA (EPA, 2014b). This data is summarized in Table 2-4.

For the purposes of the CDR, “industrial use” means use at a site where one or more chemical substances or mixtures are manufactured (including imported) or processed. “Consumer use” means the use of a chemical substance or a mixture containing a chemical substance (including as part of an article) when sold to or made available to consumers for their use.

2.2.1.2.1 Past Use as a Plasticizer

Additionally, TBBPA has been used as a plasticizer (NIEHS, 2002). However, this use has not been documented in more recent years (EC, 2006; EC/HC, 2013; EPA, 2014b, 2014h).

Table 2-4: Industrial and Consumer Use Data for TBBPA from the CDR

Company Site	Type of Processing	Industrial Use Data			Consumer Use Data		
		Sector	Industrial Use	Percent of Production Volume	Consumer Use Product Category	Commercial or Consumer Use	Percent of Production Volume
Albemarle Corp South Plant 2270 Highway 79 South Magnolia, AR 71753-9129	Processing-incorporation into formulation, mixture or reaction product	Plastics Material and Resin Manufacturing	Flame retardants	26	Electrical and Electronic Products	Commercial	26
	Not Known or Reasonably Ascertainable	Not Known or Reasonably Ascertainable	Not Known or Reasonably Ascertainable	71	Not Known or Reasonably Ascertainable	Not Known or Reasonably Ascertainable	71
ICL-IP America, Inc. 622 Emerson Road, Suite 500 St. Louis, MO 63141-6742	Processing-incorporation into formulation, mixture or reaction product	Computer and Electronic Product Manufacturing	Flame retardants	100	Electrical and Electronic Products	Both	100
LG Chemical America 910 Sylvan Avenue Englewood Cliffs, NJ 07532	Processing-incorporation into formulation, mixture or reaction product	Plastics Material and Resin Manufacturing	Flame retardants	100	Plastic and Rubber Products not covered elsewhere	Commercial	100
Sabic Innovative Plastics US, LLC State Route 892 Washington, WV 26181-0068	ND	ND	ND	ND	ND	ND	ND
CBI	Processing as a reactant	All Other Basic Organic Chemical Manufacturing	Flame retardants	100	ND	ND	ND

ND = No Data; the company did not provide the requested information.
Source: EPA (2014b)

2.2.1.2.2 Flame Retardant and Other Uses

TBBPA is one of the most widely used brominated flame retardants and is used as both an additive and reactive flame retardant (EPA, 2008a). Additive flame retardants are incorporated into polymers via physical mixing and are not chemically bound to the polymer. Reactive flame retardants are incorporated into polymers via chemical reactions at an early stage of manufacturing. Because manufacturers can incorporate additive flame retardants into the product up until the final stages of manufacturing, it is usually easier for them to use additive rather than reactive flame retardants. Reactive flame retardants have a greater effect on the chemical and physical properties of the polymer into which they are incorporated than do additive flame retardants (EPA, 2008a).

TBBPA has also been used as a chemical intermediate in the synthesis of other brominated flame retardants (NIEHS, 2002).

As stated in Table 2-4, TBBPA's main consumer use categories as a flame retardant are 1) electrical and electronic products and 2) plastic and rubber products not covered elsewhere. The category "plastic and rubber products not covered elsewhere" means that products are not covered under any other plastic or rubber product categories within the CDR. In electrical and electronic products, TBBPA is primarily used in printed circuit boards in the following products: telecommunications equipment, computers, industrial controls, remote controls, video recorders and electronics (EC, 2006; Qu et al., 2013). TBBPA is incorporated into epoxy resins for printed circuit boards as a reactive flame retardant at 15 to 17% by weight (EC, 2006).

Epoxy resins are also used to encapsulate electronic components (Morose, 2006). Electronic component encapsulates, which incorporate TBBPA at 2% by weight, are used to protect products from hazardous environmental conditions, such as moisture and dust. These products include plastic and paper capacitors, microprocessors, bipolar power transistors and other components of electrical equipment (EC, 2006; Morose, 2006).

With respect to TBBPA's use in plastics and rubber products, it is likely the majority of this use is in electrical and electronic products. For example, a primary application of TBBPA is its use as an additive flame retardant in acrylonitrile butadiene styrene (ABS) resins (a type of plastic). These ABS resins are used in the enclosures or casings around electronics such as TV or computer monitor casings or components in printers, fax machines, photocopiers, vacuum cleaners, coffee machines and plugs/sockets. TBBPA is used in ABS and other plastics at 14 to 22% by weight, often in combination with antimony trioxide (EC, 2006).

In addition to the CDR another dataset, which contains information on types of products that may use TBBPA is Washington State's Children's Safe Product Act (CSPA) database[8]. Under CSPA, manufacturers, importers or whole sale distributors of children's products sold in Washington are required to report if their products contain a Chemical of High Concern to Children – one of which is TBBPA (Washington_State_DEC, 2014). As of September 6, 2014, TBBPA has been reported for use as a

[8] https://fortress.wa.gov/ecy/cspareporting

surface coating flame retardant in artists' accessories[9]. It has also been reported to be present as synthetic polymer flame retardant in powered "viewing toys[10]", "toy/games variety packs[11]" and in powered toy vehicles. Additionally, it is reported to be used as a flame retardant in textiles in baby car/booster seats; baby carriers; baby play pens/dens and baby swings. The concentrations of TBBPA in these products were reported as ranging from < 0.05 to > 1% (Washington State Department of Ecology, 2014b). It is not clear from the database whether these products were manufactured in the United States or imported as articles. The use of TBBPA in textiles is not reported in the publically available CDR.

Non-flame retardant applications of TBBPA reported in Washington's database of children's products include the chemical's use as an adhesive in jewelry craft supplies, as a pigment in powered non-ride toy vehicles, as a stabilizer in clothing accessories and as a component of plastic resin or polymers in toys. The concentrations of TBBPA in these products were reported as ranging from < 0.01 to > 1% (WSDE, 2014a).

TBBPA has also been reported as a contaminant with no function in children's footwear, clothing, personal accessories, arts and crafts, baby feeding products (i.e., baby bibs, according to a single report) and bedding in the CSPA database. All contaminant concentrations were reported as less than 0.05%, with about half reported as less than 0.01% (WSDE, 2014a).

SAYTEX® CP-2000 (Albemarle's TBBPA product) is used as a reactive or additive flame retardant and is usually used in combination with other additives, such as antimony trioxide (Albemarle, 1999; EC, 2006). Additionally, ICL-IP's FR-1524 is used in epoxy, polycarbonate and phenolic resins (ICL-IP, 2013b).

ICL-IP's Web site also states that TBBPA is "an important intermediate in the preparation of more sophisticated flame retardants" (ICL-IP, 2013b). Chemtura and Dover Chemical Corporation state that their TBBPA products, BA-59P™ and Doverguard 59, respectively, are intended for use in "thermoplastic and thermoset resin systems." These resin systems include epoxy resins, polycarbonates, ABS and high impact polystyrene (Chemtura, 2013; Dover_Chemical, 2012, 2013).

[9] The product categories used by Washington State are defined by GS1 Global Product Classification Standards (WSDE, 2013). Artists' accessories are defined as any products that can be described/observed as an item designed to aid the artistic painting process (GS1, 2015).

[10] Includes any products that can be described/observed as a powered educational toy designed to entertain and encourage learning by viewing changing scenes or patterns (GS1, 2015)

[11] Includes any products that can be described/observed as two or more distinct Toys/Games 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 Toys/Games family.

2.2.1.2.3 Regulatory Status and Future Trends Regarding Uses

No current state or federal legislation restricts the use of TBBPA (BSEF, 2013). The European Union's REACH regulations require manufacturers and importers to report the properties and uses of substances that they manufacture or import at or above one metric ton per year, including TBBPA REACH does not, however, restrict the use of TBBPA or similar substances (ECHA, 2015b).

Although not a formal regulation, Underwriters Laboratories (UL) 94 is a predominant standard for the level of flame retardancy within products that can influence the specific flame retardant or the amount of a flame retardant that is used in electronic products. Compliance with the standard is not required nationally. However, individual companies, trade associations or local governments may choose to require electronic products under their jurisdiction to meet a UL 94 rating (UL_IDES, n.d.).

2.2.1.3 Summary of Production and Use

TBBPA has the highest production volume of the brominated flame retardants. Five companies reported a total of 120 million pounds manufactured or imported in 2011, according to CDR data. It is used primarily as a reactive flame retardant, with uses as an additive flame retardant as well. Its use as a flame retardant is primarily for electrical or electronic products, where it may be present at levels up to 22%. A vast majority of printed circuit boards that meet stringent flame retardancy standards use TBBPA to achieve these ratings. TBBPA may also be used as an intermediate in the production of other flame retardants.

2.3 Fate and Transport

In air, TBBPA may undergo direct photolysis and indirect photo-oxidation, although low vapor pressure limits the amount of TBBPA vapor in air. In water TBBPA does not hydrolyze but may undergo photolysis. TBBPA is expected to have low volatility and low mobility in soil. Under anaerobic conditions, TBBPA may biodegrade to BPA. It may also undergo microbial O-methylation to form TBBPA-bis(methyl ether). Based on available data, TBBPA is considered moderately to highly persistent in water, soil and sediment and has a low bioaccumulation potential. Limited and uncertain data preclude assessment of risks from TBBPA's degradation products as part of the proposed risk assessment for TBBPA.

Appendix C includes details related to the fate and transport of TBBPA in air, water, soil and sediment as well as information on degradation products.

2.4 Exposures

2.4.1 Releases to the Environment

TBBPA is a solid, is manufactured in plants in Arkansas and is then incorporated into polymer matrices either additively or reactively as noted in Section 2.2.1.2.2. Products in which TBBPA is used as a flame retardant are largely electronics; TBBPA can be used reactively in printed circuit boards and also incorporated into the acrylonitrile butadiene styrene (ABS) resins used in plastic housing of electronic products. TBBPA may be released at various stages of the life cycle: manufacture, processing, disposal, recycling and use. Toxics Release Inventory (TRI) data are available for manufacturers and processors. Information on releases is described in Appendix D.

2.4.1.1 Chemical Manufacturing

Based on North American Industry Classification System (NAICS) codes reported by facilities to TRI (EPA, 2012e) as well as production volume and use data reported to EPA under CDR (2011 reporting year) (EPA, 2014b) and IUR (2005 reporting year) (EPA, 2014h), three facilities are likely to manufacture all of the TBBPA that is produced domestically.

Of the years of available TRI reporting (2000 to 2012), two of these manufacturers were in operation from 2000 to 2011. In 2012, one of these manufacturing sites did not report TBPPA releases, and a different manufacturer reported emissions instead.

According to TRI reports (EPA, 2012e), manufacturers and processors reported stack emissions to air. TBBPA is likely to be emitted as dust rather than vapor based on its low vapor pressure. Companies also released TBBPA to landfills.

2.4.1.2 Processing

Several facilities process TBBPA in the United States. The following processing sectors have reported TBBPA releases to TRI: chemicals, textiles, hazardous waste/solvent recovery, transportation equipment, plastics and rubber, paper and computers and electronic products (EPA, 2012e). For the years 2000-2012, processors emitted approximately 0.24 to 6.2% of the air releases reported by the manufacturing site with the highest release for these years (EPA, 2012e).

2.4.1.3 Recycling

EPA's Office of Resource Conservation and Recovery (ORCR) estimated that approximately 25% of electronic waste (e-waste) was collected for recycling in 2009 (EPA, 2013d). After collection, electronic products that contain TBBPA might be reused, refurbished or recovered for their materials (EPA, 2011a). Plastics can be recovered by chemical, mechanical or thermal processes (Kang and Schoenung, 2005). Kang and Schoenung (2005) state that plastics recovered from electronics in the United States are used primarily in plastic lumber, outdoor furniture and road materials. However, it is not clear

whether this statement refers to plastic housing that contains flame retardants because the presence of additives (such as flame retardants) in plastics can act as an obstacle to recycling (Kang and Schoenung, 2005).

Generally, circuit boards with epoxy resins that contain TBBPA are shredded because they cannot be re-melted to be used again. However, some boards are smelted as part of the recycling process to recover precious metals (EC, 2006; Kang and Schoenung, 2005).

In the European Union, computer recycling companies often incinerate plastic housing from electronics (EC, 2006). If US recyclers operate in a similar manner, plastics that contain TBBPA may be incinerated with the potential for emissions.

Products collected for recycling can also be exported. Yet estimates of such exports can range widely. Some estimates include 7% of the total monetary value of collected e-waste (ITC, 2013) to 50% of amounts generated in the western United States (BAN/SVTC, 2002). Due to these and other uncertainties, EPA/ORCR has not developed a method to estimate the total amount of e-waste that is collected in the United States and subsequently managed and processed domestically or exported (EPA, 2013d).

2.4.1.4 Disposal

2.4.1.4.1 Disposal from Manufacturing, Processing and Recycling Facilities

Manufacturers dispose of TBBPA in onsite and offsite landfills. The offsite landfills were primarily RCRA Subtitle C hazardous waste landfills. One manufacturing facility also reported disposal of TBBPA in the category of "other off-site landfills" for 2002. "Other landfills" are non-hazardous waste landfills that may be regulated under a variety of other federal, state and local programs. Processors also reported disposal to RCRA Subtitle C and other landfills (EPA, 2012e). Finally, computer recycling companies usually landfill (or incinerate) plastic housing from electronics in the European Union (EC, 2006); these practices might be applicable to the United States.

2.4.1.4.2 Disposal of Consumer Products Containing TBBPA

Products that contain TBBPA can be disposed in various ways. In 2009, electronic waste (TVs, computers, peripherals, mice, keyboards and cell phones) totaled approximately 2.37 million short tons, as estimated by EPA/ORCR. The amount of this waste that contains TBBPA is unknown. This amount of electronic waste (also called e-waste) is about 1-2 percent of the total municipal waste stream (EPA, 2013d). Approximately 75% of e-waste was disposed in landfills and by other methods compared with 25% that was collected for recycling.

Electronic waste after use is typically sent to landfills (EPA, 2011a). Electronic waste can also be sent to waste-to-energy incinerators (EPA, 2011a). Products that contain TBBPA can also be sent to municipal incinerators (Borgnes and Rikheim, 2004). Furthermore, ash generated from incineration can also be sent to landfills.

General household waste and landfill leachates can be sent to WWTPs, which can discharge effluents to water. Contaminants in the effluents can either remain in surface water or partition to sediments. WWTPs also generate sewage sludge, which can be processed to yield nutrient-rich organic materials called biosolids that can be applied to agricultural land as fertilizer (EPA, 2014j).

2.4.2 Presence in the Environment and Biomonitoring Data

Table 2-5 outlines the type of data available regarding presence in the indoor and outdoor environment as well as biomonitoring data available for TBBPA. Other sections in this Chapter describe results of individual monitoring studies likely to be most representative of individual exposure pathways. Details regarding individual studies are described in detail in Supplemental Files 1 (Biomonitoring), 2 (Environmental and Wildlife Monitoring) and 3 (Residential Monitoring).

Table 2-5: Availability of Exposure Data for TBBPA

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	●

Table 2-5: Availability of Exposure Data for TBBPA

WATER	
drinking water	
groundwater	
leachate	●
precipitation	●
surface water	●
wastewater	●
AIR AND WATER	
deposition	
BIOTA	
avian	●
fish	●
aquatic animals (including shellfish)	●
terrestrial animals	●
vegetation	●

● = some data available, US or international

2.4.3 Occupational Exposures

TBBPA is manufactured primarily at three plants in the United States. TBBPA is also processed at other sites and electronic and other consumer products can be recycled. Thus, there is a potential for exposure to workers in all of these sectors.

EPA/OPPT considers inhalation of dust to be the most important TBBPA exposure pathway for workers. In particular, the inhalation of air-suspended dust (particulate matter) that is subsequently trapped in mucous and moved from the respiratory system to the gastrointestinal tract (EPA, 2011b) may contribute to exposures. This will be referenced in the current document as incidental ingestion of inhaled dust. Dermal exposure is also possible but available data indicates that absorption is limited.

Information on concentrations of TBBPA and particles not otherwise regulated within workplaces relevant to TBBPA is described in Appendix E.

2.4.4 General Population Exposures

The general population may be exposed to TBBPA due to its widespread detection in the indoor and outdoor environment. TBBPA has also been detected in several human and fish biomonitoring studies. The general population may be exposed to TBBPA through oral, inhalation or dermal exposure, although aggregate oral exposure is the focus of this assessment. Data summaries and references are available in Supplementary Files 1 through 3.

2.4.5 Consumer Exposures

TBBPA is used as a flame retardant, primarily in electronic products (such as TVs and computers). TBBPA has also been found in a variety of other products such as small plastic toys, jewelry and other children's products as identified in recent studies (Di Napoli-Davis and Owens, 2013; Gallen et al., 2014; Keller et al., 2014; van Bergen and Stone, 2014).

Direct contact with products may lead to exposures depending on the conditions of use, such as frequency and duration of contact with the skin and subsequent hand to mouth or object to mouth contact. These products may also contribute to variable levels within indoor dust and air depending on the diversity of products present within a given building. A number of published studies have reported levels of TBBPA in indoor air and dust (see summaries of these studies in Supplementary File z).

Note that although exposure from contact with consumer products is proposed for assessment in Section 2.6, the types of exposures are primarily are not from contact of using the product directly (e.g., using a keyboard for a computer). Thus, they are discussed in the context of the general population (or of individuals living near manufacturing facilities).

2.5 Hazard Endpoints

2.5.1 Ecological Hazard

Ecotoxicity tests of aquatic and some terrestrial organisms exposed to TBBPA have evaluated a variety of effects including survival, immobilization, growth rate/biomass/yield, reproduction, emergence, growth and shell deposition. Depending on the type of organism, both acute and chronic studies are available. Based on results from some of these studies, TBBPA can be considered to be hazardous to the environment.

In aquatic studies, a range of values and effects have been identified. The most sensitive species and effects from acute and chronic studies are reported here. TBBPA exposure by the marine diatom *Skeletonema costatum* resulted in a 72-hr EC_{50} of 0.09 mg/L, based on decreased growth (Walsh et al., 1987). One of the lowest ecotoxicity endpoint values for a water-column species is the 96-hr EC_{50} of 0.098 mg/L based on shell deposition in the Eastern oyster, a marine invertebrate species (SLS, 1989a). In a 70-day study using the blue mussel, a MATC of 0.023 mg/L was calculated based on growth rate and shell length (ACC, 2005). In fish, acute LC_{50} values are all at or less than 1 mg/L, with the lowest value reported as 0.4 mg/L in rainbow trout (GLCC, 1978b). A MATC of 0.22 mg/L was determined for fathead minnows in a 35-day test (SLS, 1989c).

In sediment, several 28-day studies using worms, emergent flies or amphipods have been conducted, with the lowest MATC reported as 117 mg/L, based on effects on reproduction of a freshwater blackworm (Krueger, 2002a).

A range of terrestrial plants that include corn, cucumber, onion, ryegrass and tomato have been tested in 21-day studies, with the lowest MATC of 32 mg/kg dry soil (ACC-BFRIP, 2002). One 21-day and two

56-day studies have been conducted using terrestrial earthworms. The lowest MATC was 0.44 mg/kg dry weight in soil in one of the 56-day studies (ACC-BFRIP, 2005a).

Avian studies are limited, and reproductive and endocrine effects were not observed in the adult quail after *in ovo* exposure via injection of TBBPA into yolks (Berg et al., 2001; Halldin et al., 2001). In tadpoles, endocrine-related effects were not seen up to 500 ug/L (Garber et al., 2001) but thyroid hormone mediated gene expression was affected at 5.4 and 54 ug/L (Veldhoen et al., 2006).

See Appendix F for details related to these ecotoxicological studies.

2.5.2 Human Health Hazard

Available toxicokinetics data in rodents indicate that TBBPA is absorbed by the gastrointestinal tract, metabolized and excreted in the feces with limited tissue retention, with a half-life in humans of 2 days. There is limited transfer of TBBPA to the fetus. The acute hazard concern is low via the oral, dermal and inhalation routes. Also, many repeated-dose, reproductive and developmental toxicity studies in rodents found no effects, some at doses $\geq$ 1000 mg/kg-bw/day. TBBPA has tested negative in genotoxicity studies. Yet, there is some concern for cancer of the uterus as well as hemangiosarcomas and hemangiomas in all organs as observed in a cancer bioassay (NTP, 2014a). There is also a possible concern for developmental effects at 200 mg/kg-bw/day based on slight kidney lesions in newborn rats exposed to TBBPA. The lesions persisted after cessation of exposure, possibly due to immature metabolic capability or kidneys of these rats (Fukuda et al., 2004). Another study found very slight hepatocyte necrosis at 140.5 mg/kg-bw/day in offspring of female mice exposed to TBBPA during gestation through weaning of the offspring (Tada et al., 2006).

Neurotoxicity and neurobehavioral effects have not been confirmed. One study found some potential for hearing loss when dams and newborns were dosed (Lilienthal et al., 2008) but there are questions about methods and uncertainty about which are the most relevant doses (e.g., both newborns and dams were exposed to TBBPA). An acute study resulted in some neurobehavioral effects but didn't show a dose-response (Nakajima et al., 2009). No consistent neurobehavioral changes were seen in adolescents exposed to TBBPA (Kicinski et al., 2012).

Appendix G presents a more detailed discussion of human health endpoints considered for the proposed assessment.

2.6 Results of Problem Formulation

2.6.1 Conceptual Models

During problem formulation, two conceptual models were developed to identify important sources, pathways, receptors and effects. See Figure 2-1 and Figure 2-2 respectively, for the proposed environmental and human health assessments. The scenarios that EPA/OPPT proposes to quantify for TBBPA are identified using solid arrows. Dotted lines are used for scenarios that cannot be evaluated

quantitatively due to lack of applicable or adequate data or information. Table 2-6 and Table 2-7 outline the scenarios that are being assessed and those that will not be assessed for TBBPA.

Figure 2-1: Conceptual Model for the TBBPA Environmental Assessment

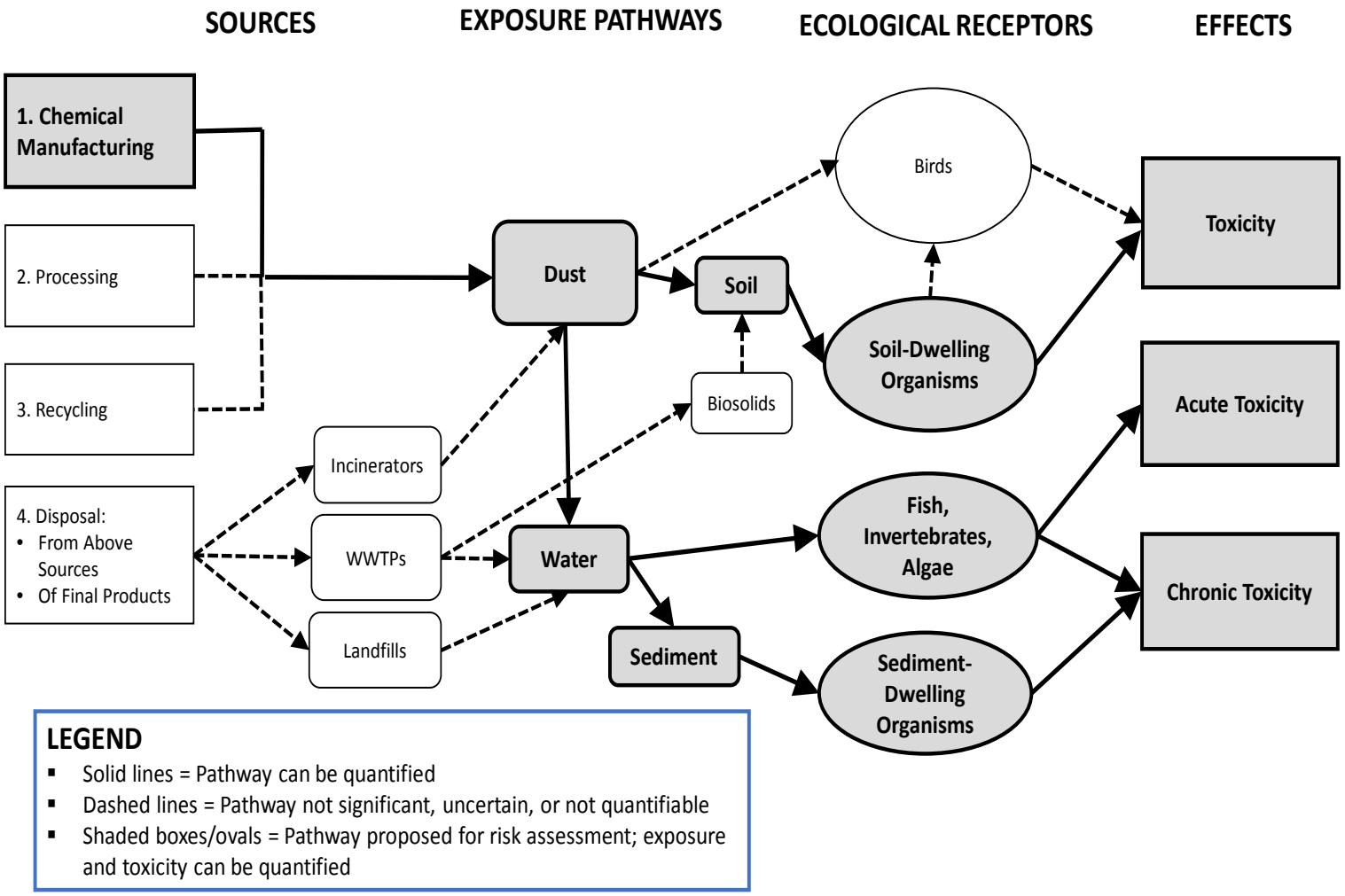


Table 2-6: Environmental Exposure Scenarios Considered for Assessment

#	Sources/Exposure Pathways		Ecological Receptors	Included in Assessment?	Rationale, Limitations and Uncertainties
1	Chemical manufacturing	Air – Particulates	Birds	NO	Adequate toxicity data not available for avian species using inhalation as the exposure route
		Soil	Soil-dwelling organisms	YES	Preliminary evaluation using data from 1977 for an Arkansas site and preliminary concentrations of concern from key ecotoxicity studies suggests there is a potential risk.
		Water	Fish, Invertebrates, Algae	YES	Although physical properties limit TBBPA concentrations in surface water, TBBPA deposition from manufacturing facilities might be of concern.
		Sediment	Sediment-dwelling organisms	YES	Preliminary evaluation using data from 1977 for an Arkansas site and preliminary concentrations of concern from key ecotoxicity studies suggests there is a potential risk
2	Processing	Air – Particulates	Birds	NO	Air emissions from processing plants are much smaller than those from manufacturing plants
		Soil	Soil-dwelling organisms		
		Water	Fish, Invertebrates, Algae		
		Sediment	Sediment-dwelling organisms		
3	Recycling	Air – Particulates	Birds	NO	Several factors result in significant uncertainty regarding use of existing data from other countries to evaluate the risks from recycling: • differences in environmental monitoring results among countries • Potential differences in recycling practices among countries • unknown amount of e-waste exported from the United States; and • no current methods to assess the recycling process identified by EPA/ORCR
		Soil	Soil-dwelling organisms	NO	
		Water	Fish, Invertebrates, Algae	NO	
		Sediment	Sediment-dwelling organisms	NO	

Table 2-6: Environmental Exposure Scenarios Considered for Assessment

#	Sources/Exposure Pathways		Ecological Receptors	Included in Assessment?	Rationale, Limitations and Uncertainties
4	Disposal	Incinerators: Air-particulates	Multiple	NO	Limited data are available and destruction of TBBPA is likely when incinerated
		WWTPs: Biosolids and water	Multiple	NO	Preliminary calculations using conservative assumptions regarding application of biosolids to agricultural land and high-end exposure values in water near a sewage treatment plant suggests low concerns
		Landfills	Multiple	NO	*Hazardous waste landfills (Title C):* The majority of TRI releases are to hazardous waste landfills; controls are in place to limit exposure (e.g., sites are covered). *Other landfills:* It is expected that only a small amount of TBBPA would be available and mobility in soil is limited given physical-chemical properties. (Note that some leachate analyses have shown TBBPA concentrations associated with particulate matter.)

Figure 2-2: Conceptual Model for the TBBPA Human Health Assessment

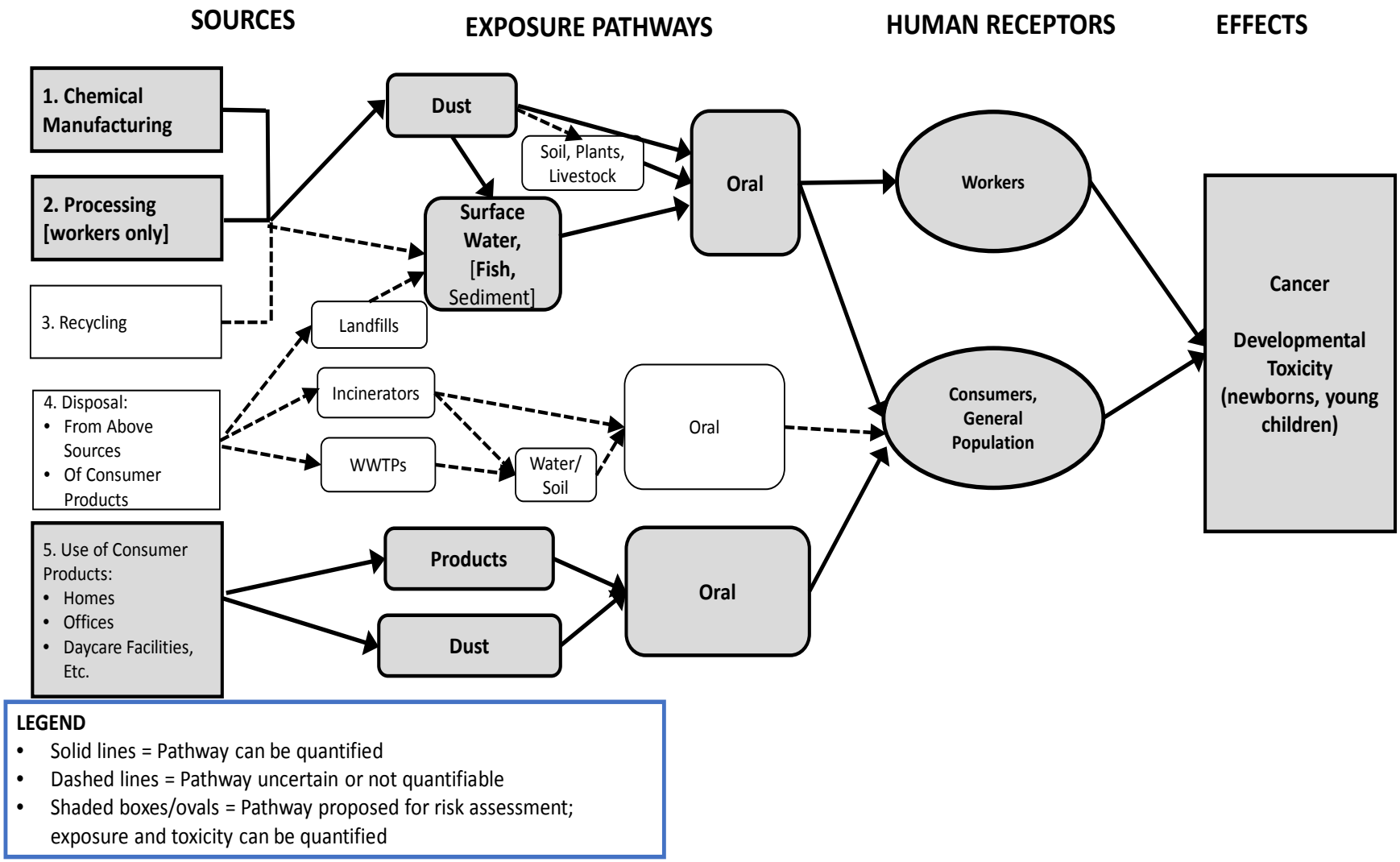


Table 2-7: Human Health Exposure Scenarios Considered for Assessment[a]

#	Sources/Exposure Pathways[b]		Human Receptors	Included in Assessment?	Rationale, Limitations and Uncertainties
1	Chemical manufacturing	Dust [unintended exposure from incidental ingestion of inhaled particles/dust]	Workers	YES	Information on TBBPA and non-specific dust concentrations in air of manufacturing sites suggests potential concerns.
			General population near facilities	YES	TRI reports that manufacturers emit TBBPA to air; there is potential concern for individuals who live near manufacturing facilities
		Soil/plants/livestock – dietary		NO	Data on plant uptake from soil are limited and no data are available for bioaccumulation into livestock
		Surface water – fish ingestion		YES	Although physical properties limit TBBPA concentrations in surface water, TBBPA deposition from manufacturing facilities might be of concern; EPA/OPPT will estimate bioaccumulation of TBBPA into fish from the water column [but bioaccumulation from sediment-dwelling organisms to fish is not available].
2	Processing	Dust [unintended ingestion]	Workers	YES	Information on TBBPA and non-specific dust concentrations in air of processing sites suggests potential concerns.
			General population near facilities	NO	Air emissions from processing plants are much smaller than those from manufacturing plants. Therefore, these emissions will not be modeled.
		Soil/plants/livestock			
		Surface water – Fish ingestion			
3	Recycling	Dust [unintended ingestion]	Workers	NO	Several factors result in significant uncertainty regarding use of existing data from other countries to evaluate the risks from recycling: • differences in environmental monitoring results among countries • Potential differences in recycling practices among countries • unknown amount of e-waste exported from the United States; and • no current methods to assess the recycling process identified by EPA/ORCR
		Soil/plants/livestock - dietary	General population near facilities		
		Surface water – fish ingestion			

Table 2-7: Human Health Exposure Scenarios Considered for Assessment[a]

#	Sources/Exposure Pathways[b]		Human Receptors	Included in Assessment?	Rationale, Limitations and Uncertainties
4	Disposal	Incinerators: Dust/[unintended ingestion]	General population	NO	Limited data are available and destruction of TBBPA is likely when incinerated
		WWTPs: Water/soil			Preliminary calculations using conservative assumptions regarding high-end exposure values in water near a sewage treatment plant and application of biosolids to agricultural land and suggests low concerns
		Landfills: Surface water – fish ingestion			*Hazardous waste landfills (Title C):* The majority of TRI releases are to hazardous waste landfills; controls are in place to limit exposure (e.g., sites are covered). *Other landfills:* It is expected that only a small amount of TBBPA would be available and mobility in soil is limited given physical-chemical properties. (Note that some leachate analyses have shown TBBPA concentrations associated with particulate matter.)
5	Consumer Product Use	Products	Children	YES	Data available on TBBPA concentrations and surface loadings in products, including children's products, suggests some potential for concern
		Indoor dust	General population [adults and children]	YES	Preliminary calculations suggest that risks from this pathway alone are low, yet this pathway is included to assess aggregate exposure

[a]Some pathways in this table are not being formally assessed. However, when conducting aggregate risk assessments, there may be contribution from one or more of these 'unassessed' pathways because EPA/OPPT will use data, such as TBBPA concentrations in outdoor dust levels or in fish eaten by the general population, that do not have identified TBBPA sources; this table simply indicates the pathways that are not being assessed as major sources of TBBPA exposure.

[b]Exposure pathways that depend on either inhalation of vapor or dermal uptake are not included in this table or in the conceptual models. TBBPA has a very low vapor pressure and therefore, exposure to vapor is negligible. Available information also suggests limited dermal uptake.

[c]Drinking water from different sources/pathways could contain TBBPA; however, data are not available for TBBPA in drinking water.

[d]Food other than fish is not assessed because it is the purview of other agencies.

2.6.2 Analysis Plan

EPA/OPPT proposes assessing both environmental and human health risks for the scenarios outlined below based on available data and modeling of exposure. In the final risk assessment, EPA/OPPT will characterize the assumptions, limitations and uncertainties of the assessment that is generated. Qualitative levels of confidence in the information used for the risk assessment will be discussed for transparency.

2.6.2.1 Environmental Assessment near Manufacturing Facilities

EPA/OPPT proposes to conduct an environmental assessment that focuses on the following key question:

1. **Are air releases from two manufacturing facilities occurring at levels that would result in risk to aquatic, sediment-dwelling or soil-dwelling organisms?**

During problem formulation, EPA/OPPT identified high-end concentrations of TBBPA in environmental media surrounding two US TBBPA manufacturing facilities (Pellizzari et al., 1978; Zweidinger, Cooper, Erickson, et al., 1979; Zweidinger, Cooper, and Pellizzari, 1979). EPA/OPPT also considered other data near brominated flame retardant manufacturers in China (Yang et al., 2012) when choosing exposure scenarios of concern. Although the US data are from 1977, sediment concentrations ranged from undetected to 330 mg TBBPA per kg sediment (Pellizzari et al., 1978; Zweidinger, Cooper, and Pellizzari, 1979). In soil, concentrations ranged from undetected to 150 mg/kg in 1977 (Pellizzari et al., 1978). One very high-end surface water concentration of 4.87 µg/L was measured in a lake in China (Yang et al., 2012), which is located near several brominated flame retardant producers.

From preliminary comparison of these high-end environmental concentrations with provisional COCs, EPA/OPPT determined that there might be current risk concerns for ecological receptors surrounding manufacturers of TBBPA given the likelihood that TBBPA persists in the environment.

EPA/OPPT plans to use estimated stack air release data (see Appendix D) for the two manufacturers that reported the highest releases over 13 years of TRI reporting (EPA, 2012e) as inputs to the AERMOD air deposition model (EPA, 2014i). Using facility air releases and site-specific inputs (e.g., meteorology, terrain), EPA/OPPT can calculate high-end estimates of the yearly TBBPA depositions onto water, sediment and soil for each year of TRI release data (from 2000 to 2012).

For the environmental risk assessment, the environmental concentrations estimated from TRI releases can be compared with COCs to determine environmental risks for aquatic, sediment-dwelling and soil-dwelling organisms, expressed as risk quotients (RQs). A review of available ecological toxicity data and recommended COC values are presented in Appendix F.

EPA/OPPT may consider estimates from all years of TRI reporting and their associated environmental concentrations to estimate risks, and could accomplish this in different ways. EPA/OPPT could add

exposures over multiple years of TRI reports, could focus on high-end exposures for a given year or could evaluate both. EPA/OPPT will assume no degradation of TBBPA in the proposed assessment.

2.6.2.2 Human Health Risk Assessment

EPA/OPPT proposes to conduct human health risk assessments that focuses on the following two key questions:

1. **Are there risks to workers from exposure to TBBPA through ingestion of suspended particulates/dust during manufacturing and processing activities?**

As noted previously, workers may be exposed primarily by ingesting TBBPA dust from the air at work sites. During bagging or loading operations, dust may be generated within facilities that manufacture TBBPA and workers may be exposed by ingesting particles that are inhaled from the air. Also, during loading and unloading operations, dust may be generated within facilities that process or compound TBBPA. Dust generated from unloading operations is expected to be pure TBBPA. However, dust generated from compounding and loading operations is not expected to be pure TBBPPA. These two types of dust (pure vs. mixture) may have differences in bioavailability.

EPA/OPPT will evaluate risks from occupational exposure at manufacturing and processing plants. Methods to quantify incidental ingestion of inhaled dust that consider issues such as bioavailability must be developed.

2. **Are there risks from aggregate exposures for the general population based on ingestion of suspended particles/dust from outdoor air; dust ingestion from indoor environments; fish ingestion; and/or mouthing of objects containing TBBPA?**

Based on past TBBPA concentrations in environmental media at manufacturing facilities and more recent information on TBBPA emissions from manufacturers, there is potential concern for individuals living near such facilities. EPA/OPPT will investigate exposure for these individuals. In addition, EPA/OPPT will aggregate the relevant facility-specific exposures with other known exposures to TBBPA that focus on the oral route, including incidental ingestion of particles/dust from air. Although some of the additional exposures considered for aggregation are expected to be minor, EPA/OPPT is nonetheless interested in how such aggregation will affect risk estimates. These exposure estimates will be developed for adults and children as appropriate. Risks near facilities can then be compared with risks estimates calculated for individuals living farther away from manufacturing facilities.

Suspended particles/dust in outdoor air. As noted in Section 2.6.2.1, EPA/OPPT plans to estimate TBBPA air concentrations as a result of air releases at TBBPA manufacturing plants to the external environment. EPA/OPPT will estimate risks as incidental ingestion of inhaled dust after emissions from manufacturers, and EPA/OPPT will further consider methods to quantify such incidental ingestion. There are also several studies in various countries that measured TBBPA concentrations in ambient air in different types of environments (e.g., rural, urban) that may represent exposures away from facilities (see Supplemental File 2 for studies of TBBPA concentrations in outdoor air).

Dust from indoor environments. A wide range of studies have reported TBBPA in dust in a variety of indoor environments that can be ingestion directly from the air or from hand-to-mouth transfer of settled dust. EPA will review these studies and combine this information with age-specific activity patterns and exposure factors to estimate this type of exposure.

Fish ingestion. EPA/OPPT also plans to estimate exposure from fish ingestion. As described in Section 2.6.2.1, air emissions deposited to water can be combined with estimates of TBBPA bioconcentration into fish and fish ingestion rates for families of recreational anglers living near the manufacturing facilities. There are also data available on concentrations of TBBPA in fish in various environments that may be appropriate to assess risks for individuals who live farther away from manufacturing facilities (see Supplemental File 2 for information on TBBPA concentrations in fish). More details on parameters that can be used for evaluation of fish ingestion are located in Appendix H.

Mouthing of products by children. Young children are likely to exhibit higher exposure than older children and adults due to their more prevalent object-to-mouth behavior. Therefore, EPA/OPPT will assess ingestion of TBBPA by children from direct contact with objects and hands that have touched such objects.

EPA/OPPT has found some data on both the concentrations and surface loadings of TBBPA in consumer products to which routine contact is possible. This information can be combined with information from Agency models and age-specific activity patterns and exposure factors to estimate exposure. More details about the proposed assessment approach are described in Appendix I.

For both key questions, the exposure estimates will be compared against relevant toxicity benchmarks. A cancer benchmark (uterine tumors for females; hemangiomas/hemangiosarcomas for males) developed using a linear low-dose model and a developmental toxicity benchmark will be used as appropriate for each exposure pathway (see Appendix J for the dose-response modeling of tumor data; and Appendix G for hazard information).

2.6.3 Sources and Pathways Excluded from Further Assessment

Several sources and pathways were excluded from further assessment for lack of data or expected low risks and are indicated in the conceptual models using dotted arrows.

2.6.3.1 Chemical Manufacturing

Environment. Exposure via directly inhaling TBBPA will not be assessed because no information is available on the toxicity of tetrabromobisphenol A to plants and other wildlife organisms (e.g., birds) exposed via the air.

Human Health. EPA/OPPT is not proposing to assess the potential for dietary intake from eating crops and livestock around manufacturers for several reasons. Although the EU Risk Assessment (EC, 2008) used K_{OW} instead of measured bioconcentration or bioaccumulation factors and Koc values were used to determine uptake to plants and then livestock, more recent data of the uptake of TBBPA by cabbage and radishes from soil showed that a large amount of TBBPA was adsorbed to soil and not available for

transfer to plants (Li et al., 2011). Second, no data were found regarding the bioaccumulation of TBBPA into livestock. Third, the evaluation of exposures from food other than fish is the purview of agencies other than EPA. Appendix K presents details of the EU scenarios that resulted in risks to the environment.

2.6.3.2 Processing

The EU risk assessment for the environment found risks surrounding both acrylonitrile butadiene styrene (ABS) compounding sites and ABS conversion/epoxy resin manufacturing facilities from disposal to waste water and subsequent application to agricultural land or from air releases (EC, 2008). However, in the category of US plastics and rubber processors reporting to TRI, very minimal releases to wastewater and air were reported, with none reported as being used for treatment on agricultural land (EPA, 2012e).

US processing sites in sectors *other than* the plastics and rubber sector have reported higher stack air releases to TRI (EPA, 2012e) than for the plastics/rubber sector. However, EPA/OPPT does not propose evaluating these releases either because they are only a small proportion of the air emissions from manufacturing sites.

Appendix K presents details of the EU scenarios that resulted in risks to the environment.

2.6.3.3 Recycling

Environment. TBBPA has been found in areas surrounding electronics recycling facilities in China, in soil, sediment and nearby waterways (Xu et al., 2012; Feng et al., 2012; He et al., 2010). In contrast, Schlabach et al. (2011) did not find TBBPA in sludge near car demolishing, waste recycling and municipal recycling/landfills in Norway. See Supplemental File 2 for details on TBBPA concentrations near recycling facilities.

There is significant uncertainty in evaluating the risks from recycling: consumption of TBBPA is expected to be higher in Asia than in the United States (He et al., 2010) whereas TBBPA was not detected in sediment and sludge in Norway; regulations for handling e-waste may differ between countries; a significant (yet unknown) amount of e-waste may be exported from the United States; and methods to assess other aspects of the recycling process have not been identified by EPA/ORCR. Because of these uncertainties, EPA/OPPT will not evaluate risks from TBBPA present in environmental media surrounding recycling facilities.

Human Health. Workers at recycling plants may be exposed to TBBPA particulates. Based on an assessment of computer and plastic recycling operations, the European Union estimated typical and reasonable worst case exposures as 0.02 and 4 mg/m^3, respectively. The highest exposure potential was associated with plastic recycling (EC, 2006). Also, TBBPA concentrations were found in environmental media near e-waste recyclers as noted in the previous section, and these concentrations could affect the general population living near such facilities.

EPA/OPPT is not planning to evaluate risks for workers or the general population given significant uncertainties regarding the recycling process in the United States as defined by EPA/ORCR.

2.6.3.4 Disposal

2.6.3.4.1 Landfills

Some waste that contains TBBPA may be classified as hazardous and must be sent to RCRA Subtitle C hazardous waste landfills. EPA regulations at such landfills would significantly limit any exposure from these off-site disposals. Controls include double liners, double leachate collection and removal systems, a leak detection system, along with additional measures (EPA, 2013c). When non-hazardous waste is disposed in properly-managed municipal solid waste landfills (which also must comply with regulations to limit exposure), e-waste is not expected to threaten human health or the environment according to EPA/ORCR (EPA, 2013d).

Furthermore, only limited leaching of TBBPA from landfills is likely because TBBPA is expected to adsorb to soil particles (based on its log K_{OC} of 5.4). In their assessment, Canada noted the limited potential for TBBPA to reach groundwater (EC/HC, 2013). TBBPA has been measured in leachates from landfills in the Netherlands, Finland and Japan (de Boer et al., 2002; Osako et al., 2004; Peltola, 2002; Suzuki and Hasegawa, 2006). Most often TBBPA concentrations are quite low. Prior to treatment, however, TBBPA may be found at higher concentrations (up to 320 µg/kg dry weight), as seen in the Netherlands (de Boer et al., 2002); data on pre- and post-treatment suggests that concentrations could decrease by > 88 to 98% *after* treatment (Osako et al., 2004). Supplemental File 2 presents data on measured TBBPA levels in leachates and other environmental monitoring studies.

For the above reasons, EPA/OPPT will not evaluate risks from disposal of final products after use for the environment or humans.

Landfills that are no longer in operation or that are out of compliance with regulations limiting releases may result in the potential for exposure. However, an evaluation of these situations is beyond the scope of the proposed assessment.

2.6.3.4.2 Incinerators

EPA/OPPT found only one study measured TBBPA emissions (0.008 ng/L to air) from a mixed household and commercial waste incinerator in Japan (Borgnes and Rikheim, 2004). Also, EC/HC (2013) assumed that control devices on incinerators would limit releases of TBBPA to air. Therefore, due to limited data and likely destruction of TBBPA during incineration, EPA/OPPT will not calculate risks from incineration of TBBPA-containing products for the environment or humans.

2.6.3.4.3 Wastewater Treatment Plants (WWTPs)

Facility waste and final consumer products that contain TBBPA may be sent to WWTPs. Exposure to TBBPA could occur after discharge of effluents from WWTPs to water, where it could remain in surface water or partition to sediments or from generation of sludge that is then applied to agricultural land.

Environment - Water. TBBPA has been found in WWTP effluents, waterbodies, sediment and sewage sludge/biosolids (see Supplemental File 2 for individual study data). Comparing a high-end surface value of 0.02 µg/L downstream from a sewage treatment plant in Germany (Kuch et al., 2001) with a chronic COC of 1 µg/L suggests low concern. Also, previous assessments have not identified risks from disposal of consumer products (EC, 2008; EC/HC, 2013).

Environment - Sludge Applied to Land. EPA/OPPT conducted a preliminary calculation to estimate potential TBBPA concentrations in soil after application of sewage sludge to land using conservative assumptions (no degradation and ten years of application) and a high-end TBBPA concentration in sludge (1329 µg/kg) from Spain (Guerra et al., 2010). The resulting TBBPA concentration after soil mixing is below the COC determined for earthworms (= 44 µg/kg), suggesting low concern. North American levels in sludge (Quade, 2003), although older by a few years, are all lower than Guerra et al. (2010).

Human Health -Water. It is possible that individuals may eat fish or obtain drinking water in areas near WWTPs. Data on TBBPA concentrations in fish were not located for areas specifically located near WWTPs.[12] Also, data on TBBPA concentrations in treated drinking water is not available. Therefore, EPA/OPPT will not assess these pathways in the current assessment.

However, as a preliminary exercise to determine whether there are *possible* concerns for people in the vicinity of WWPTs, EPA/OPPT used an exposure estimate from the Canadian assessment (EC/HC, 2013) based on a high-end surface water TBBPA concentration of 0.02 µg/L from Kuch et al. (2001) obtained near a WWTP; the highest exposure estimate from EC/HC (2013) was 1.0×10^{-6} mg/kg-bw/day, for ages 0.5 to 11 years. EPA/OPPT multiplied this exposure value by the most health-conservative slope factor from the NTP (2014a) bioassay.[13] The preliminary risk of 3.3×10^{-9} is approximately 300 times lower than the target risk level of 1×10^{-6}.[14]

Note that other surface water values in non-manufacturing areas were lower than the values in Kuch et al. (2001). Therefore, based on information from current published studies on TBBPA in surface waters, risk from TBBPA in drinking water is likely to be of low concern for non-industrial areas.

Although sewage sludge can be applied to agricultural land, risks resulting from this possible scenario are not being considered for lack of information on uptake from soil, as described in Section 2.6.3.1.

2.6.3.5 Other Excluded Pathways

[12] Fish ingestion for the general population not specific to this exposure pathway will be included in the risk assessment as a part of the aggregate risk assessment.

[13] Value is 0.00329/[mg/kg-bw/day] for development of uterine tumors

[14] The age group of 0.5 to 11 years combines two ranges (0.5-4 years; 5-11 years) from EC/HC (2013) and was used because several years of exposure are most appropriate (e.g., roughly $1/10^{th}$ of the human life span) when comparing with the cancer benchmark. The resulting estimated risk is calculated as 0.00329/[mg-kw/bw/day] * 0.000052 mg/kg-bw/day = 1.7×10^{-7} and is lower than the target risk level of 1.0×10^{-6}.

Mouthing Products with TBBPA for Adults. Although children may place products that contain TBBBPA in their mouths frequently, this is not considered a pathway of concern for adults, given the low likelihood of such behavior for this population.

Drinking Water. As noted in Section 2.6.3.4.3, intake of TBBPA from drinking water is not being assessed as part of the aggregate exposure estimates because data on TBBPA concentrations in treated drinking water are not available. Yet, a preliminary calculation of specific to WWTPs suggests this pathway may be of low concern.

Food. Because the presence of TBBPA in food is the purview of other agencies, it will not be evaluated in the proposed TBBPA risk assessment, except that the ingestion of fish by the general population will be used as a comparison to fish intake for individuals who live near manufacturing facilities.

2.6.4 Uncertainties and Data Gaps

2.6.4.1 Environmental Fate Data

Biodegradation data are lacking for organisms that have not already been acclimated to TBBPA. In addition, for biodegradation and photolysis endpoints, d**a**ta on rates of transformation and identity of degradation products are limited.

2.6.4.2 Release Data

The TRI database is a comprehensive source of environmental release data for the United States. However, there are certain limitations and uncertainties when using the data for a risk assessment.

For example, TRI information is self-reported and limited to those facilities that meet certain criteria (EPA, 2012e). A facility must report to TRI if it:

1. is in a specific industry;
2. employs 10 or more full-time equivalent employees; and
3. manufactures or processes more than 25,000 pounds of a TRI-listed chemical or otherwise uses more than 10,000 pounds of a TRI-listed chemical in a given year.

In addition, facilities can use various methods to estimate the releases they report to TRI (EPA, 2012e). These methods can include continuous monitoring, periodic monitoring, and use of emission factors, best engineering judgment and other methods.

Over the past 13 years, the two facilities considered for quantitative risk assessment – Great Lakes Chemical Solutions (with Chemtura as the parent company) and Albemarle – have used engineering calculations, published emission factors or site specific emission factors as a basis for reporting their air emissions to TRI.

2.6.4.3 Exposure Information

Several exposure parameters to be included in any modeling for TBBPA are variable and limited data exist. Therefore, there is uncertainty in evaluating risks for children exposed through contact with consumer products and subsequent ingestion of TBBPA. Furthermore, there is a lack of current measured TBBPA concentrations in environmental media. There is a lack of measured TBBPA concentrations in sediment in a variety of areas in the United States. Finally, very limited data are available on TBBPA concentrations in the workplaces specific to manufacture and use of TBBPA.

2.6.4.4 Ecological Hazard Data

Uncertainties and limitations of the hazard data may result from the lack of robust data for aquatic, sediment, terrestrial and avian species. Most importantly, exposure to TBBPA will likely occur primarily in sediments and soil. Yet, few acceptable sediment and soil toxicity experiments have been conducted on TBBPA.

Uncertainties also exist in the assessment factors typically used with toxicity values to determine concentrations of concern. Actual variability may differ from the values of 4 or 5 for acute studies and 10 for chronic studies typically used by EPA/OPPT for TSCA-related activities.

2.6.4.5 Human Health Hazard Data

NTP concluded that for hepatoblastomas in male mice, there is some evidence of carcinogenic activity that can be attributed to TBBPA. However, the data did not provide a good fit using the cancer multistage model (Hummel, 2013b), and none of the other models available in the benchmark dose response modeling software resulted in goodness of fit p-values at acceptable levels of > 0.1 when considering the full shape of the dose-response curve (Hummel, 2013a). Thus, this tumor type cannot be considered in a quantitative risk assessment of TBBPA.

The CARC noted that according to the IPCS MOA framework (IPCS, 2007), data are not adequate to draw conclusions about the mode(s) of action for the tumor incidence associated with TBBPA. Therefore, as recommended by EPA (2005), linear low dose extrapolation was used as the default option for modeling tumor data. Yet, because mode of action data are not conclusive, it is possible that a non-linear mode of action could explain the relationship between TBBPA and tumor incidence.

Cancer multistage models were chosen for modeling the cancer bioassay data based on adequate fits for two tumor types and biological considerations even though other models also resulted in adequate fits of the data.

NTP (2014a) administered TBBPA to rodents via oral gavage throughout their lifetime at doses from 250 to 1000 mg/kg-bw/day. Thus, there is uncertainty as to whether less than lifetime or even lifetime exposure by humans exposed to lower doses of TBBPA associated with dust particles or as other forms for less than a lifetime or even a full lifetime. Data are not available to determine quantitative TBBPA disposition for time periods longer than those evaluated in available toxicokinetics studies.

The studies evaluating reproductive and developmental toxicity show a wide variety of results from no effects up to very high doses to subclinical effects at low doses when using TBBPA as the test

substance. Thus, there is uncertainty in choosing any developmental toxicity study for evaluation in a quantitative risk assessment of TBBPA.

Only few inhalation and dermal studies are available and therefore, there is uncertainty as to effects specifically from these routes. There are also only limited studies in humans.

References

Abbott, L., L. Altringer, A. F. Kingery, and D. A. Mayhew. 1981. *Acute Dermal LD50 Toxicity Study in Albino Rabbits, Acute Eye Irritation Study in Albino Rabbits, Acute Oral LD50 Toxicity Study in Albino Rats, Primary Skin Irritation Study in Albino Rabbits with BE-51*. WIL-81225. WIL Research Laboratories, Inc. for Great Lakes Chemical Corporation. (as cited in IPCS, 1995).

ACC-BFRIP (American Chemistry Council Brominated Flame Retardant Industry Panel). 2002. *Tetrabromobisphenol A: A Toxicity Test to Determine the Effects of the Test Substance on Seedling Emergence of Six Species of Plants*. Study conducted by, Wildlife International Ltd., (March 5, 2002). Project No 439-102 (as cited in ACC, 2006).

ACC-BFRIP (American Chemistry Council - Brominated Flame Retardants Industry Panel). 2003. *Effect of Tetrabromobisphenol A on the Survival and Reproduction of the Earthworm, Eisenia fetida*. Study conducted by Aufterhiede, J., T. Kendall , and W. Nixon, ABC Laboratories, Inc. and Wildlife International, Ltd., (February 12, 2003), Columbia, MO and Easton, MD. ABC Study No. 47014 and Wildlife International Project No. 439C-131.

ACC-BFRIP (American Chemistry Council-Brominated Flame Retardants Industry Panel). 2005a. *Effect of Tetrabromobisphenol A on the Reproduction of the Earthworm, Eisenia fetida*. ABC Study No. 49264/Wildlife International, Ltd. Project No. 439C-145. ABC Laboratories Inc. and Wildlife International, Ltd. (as cited in EC/HC, 2013).

ACC-BFRIP (American Chemistry Council - Brominated Flame Retardants Industry Panel). 2005b. *Tetrabromobisphenol-A (TBBPA): A 28-Day Sediment Toxicity Test with Chironomus riparius Using Spiked Sediment*. Project Number 439A-130. Easton, MD. (as cited in EC/HC, 2013).

ACC-BFRIP (American Chemistry Council - Brominated Flame Retardants Industry Panel). 2006. *Tetrabromobisphenol-A (TBBPA): A Prolonged Sediment Toxicity Test with Hyalella azteca Using Spiked Sediment*. Study conducted by Krueger, H., S. T. Thomas , and T. Z. Kendall, Wildlife International, Ltd., Easton, MD.

ACC (American Chemistry Council). 2000. *Brominated Flame Retardant End-User Survey - Phase 1*. Study conducted by Breysse, P. , and J. Kacergis, Johns Hopkins School of Hygiene and Public Health, (May 19, 2000), Baltimore, MD. Doc ID 84010000001.

ACC (American Chemistry Council). 2003. *Tetrabromobisphenol A: A 96-Hour Flow-through Acute Toxicity Test with the Rainbow Trout (Oncorhynchus mykiss). Final Report*. Study conducted by Blankenship, A., R. Van Hoven , and H. Krueger, Wildlife International, Ltd., (July 8, 2003), Easton, MD. FYI-1103-01472.

ACC (American Chemistry Council). 2005. *Determination of Effects on the Growth of the Common Mussel Mytilus edulis*. Study conducted by Brown, R., D. Smyth , and S. Kent, Brixham

Environmental Laboratory and Wildlife International, Ltd., (April 2005), Brixham, UK and Arlington, VA. FYI-0705-01497.

ACC. 2006. *HPV Data Summary and Test Plan for Phenol, 4,4'-Isopropylidenbis[2,6-Dibromo- (Tetrabromobisphenol a, TBBPA)*. Test plan revision/updates, revised test plan. Robust summaries & test plans: Phenol, 4,4'-isopropylidenbis[2,6-dibromo-. http://www.epa.gov/chemrtk/pubs/summaries/phenolis/c13460rt3.pdf.

ACS (American Cancer Society). 2015. *What Are the Key Statistics About Endometrial Cancer?* http://www.cancer.org/cancer/endometrialcancer/detailedguide/endometrial-uterine-cancer-key-statistics (accessed on March 20, 2015).

Ahlers, J., C. Riedhammer, M. Vogliano, R. Ebert, R. Kühne, and G. Schüürmann. 2008. *Acute to Chronic Ratios in Aquatic Toxicity – Variation across Trophic Levels and Relationship with Chemical Structure*. Environmental Toxicology and Chemistry, 25(11), 2937-2945.

Albemarle. 1999. *Saytex® Cp-2000 Flame Retardant*. Baton Rouge, Louisiana. http://albemarle.com/Products-and-Markets/Polymer-Solutions/Fire-Safety-Solutions/SAYTEX-CP-2000-169C183.html (accessed on October 24, 2013).

Alison, R. H., C. C. Capen, and D. E. Prentice. 1994. *Neoplastic Lesions of Questionable Significance to Humans*. Toxicologic Pathology, 22(2), 179-186.

Allard, A. S., M. Remberger, and A. H. Neilson. 1987. *Bacterial O-Methylation of Halogen-Substituted Phenols*. Applied and Environmental Microbiology, 53(4), 839-845.

Arbeli, Z., and Z. Ronen. 2003. *Enrichment of a Microbial Culture Capable of Reductive Debromination of the Flame Retardant Tetrabromobisphenol a, and Identification of the Intermediate Metabolites Produced in the Process*. Biodegradation, 14(6), 385-395.

Babich, M. 2014. *Report to the US CPSC: Appendix E2 - Children's Oral Exposure to Phthalate Alternatives from Mouthing Soft Plastic Children's Articles*. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives, Bethesda, MD.

Balch, G. C., and C. D. Metcalfe. 2001. *In Vivo Toxicity Testing of PBDEs Using Early Life Stages of the Japanese Medaka and the Xenopus Tail Resorption Model*. 3rd Annual Workshop on Brominated Flame Retardants in the Environment. Canada Centre for Inland Waters, August 23-24, pp. 59-60. (as cited in EC, 2006 and ACC, 2006).

BAN/SVTC (The Basel Action Network and Silicon Valley Toxics Coalition). 2002. *Exporting Harm: The High-Tech Trashing of Asia*. (as cited in Kang and Schoenung, 2005).

Banasik, M., M. Hardy, R. D. Harbison, C. H. Hsu, and T. Stedeford. 2009. *Letter to the Editor: Tetrabromobisphenol A and Model-Derived Risks for Reproductive Toxicity*. Toxicology, 260, 150-152.

Bansal, N., V. Yendluri, and R. M. Wenham. 2009. *The Molecular Biology of Endometrial Cancers and Their Implications for Pathogenesis, Classification, and Targeted Therapies*. Cancer Control, 16, 8-13.

Berg, C., K. Halldin, and B. Brunstrom. 2001. *Effects of Bisphenol a and Tetrabromobisphenol a on Sex Organ Development in Quail and Chicken Embryos*. Environmental Toxicology and Chemistry, 20(12), 2836-2840.

Blagosklonny, M. V. 2000. *p53 from Complexity to Simplicity: Mutant p53 Stabilization, Gain-of-Function, and Dominant-Negative Effect*. The FASEB Journal, 14, 1901-1907.

Borgnes, D., and B. Rikheim. 2004. *Decomposition of BFRs and Emission of Dioxins from Co-Incineration of MSW and Electrical and Electronic Plastics Waste*. Organohalogen Compounds, 66, 890-898.

Brown, D. D., Z. Wang, J. D. Furlow, A. Kanamori, R. A. Schawartzman, B. F. FRemo, and A. Pinder. 1996. *The Thyroid Hormone-Induced Tail Resorption Program During Xenopus laevis Metamorphosis*. Developmental Biology, 93, 1924-1929.

Brusick, D. 1977. *Mutagenicity Evaluation of Compound 279-117-2: Final Report*. Litton Biometrics, Inc. to Great Lakes Chemical Corporation. (as cited in IPCS, 1995).

BSEF (Bromine Science Environmental Forum). 2013. *TBBPA Factsheet: Tetrabromobisphenol A for Printed Circuit Boards and ABS Plastics*. Brussels, Belgium.

BSEF (Bromine Science and Environmental Forum). 2014. *About Tetrabromobisphenol A (TBBPA)*. Brussels, Belgium. http://www.bsef.com/about-tbbpa/ (accessed on May 19, 2014).

CalEPA (California Environmental Protection Agency). 2013. *Safer Consumer Product Regulations - Informational "Initial" List of Candidate Chemicals and Chemical Groups, October 18, 2013*. California Department of Toxic Substances Control, Sacramento, California. https://dtsc.ca.gov/SCP/upload/Informational_Initial_Candidate-Chemicals-List_10-18-13.pdf (accessed on June 19, 2014).

California_Biomonitoring (California Contaminant Biomonitoring Program). 2013. *Priority Chemicals, May 2013*. California Department of Public Health, Department of Toxic Substances Control, and Office of Environmental Health Hazard Assessment, Sacramento, California. http://www.biomonitoring.ca.gov/chemicals/priority-chemicals (accessed on June 19, 2014).

California_Biomonitoring (California Contaminant Biomonitoring Program). 2014a. *Designated Chemicals, February 2014*. California Department of Public Health, Department of Toxic Substances Control, and Office of Environmental Health Hazard Assessment, Sacramento, California. http://www.biomonitoring.ca.gov/chemicals/designated-chemicals (accessed on June 19, 2014).

California_Biomonitoring (California Contaminant Biomonitoring Program). 2014b. *Designated Chemicals, October 2014*. California Department of Public Health, Department of Toxic Substances Control, and Office of Environmental Health Hazard Assessment, Sacramento, CA. http://www.biomonitoring.ca.gov/sites/default/files/downloads/DesignatedChemicalList_October2014.pdf (accessed on March 16, 2015).

California_Biomonitoring (California Contaminant Biomonitoring Program). 2014c. *Priority Chemicals, June 2014*. California Department of Public Health, Department of Toxic Substances Control, and Office of Environmental Health Hazard Assessment, Sacramento, CA. http://biomonitoring.ca.gov/sites/default/files/downloads/PriorityChemicalsList_June2014.pdf (accessed March 16, 2015).

Canton, R. F., J. T. Sanderson, S. Nijmeijer, A. Bergman, R. J. Letcher, and M. van den Berg. 2006. *In Vitro Effects of Brominated Flame Retardants and Metabolites on CYP17 Catalytic Activity: A Novel Mechanism of Action?* Toxicology and Applied Pharmacology, 216, 274-281.

CARC (Cancer Assessment Review Committee). Cancer Assessment Document: Evaluation of the Carcinogenic Potential of Tetrabromobisphenol A (TBBPA). memorandum to Lai, D. (Office of Pollution Prevention and Toxics, US Environmental Protection Agency), September 17, 2014.

Chemtura. 2013. *Flame Retardants - Products - BA-59P™*. Great Lakes Solutions, West Lafayette, Indiana. http://www.greatlakes.com/Flame_Retardants/Products/BA-59P (accessed on October 24, 2013).

Chemtura. 2014. *About Chemtura*. http://www.chemtura.com/corporatev2/v/index.jsp?vgnextoid=6a6238f220d6d210VgnVCM100000753810aRCRD&vgnextchannel=6a6238f220d6d210VgnVCM1000000753810aRCRD&vgnextfmt=default (accessed on May 19, 2014).

Chen, J. Q., T. R. Brown, and J. D. Yager. 2008. *Mechanisms of Hormone Carcinogenesis: Evolution of Views, Role of Mitochondria*. Advances in Experimental Medicine and Biology, 630, 1-18.

Chen, S.-J., Y.-J. Ma, J. Wang, D. Chen, X.-J. Luo, and B.-X. Mi. 2009. *Brominated Flame Retardants in Children's Toys: Concentration, Composition and Children's Exposure and Risk Assessment*. Environmental Science and Technology, 43(11), 4200-4206.

Chow, W. S., W. K. L. Chan, and K. M. Chan. 2013. *Toxicity Assessment and Vitellogenin Expression in Zebrafish (Danio rerio) Embryos and Larvae Acutely Exposed to Bisphenol a, Endosulfan, Heptachlor, Methoxychlor and Tetrabromobisphenol A*. Journal of Applied Toxicology, 33(7), 670-678.

Conova, S. 2003. *Estrogen's Role in Cancer*. In Vivo, 2(10), http://www.cumc.columbia.edu/publications/in-vivo/Vol2_Iss10_may26_03/.

de Boer, J., C. Allchin, B. Zegers, J. P. Boon, S. H. Brandsma, S. Morris, A. W. Kruijt, I. van der Veen, J. M. van Hesselingen, and J. J. H. Haftka. 2002. *HBCD and TBBPA in Sewage Sludge, Sediments and Biota, Including Interlaboratory Study*. RIVO report number CO33/02. RIVO - the Netherlands Institute for Fisheries Research, Ymuiden and Yerseke, Netherlands.

de Winter-Sorkina, R., M. I. Bakker, G. van Donkersgoed, and J. D. van Klaveren (RIVM – Netherlands Institute of Public Health and the Environment). 2003. *Dietary Intake of Brominated Flame Retardants by the Dutch Population*.

Di Napoli-Davis, G., and J. E. Owens. 2013. *Quantitation of Tetrabromobisphenol-a from Dust Sampled on Consumer Electronics by Dispersed Liquid-Liquid Microextraction*. Environmental Pollution, 180, 274-280.

Dover_Chemical. 2012. *Doverguard 59: Tetrabromobisphenol A*. Dover, Ohio. http://www.doverchem.com/Portals/0/DG59.pdf (accessed on October 24, 2013).

Dover_Chemical. 2013. *Doverguard® Brominated Flame Retardants*. Dover, Ohio. http://www.doverchem.com/Products/DoverguardBrominatedFlameRetardants.aspx (accessed on October 24, 2013).

Dow_Chemical. 1975. *Results of a 90-Day Toxicological Study in Rats Given Tetrabromobishphenol a in the Diet*. Study conducted by Quast, J. F., C. G. Humiston , and B. A. Schwetz, Toxicology Research Laboratory, Health and Environmental Research, The Dow Chemical Company, (July 11, 1975), Midland, MI. OTS#0206824. Doc ID 878216066.

Driffield, M., N. Harmer, E. Bradley, A. R. Fernandes, M. Rose, D. Mortimer, and P. Dicks. 2008. *Determination of Brominated Flame Retardants in Food by LC-MS/MS: Diastereoisomer-Specific Hexabromocyclododecane and Tetrabromobisphenol A*. Food Additives and Contaminants. Part A: Chemistry, Analysis, Control, Exposure and Risk Assessment, 25(7), 895-903.

EC (European Commission). 2000. *Iuclid Dataset: Existing Chemical Substance Id 79-94-7*. European Chemicals Bureau, Joint Research Centre, Institute for Health and Consumer Protection, European Chemical Substances Information System. http://esis.jrc.ec.europa.eu/index.php?PGM=hpv.

EC (European Commission). 2006. *European Union Risk Assessment Report for 2,2',6,6'-Tetrabromo-4,4'-Isopropylidenediphenol (Tetrabromobispheonl-a or TBBP-A) Part II – Human Health, CAS No. 79-94-7, EINECS No. 201-236-9*. 4th Priority List, Volume: 63, EUR22161 EN. Institute for Health and Consumer Protection, Joint Research Centre, Luxembourg. http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/tbbpaHHreport402.pdf.

EC (European Commission). 2008. *Risk Assessment of 2,2',6,6-Tetrabromo-4,4'-Isopropylidene Diphenol (Tetrabromobisphenol-A): CAS Number: 79-94-7; EINECS Number: 201-236-9; Final Environmental Rar of February 2008*. R402_0802_env. Rapporteur: United Kingdom. http://echa.europa.eu/documents/10162/17c7379e-f47b-4a76-aa43-060da5830c07.

EC/HC (Environment and Health Canada). 2013. *Screening Assessment Report: Phenol, 4,4'-(1-Methylethylidene)Bis[2,6-Dibromo- (CASRN 79-94-7); Ethanol, 2,2'-[(1-Methylethylidene)Bis[(2,6-Dibromo-4,1-Phenylene)Oxy]]Bis (CASRN 4162-45-2); Benzene, 1,1'-(1-Methylethylidene)Bis[3,5-Dibromo-4-(2-Propenyloxy)- (CASRN 25327-89-3)*. Government of Canada. http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=BEE093E4-1.

ECHA (European Chemicals Agency). 2013. *Registered Substances - Search Page*. European Commission, Helsinki, Finland. http://echa.europa.eu/information-on-chemicals/registered-substances (accessed on November 4, 2013).

ECHA (European Chemicals Agency). 2014. *Pre-Registered Substances - Search Page*. European Commission, Helsinki, Finland. http://echa.europa.eu/information-on-chemicals/pre-registered-substances (accessed on June 19, 2014).

ECHA (European Chemicals Agency). 2015a. *Substance Evaluation*. Agency of the European Union, Helsinki, Finland. http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation (accessed on Februrary 10, 2015).

ECHA (European Chemicals Agency). 2015b. *Understanding Reach*. Agency of the European Union, Helsinki, Finland. http://echa.europa.eu/web/guest/regulations/reach/understanding-reach (accessed on February 5, 2015).

EFSA. 2011. *Scientific Opinion on Tetrabromobisphenol A (TBBPA) and Its Derivatives in Food*. EFSA Journal, 9(12), 2477 +.

EPA (US Environmental Protection Agency). 1998. *Guidelines for Ecological Risk Assessment*. EPA/630/R-95/002F. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf.

EPA (US Environmental Protection Agency). 1999a. *Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances*. 64 US Government Printing Office, Washington, DC 213 (November 4, 1999), pp. 60194-60204.

EPA (US Environmental Protection Agency). 1999b. *Determining the Adequacy of Existing Data - Draft*. Office of Pollution Prevention and Toxics, Washington, DC. http://www.epa.gov/hpv/pubs/general/datadfin.htm.

EPA (US Environmental Protection Agency). 2005. *Guidelines for Carcinogen Risk Assessment*. EPA/630/P-03/001F. Risk Assessment Forum, Washington, DC. http://epa.gov/cancerguidelines/.

EPA (US Environmental Protection Agency). 2008a. *Partnership to Evaluate Flame Retardants in Printed Circuit Boards: Draft Report*. Design for the Environment, Office of Pollution Prevention and Toxics, Washington, DC.

http://www.epa.gov/dfe/pubs/projects/pcb/full_report_pcb_flame_retardants_report_draft_11_10_08_to_e.pdf.

EPA (US Environmental Protection Agency). 2008b. *Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multipathway Chemicals: SHEDS-Multimedia Model Version 3 Technical Manual*. 600/R-08/118. Office of Research and Development, USEPA and with help from Alion Science and Technology, Inc., Washington, DC.

EPA (US Environmental Protection Agency). 2011a. *Electronics Waste Management in the United States through 2009*. EPA 530-R-11-002. Office of Resource Conservation and Recovery, Washington, D. C. . http://www.epa.gov/osw/conserve/materials/ecycling/docs/fullbaselinereport2011.pdf.

EPA (US Environmental Protection Agency). 2011b. *Exposure Factors Handbook*. EPA/600/R-09/052F. National Center for Environmental Assessmet, Office of Research and Development, Washington, DC. http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf.

EPA (US Environmental Protection Agency). 2011c. *Integrated Risk Information System (IRIS) Glossary*. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary (accessed on September 24, 2014).

EPA (US Environmental Protection Agency). 2012a. *Benchmark Dose Technical Guidance*. EPA/100/R-12/001. Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf/publications/pdfs/benchmark_dose_guidance.pdf.

EPA (US Environmental Protection Agency). 2012b. *Estimation Programs Interface Suite™ for Microsoft® Windows, V 4.11*. Washington, DC. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

EPA (US Environmental Protection Agency). 2012c. *Standard Operating Procedures for Residential Pesticide Exposure Assessment*. Health Effects Division, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, Washington, DC. http://www.epa.gov/opp00001/science/USEPA-OPP-HED_Residential%20SOPs_Oct2012.pdf.

EPA (US Environmental Protection Agency). 2012d. *Sustainable Futures and P2 Framework Manual*. EPA/748/B-12/001. Office of Chemical Safety and Pollution Prevention, Washington, DC. http://www.epa.gov/oppt/sf/pubs/sf-p2-manual.html.

EPA (US Environmental Protection Agency). 2012e. *Toxics Release Inventory (TRI) Program*. Washington, DC. http://www.epa.gov/tri/index.htm (accessed on June 9 and 19, 2014).

EPA (US Environmental Protection Agency). 2013a. *Estimation Programs Interface Suite™ for Microsoft® Windows, V4.10*. Washington, DC.

http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm (accessed on September 18, 2013).

EPA (US Environmental Protection Agency). 2013b. *Interpretive Assistance Document for Assessment of Discrete Organic Chemicals - Sustainable Futures Summary Assessment*. Washington, DC. http://www.epa.gov/oppt/sf/pubs/iad_discretes_june2013.pdf.

EPA (US Environmental Protection Agency). 2013c. *Wastes - Hazardous Waste - Treatment and Disposal: Hazardous Waste Land Disposal Units (LDUs)*. Office of Resource Conservation and Recovery, Washington, DC. http://www.epa.gov/epawaste/hazard/tsd/td/index.htm (accessed on November 22, 2013).

EPA (US Environmental Protection Agency). 2013d. *Wastes - Resource Conservation - Common Wastes and Materials - Ecycling: Frequent Questions*. Office of Resource Conservation and Recovery, Washington, DC. http://www.epa.gov/epawaste/conserve/materials/ecycling/faq.htm (accessed on November 25, 2013).

EPA (US Environmental Protection Agency). 2014a. *An Alternatives Assessment for the Flame Retardant Decabromodiphenyl Ether (Decabde): Final Report*. Design for the Environment, Office of Pollution Prevention and Toxics, Washington, DC. http://www.epa.gov/oppt/dfe/pubs/projects/decaBDE/deca-report-complete.pdf.

EPA (US Environmental Protection Agency). 2014b. *Chemical Data Reporting*. Office of Pollution Prevention and Toxics, Washington, DC. http://www.epa.gov/oppt/cdr/ (accessed on June 19, 2014).

EPA (US Environmental Protection Agency). 2014c. *ECOTOX Database*. Mid-Continent Ecology Division, Duluth, MN. http://cfpub.epa.gov/ecotox/.

EPA (US Environmental Protection Agency). 2014d. *Estimated Fish Consumption Rates for the U.S. Population and Selected Subpopulations (NHANES 2003-2010)*. EPA-820-R-14-002. Washington, DC. http://water.epa.gov/scitech/swguidance/fishshellfish/fishadvisories/upload/Estimated-Fish-Consumption-Rates-for-the-U-S-Population-and-Selected-Subpopulations-NHANES-2003-2010.pdf.

EPA (US Environmental Protection Agency). 2014e. *Flame Retardants in Printed Circuit Boards: Updated Draft Report*. Design for the Environment, Washington, DC. http://www.epa.gov/dfe/pubs/projects/pcb/index.htm.

EPA (US Environmental Protection Agency). 2014f. *Framework for Human Health Risk Assessment to Inform Decision Making*. EPA/100/R-14/001. Office of the Science Advisor, Risk Assessment Forum, Washington, DC. http://www.epa.gov/raf.

EPA (US Environmental Protection Agency). 2014g. *Harmonized Test Guidelines*. Office of Chemical Safety and Pollution Prevention. http://www.epa.gov/ocspp/pubs/frs/home/guidelin.htm.

EPA (US Environmental Protection Agency). 2014h. *Non-Confidential 2006 IUR Company/Chemical Records*. Office of Pollution Prevention and Toxics, Washington, DC. http://cfpub.epa.gov/iursearch/ (June 20, 2014).

EPA (US Environmental Protection Agency). 2014i. *Technology Transfer Network - Support Center for Regulatory Atomospheric Modeling: Preferred/Recommended Models*. Office of Air and Radiation, Office of Air Quality Planning and Standards, Research Triangle Park, NC. http://www.epa.gov/scram001/dispersion_prefrec.htm (accessed on February 11, 2015).

EPA (US Environmental Protection Agency). 2014j. *Water: Sewage Sludge (Biosolids)*. Office of Water, Washington, DC. http://water.epa.gov/polwaste/wastewater/treatment/biosolids/ (October 14, 2014).

EPA (US Environmental Protection Agency). 2015. *Substance Registry Services*. Washington, DC. http://ofmpub.epa.gov/sor_internet/registry/substreg/home/overview/home.do (accessed on March 9, 2015).

Eriksson, J., S. Rahm, N. Green, A. Bergman, and E. Jakobsson. 2004. *Photochemical Transformations of Tetrabromobisphenol a and Related Phenols in Water*. Chemosphere, 54, 117-126.

Eriksson, P., E. Jakobsson, and A. Frederiksson. 2001. *Brominated Flame Retardants: A Novel Class of Developmental Neurotoxicants in Our Environment?* Environmental Health Perspectives, 109, 903-908.

Eriksson, P., E. Jakobsson, and A. Fredriksson. 1998. *Developmental Neurotoxicity of Brominated Flame Retardants, Polybrominated Diphenyl Ethers, and Tetrabromobisphenol A*. Organohalogen Compounds, 35, 375-377.

Fackler, P. 1989. *Tetrabromobisphenol A. Determination of Biodegradability in a Sediment/Water Microbial System*. SLS Report 89-8-3070. Springborn Life Sciences, Inc., Wareham, MA. http://www.epa.gov/chemrtk/pubs/summaries/phenolis/c13460rr3.pdf. (as cited in ACC, 2006).

FSAI (Food Safety Authority of Ireland). 2010. *Investigation into Levels of Chlorinated and Brominated Organic Pollutants in Carcass Fat, Offal, Eggs and Milk Produced in Ireland, Monitoring and Surveillance Series*. http://www.fsai.ie/search-results.html?searchString=offal%20chlorinated%20brominated.

Fukuda, N., Y. Ito, M. Yamaguchi, K. Mitumori, M. Koizumi, R. Hasegawa, E. Kamata, and M. Ema. 2004. *Unexpected Nephrotoxicity Induced by Tetrabromobisphenol a in Newborn Rats*. Toxicology Letters, 150, 145-155.

Gallen, C., A. Banks, S. H. Brandsma, C. Baduel, P. Thai, G. Eaglesham, A. Heffernan, P. Leonards, P. Bainton, and J. F. Mueller. 2014. *Towards Development of a Rapid and Effective Non-Destructive*

Testing Strategy to Identify Brominated Flame Retardants in the Plastics of Consumer Products. Science of the Total Environment, 491-492, 255-265.

Garber, E. A. E., G. L. Larsen, H. Hakk, and A. Bergman. 2001. *Frog Embryo Teratogenic Assay: Xenopus (FETAX) Analysis of the Biological Activity of Tetrabromobisphenol a (TBBPA)*. Poster presentation at Second International Workshop on Brominated Flame Retardants, May 14-16, Stockholm University, Sweden.

George, K. W., and M. M. Haggblom. 2008. *Microbial O-Methylation of the Flame Retardant Tetrabromobisphenol-A*. Environmental Science and Technology, 42(15), 5555-5561.

GLCC (Great Lakes Chemical Corporation). 1967. *Acute Inhalation Toxicity Study of Tetrabromobisphenol A to Rats*. Sponsored by the Brominated Flame Retardants Industry Panel (Unpublished), St. Louis, MO. (as cited in EC/HC, 2013).

GLCC (Great Lakes Chemical Corporation). 1978a. *The Acute Toxicity of FMBP4A (Tetrabromobisphenol a) to the Bluegill Sunfish, Lepomis macrochirus Rafinesque*. Study conducted by Calmbacher, C. W., A. G. Vilkas , and C. Hutchinson, Union Carbide Environmental Services, prepared for Velsicol Chemical Corporation, Tarrytown, NY. OTS# 0206828. Doc ID 878216107.

GLCC (Great Lakes Chemical Corporation). 1978b. *The Acute Toxicity of FMBP4A (Tetrabromobisphenol a) to the Rainbow Trout, Salmo gairdneri Richardson*. Study conducted by Calmbacher, C. W., A. G. Vilkas , and C. Hutchinson, Union Carbide Environmental Services, prepared for Velsicol Chemical Corporation, (March 30, 1978), Chicago, IL. OTS0206828. Doc ID 878216108.

GLCC (Great Lakes Chemical Corporation). 1978c. *Acute Toxicity of FMBP4A (Tetrabromobisphenol a) to the Water Flea Daphnia magna Straus*. Study conducted by Morrissey, A. E., A. G. Vilkas , and C. Hutchinson, Union Carbide Environmental Services, prepared for Velsicol Chemical Corporation, (May 8, 1978), Tarrytown, NY. OTS# 0206828. Doc ID 878216112.

GLCC (Great Lakes Chemical Corporation). 1982. *Ames/Salmonella Plate Assay Report on Bis(2,3-Dibromopropyl)Ether of Tetrabromobisphenol a with Attachments*. Study conducted by. 0503680. 8888200436.

GLCC (Great Lakes Chemical Corporation). 1988a. *Acute Toxicity of Tetrabromobisphenol a to Fathead Minnow (Pimephales promelas) under Flow-through Conditions*. Study conducted by, Springorn Life Sciences, (November 16, 1988), Wareham, MA. OTS# 0525512. Doc ID 40-8898095.

GLCC (Great Lakes Chemical Corporation). 1988b. *Toxicity of Tetrabromobisphenol a to the Freshwater Green Alga Selenastrum capricornutum*. Study conducted by, Springborn Life Sciences, Inc., (November 16, 1988), Wareham, MA. OTS# 0525512. Doc ID 40-8898095.

GLCC (Great Lakes Chemical Corporation). 1989a. *Bioconcentration and Elimination of 14C-Residues by Fathead Minnows (Pimephales promelas) Exposed to Tetrabromobisphenol-A*. Report No. 89-3-2952. Springborn Life Sciences, Inc., Wareham, MA.

GLCC (Great Lakes Chemical Corporation). 1989b. *Bioconcentration and Elimination of C-Residues by Eastern Oysters (Crassostrea virginica) Exposed to Tetrabromobisphenol a (Final Report) with Attached Studies and Cover Letter 081889*. Study conducted by Fackler, P. H. , and P. D. Royal, Springborn Life Sciences, Inc., (August 16, 1989), Wareham, MA. OTS# 0525518. Doc ID 40-8998118.

GLCC (Great Lakes Chemical Corporation). 1989c. *Determination of the Biodegradability of Tetrabromobisphenol A in Soil under Aerobic Conditions. Final Report*. Study conducted by, Springborn Life Sciences, Inc., (January 20, 1989), Wareham, MA. OTS# 0525513. Doc ID 42083 G3-2.

GLCC (Great Lakes Chemical Corporation). 1989d. *Determination of the Biodegradability of Tetrabromobisphenol A in Soil under Anaerobic Conditions (Final Report) with Attachments and Cover Letter Dated 013189*. Study conducted by, Springborn Life Sciences, Inc., (January 19, 1989), Wareham, MA. OTS# 0525513. Doc ID 42083 G3-2.

GLCC (Great Lakes Chemical Corporation). 1989e. *The Subchronic Toxicity of Sediment-Sorbed Tetrabromobisphenol a to Chironomus tentans under Flow-through Conditions (Final Report) with Cover Sheet and Letter Dated 101689*. Study conducted by Breteler, R. J., J. R. Hoberg, N. Garvey, S. R. Connor, D. A. Hartley, S. P. Shepherd, P. H. Fackler , and P. D. Royal, Springborn Laboratories, Inc., Wareham, MA. OTS# 0525507. Doc ID 40-8998109.

Goodman, L., G. Cripe, P. Moody, and D. Halsell. 1988. *Acute Toxicity of Malathion, Tetrabromobisphenol a and Tributyltin Chloride to Mysids (Mysidopses bahia) of Three Ages*. Bulletin of Environmental Contamination and Toxicology, 41, 746-753.

Gorman, N. 2012. *The Relationship between Inadvertent Ingestion and Dermal Expousre Pathways: A New Integrated Conceptual Model and a Database of Dermal and Oral Transfer Efficiences*. Annals of Occupational Hygiene, 56(9), 1000-1012.

Gosavi, R. A., G. A. Knudsen, L. S. Birnbaum, and L. C. Pedersen. 2013. *Mimicking of Estradiol Binding by Flame Retardants and Their Metabolites: A Crystallographic Analysis*. Environmental Health Perspectives, 121(10), 1194-1199.

GS1. 2015. *GPC Browser*. http://www.gs1.org/1/productssolutions/gdsn/gpc/browser/ (accessed on March 9, 2015).

Guerra, P., E. Eljarrat, and D. Barcelo. 2010. *Simultaneous Determination of Hexabromocyclododecane, Tetrabromobisphenol a, and Related Compounds in Sewage Sludge and Sediment Samples from Ebro River Basin (Spain)*. Analytical and Bioanalytical Chemistry, 397, 2817-2824.

Gustafsson, K., and M. Wallen. 1988. *Status Report on Tetrabromobisphenol A (CAS No. 79-94-7) - Unpublished Report*. Clearing House Sweden, National Chemicals Inspectorate, Solna, Sweden. (as cited in EC/HC, 2013).

Hagmar, L., A. Sjodin, P. Hoglund, K. Thuresson, L. Rylander, and A. Bergman. 2000. *Biological Half-Lives of Polybrominated Diphenyl Ethers and Tetrabromobisphenol a in Exposed Workers*. Organohalogen Compounds, 47, 198-201.

Hakk, H., G. Larsen, A. Bergman, and U. Orn. 2000. *Metabolism, Excretion, and Distribution of the Flame Retardant Tetrabromobisphenol-a in Conventional and Bile-Duct Cannulated Rats*. Xenobiotica, 30(9), 881-890.

Halldin, K., C. Berg, A. Bergman, I. Brandt, and B. Brunstrom. 2001. *Distribution of Bisphenol a and Tetrabromobisphenol a in Quail Eggs, Embryos and Laying Birds and Studies on Reproduction Variables in Adults Following in Ovo Exposure*. Archives of Toxicology, 75, 597-603.

Hamers, T., J. H. Kamstra, E. Sonneveld, A. J. Murk, M. H. A. Kester, P. L. Andersson, J. Legler, and A. Brouwer. 2006. *In Vitro Profiling of the Endocrine-Disrupting Potency of Brominated Flame Retardants*. Toxicological Sciences, 92(1), 157-173.

Hanada, H., K. Katsu, T. Kanno, E. F. Sato, A. Kashiwagi, J. Sasaki, M. Inoue, and K. Utsumi. 2003. *Cyclosporin a Inhibits Thyroid Hormone-Induced Shortening of the Tadpole Tail through Membrane Permeability Transition*. Comparative Biochemistry and Physiology. Part B, 135, 473-483.

He, M. J., X. J. Luo, L. H. Yu, J. Liu, X. L. Zhang, S. J. Chen, D. Chen, and B. X. Mai. 2010. *Tetrabromobisphenol-A and Hexabromocyclododecane in Birds from an E-Waste Region in South China: Influence of Diet on Diastereoisomer- and Enantiomer-Specific Distribution and Trophodynamics*. Environmental Science and Technology, 44(15), 5748-5754.

Herr, D. (US EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory). Review of Lilienthal et al., 2008 Regarding Brainstem Auditory Evoked Potentials and Tetrabromobisphenol A. Memorandum to: Benson, A. (US Environmental Protection Agency, Office of Pollution Prevention and Toxics), September 3, 2013.

HTRI (Hill Top Research, Inc.). 1966. *Acute Toxicity and Irritation Studies of [Sic] Tetrabromobisphenol A (Unpublished)*. (as cited in EC, 2006).

Hummel, R. (US Environmental Protection Agency). Liver Hepatoblastoma Stats. Personal communication with: Benson, A. (US Environmental Protection Agency), November 13, 2013.

Hummel, R. (US Environmental Protection Agency). Results of Dose Response Modeling of NTP 2013 Cancer Data. Personal communication with: Benson, A. (US Environmental Protection Agency), November 14, 2013.

Hummel, R. 2014. *BMDS Wizard Output Report - Hemangiosarcomas and Hemangiomas/Hemangiosarcomas (Combined)*. Office of Pollution Prevention and Toxics, US Environmental Protection Agency, Washington, DC.

IBRI (International Bio-Research, Inc.). 1967. *Acute Oral Toxicity of Tetrabromobisphenol a to Rats (Unpublished)*. (as cited in EC, 2006).

ICL-IP (ICL Industrial Products). 2013a. *FR-720*. http://icl-ip.com/?products=fr-720 (accessed on October 24, 2013).

ICL-IP (ICL Industrial Products). 2013b. *FR-1524*. http://icl-ip.com/?post_type=products&p=3062 (accessed on October 24, 2013).

IPCS (International Programme on Chemical Safety). 1995. *Tetrabromobisphenol A and Derivatives*. Environmental Health Criteria 172. United Nations Environment Programme, the International Labor Organisation and the World Health Organization, Geneva, Switzerland. http://www.inchem.org/documents/ehc/ehc/ehc172.htm.

IPCS (International Programme on Chemical Safety). 1997. *Flame Retardants: A General Introduction*. Environmental Health Criteria 192. United Nations Environment Programme, the International Labor Organisation and the World Health Organization, Geneva, Switzerland. http://www.inchem.org/documents/ehc/ehc/ehc192.htm.

IPCS (International Programme on Chemical Safety). 2007. *IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans and Case Studies (Part 1)*. Harmonization Proejct Document No. 4. World Health Organization, the International Labour Organization, and the United Nations Environment Programme. http://www.who.int/ipcs/methods/harmonization/areas/cancer_mode.pdf.

IRDC (International Research and Development Corporation). 1975. *Fourteen-Day Inhalation Toxicity Study in Rats (Unpublished)*. (as cited in EC, 2006).

IRDC (International Research and Development Corporation). 1979. *Three Week Dermal Toxicity Study in Rabbits (Unpublished)*. (as cited in EC, 2006).

ITC (United States International Trade Commission). 2013. *Used Electronic Products: An Examination of U.S. Exports*. Investigation No. 332-528; USITC Publication 4379. Washington, DC.

Kang, H.-Y., and J. M. Schoenung. 2005. *Electronic Waste Recycling: A Review of U.S. Infrastructure and Technology Options*. Resources, Conservation and Recycling, 45, 368-400.

Kashiwagi, A., H. Hanada, M. Yabuki, T. Kanno, R. Ishisaka, J. Sasaki, M. Inoue, and K. Utsumi. 1999. *Thyroxine Enhancement and the Role of Reactive Oxygen Species in Tadpole Tail Apoptosis*. Free Radical Biology and Medicine, 26(7/8), 1001-1009.

Keller, A. S., P. N. Raju, T. F. Webster, and H. M. Stapleton. 2014. *Flame Retardant Applications in Camping Tents and Potential Exposure*. Envionmental Science and Technology Letters, 1, 152-155.

Kicinski, M., M. K. Viaene, E. D. Hond, G. Schoeters, A. Covaci, A. C. Dirtu, V. Nelen, L. Bruckers, K. Croes, I. Sioen, W. Baeyens, N. Van Larebeke, and T. S. Nawrot. 2012. *Neurobehavioral Function and Low-Level Exposure to Brominated Flame Retardants in Adolescents: A Cross-Sectional Study*. Environmental Health, 11, 1-12.

Knudsen, G. A., L. M. Jacobs, R. K. Kuester, and I. G. Sipes. 2007. *Absorption, Distribution, Metabolism and Excretion of Intravenously and Orally Administered Tetrabromobisphenol a [2,3-Dibromopropyl Ether] in Male Fischer-344 Rats*. Toxicology, 237, 158-167.

Krueger, H. e. a. (Wildlife International, Ltd.). 2002a. *Tetrabromobisphenol A: A Prolonged Sediment Toxicity Test with Lumbriculus Variegatus Using Spiked Sediment with 2% Total Organic Carbon*. Project Number: 439a-115. Easton, MD. (as cited in ACC, 2006).

Krueger, H. e. a. 2002b. *Tetrabromobisphenol A: A Prolonged Sediment Toxicity Test with Lumbriculus variegatus Using Spiked Sediment with 5% Total Organic Carbon* Project Number: 439A-116. Wildlife International, Ltd., Easton, MD. (as cited in ACC, 2006).

Kuch, B., W. Korner, and H. Hagenmaier. 2001. *[Monitoring Von Bromierten Flammschutzmitteln in Fliessgewassern, Abwassern Und Klarschlammen in Baden-Wurttemberg]*.

Kuester, R. K., A. M. Solyom, V. P. Rodriguez, and I. G. Sipes. 2007. *The Effects of Dose, Route, and Repeated Dosing on the Disposition and Kinetics of Tetrabromobisphenol a in Male F-344 Rats*. Toxicological Sciences, 96(2), 237-245.

Kuiper, R. V., E. J. van den Brandhof, P. E. Leonards, L. T. van der Ven, P. W. Wester, and J. G. Vos. 2007. *Toxicity of Tetrabromobisphenol a (TBBPA) in Zebrafish (Danio rerio) in a Partial Life-Cycle Test*. Archives of Toxicology, 81(1), 1-9.

Larsen, G., F. Casey, A. Bergman, and H. Hakk. 2001. *Mobility, Sorption and Fate of Tetrabromobisphenol a (TBBPA) in Loam Soil and Sand*. Abstracts of the 2nd International Workshop on Brominated Flame Retardants. Part 2 - Analysis and Fate, Products, Standards and Uses, Stockholm, Sweden. http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=5&ved=0CD0QFjAE&url=http%3A%2F%2Fwww.researchgate.net%2Fprofile%2FTom_Harner%2Fpublication%2F244465065_Measurements_of_OctanolAir_Partition_Coefficients_(_K_OA_)_for_Polybrominated_Diphenyl_Ethers_(PBDEs)_Predicting_Partitioning_in_the_Environment%2Ffile%2F9c960526a70f0039a2.pdf&ei=8hu8U5i5OYqqsQTUzYDwBA&usg=AFQjCNFUYNoYed3Nj0yEkmhBFMIPTfpSSg&sig2=t_o5cht8FU1t6qL4JfvgGw&bvm=bv.70138588,d.ZGU.

Lax, S. F. 2004. *Molecular Genetic Pathways in Various Types of Endometrial Carcinoma: From a Phenotypical to a Molecular-Based Classification*. Virchows Archiv: European Journal of Pathology, 444, 213-223.

Li, Y., Q. Zhou, Y. Wang, and X. Xie. 2011. *Fate of Tetrabromobisphenol a and Hexabromocyclododecane Brominated Flame Retardants in Soil and Uptake by Plants*. Chemosphere, 82(2), 204-209.

Lilienthal, H., C. M. Verwer, L. T. van der Ven, A. H. Piersma, and J. G. Vos. 2008. *Exposure to Tetrabromobisphenol a (TBBPA) in Wistar Rats: Neurobehavioral Effects in Offspring from a One-Generation Reproduction Study*. Toxicology, 246(1), 45-54.

Lipnick, R. L. 1995. Structure-Activity Relationships. In Rand, G. R., *Fundamentals of Aquatic Toxicology* (2nd ed., Chapter 20, pp. 609-655). Taylor and Francis, London, England.

Maine_DEP (Department of Environmental Protection). 2013a. *Chemicals of Concern*. http://www.maine.gov/dep/safechem/concern/documents/ChemicalsofConcernList12_2011.pdf (accessed on Februrary 3, 2015).

Maine_DEP (Department of Environmental Protection). 2013b. *Chemicals of High Concern*. http://www.maine.gov/dep/safechem/highconcern/ (accessed on February 3, 2015).

Maine_DEP (Department of Environmental Protection). 2013c. *Safer Chemicals in Children's Products*. http://www.maine.gov/dep/safechem/index.html (accessed on February 3, 2015).

Mariussen, E., and F. Fonnum. 2003. *The Effect of Brominated Flame Retardants on Neurotransmitter Uptake into Rat Brain Synaptosomes and Vesicles*. Neurochem. Int., 43, 533-542. (as cited in NTP, 2013).

MDH (Minnesota Department of Health). 2013a. *Chemicals of High Concern List*. http://www.health.state.mn.us/divs/eh/hazardous/topics/toxfreekids/chclist/mdhchc2013.pdf (accessed on July 2, 2014).

MDH (Minnesota Department of Health). 2013b. *Toxic Free Kids Act: Chemicals of High Concern, July 2013*. http://www.health.state.mn.us/divs/eh/hazardous/topics/toxfreekids/highconcern.html#list (accessed on February 3. 2015).

Meerts, I. A. T. M., Y. Assink, P. H. Cenijin, B. M. Weijers, and H. H. J. van den Berg. 1999. *Distribution of the Flame Retardant Tetrabromobisphenol a in Pregnant and Fetal Rats and Effect on Thyroid Hormone Homeostasis*. Oganohalogen Compounds, 40, 375-378. (as cited in EC, 2006).

Morf, L., R. Taverna, H. Daxbeck, and R. Smutny. 2003. *Selected Polybrominated Flame Retardants: PBDEs and TBBPA; Substance Flow Analysis*. Environmental Series No. 338. Swiss Agency for the Environment, Forests and Landscape, Berne, Switzerland.

Morose, G. 2006. *An Overview of Alternatives to Tetrabromobisphenol a (TBBPA) and Hexabromocyclododecane (HBCD)*. Lowell Center For Sustainable Production, University of

Massachusetts, Lowell, Massachusetts. http://www.chemicalspolicy.org/downloads/AternativestoTBBPAandHBCD.pdf.

MPI_Research. 2001. *Final Report - an Oral Prenatal Developmental Toxicity Study with Tatrabromobisphenol-a in Rats (Unpublished)*.

MPI_Research. 2002a. *A 90-Day Oral Toxicity Study of Tetrabromobisphenol-a in Rats with a Recovery Group (Unpublished)*. (as cited in EC, 2006).

MPI_Research. 2002b. *An Oral Two Generation Reproductive, Fertility and Developmental Neurobehavioral Study of Tetrabromobisphenol-a in Rats (Unpublished)*. (as cited in EC, 2006).

MPI_Research. 2003. *Amendment to the Final Report. An Oral Two Generation Reproductive, Fertility and Developmental Neurobehavioural Study of Tetrabromobisphenol-a in Rats (Unpublished Report)*. (as cited in EC, 2006).

Muller, P. A. J., and K. H. Vousden. 2013. *p53 Mutations in Cancer*. Nature: Cell Biology, 15(1), 2-8.

Nakajima, A., D. Saigusa, N. Tetsu, T. Yamakuni, Y. Tomioka, and T. Hishinuma. 2009. *Neurobehavioral Effects of Tetrabromobisphenol a, a Brominated Flame Retardant, in Mice*. Toxicology Letters, 189(1), 78-83.

Neumann, F. 1991. *Early Indicators for Carcinogenesis in Sex-Hormone-Sensitive Organs*. Mutation Research, 248, 341-356.

NIEHS (National Institute of Environmental Health Sciences). 2002. *Tetrabromobisphenol A [79-94-7]: Review of Toxicological Literature*. Prepared for Scott Masten, Ph.D. by Karen E. Haneke, M.S., Integrated Laboratory Systems. http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/tetrabromobisphenola_508.pdf.

NIEHS (National Institute of Enviornmental Health Sciences). 2015. *Review of the EPA Hazard Identification and Dose Response for Tetrabromobisphenol A*. National Institutes of Health. (January 7, 2015).

NITE (National Institute of Technology and Evaluation). 2010a. *#28: Biodegradation in Water: Screening Tests for CASRN 21850-44-2*. Japan Chemicals Collaborative Knowledge Database, Ministry of Economy, Trade and Industry and Ministry of the Environment, Japan. http://www.safe.nite.go.jp/jcheck/template.action?ano=8003&mno=4-212&cno=21850-44-2&request_locale=en (accessed on February 11, 2014).

NITE (National Institute of Technology and Evaluation). 2010b. *#32: Bioaccumulation: Aquatic/Sediment for TBBPA (CASRN 79-94-7)*. Japan Chemicals Collaborative Knowledge Database, Ministry of Economy, Trade and Industry and Ministry of the Environment, Japan.

http://www.safe.nite.go.jp/jcheck/template.action?ano=849&mno=4-0205&cno=79-94-7&request_locale=en (accessed on November 14, 2014).

NLM (National Library of Medicine). 2009. *Hazardous Substance Database Entry for 2-Bromophenol (CASRN 95-56-7)*. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~TtZAHq:3 (accessed on October 4, 2014).

Noda, T., S. Morita, S. Ohgaki, and M. Shimizu. 1985. *Safety Evaluation of Chemicals for Use in Household Products (VII) Teratological Studies on Tetrabromobisphenol-A in Rats*. Annual Report of the Osaka Institute of Public Health and Environmental Sciences, 48, 106-112. (as cited in EC, 2006).

NTP (National Toxicology Program). 2014a. *NTP Technical Report on the Toxicology Studies of Tetrabromobisphenol A (CAS No. 79-94-7) in F344/NTac Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Tetrabromobisphenol A in Wistar Han [Crl:WI(Han)] Rats and B6C3F1/N Mice (Gavage Studies)*. NTP TR 587. National Institutes of Helath, Public Health Service, US Department of Health and Human Services, Research Triangle Park, NC. http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr587_508.pdf.

NTP (National Toxicology Program). 2014b. *Report on Carcinogens, Thirteenth Edition, Estrogens, Steroidal*. US Department of Health and Human Services. http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html.

Nyholm, J. R., C. Lundberg, and P. L. Andersson. 2010. *Biodegradation Kinetics of Selected Brominated Flame Retardants in Aerobic and Anaerobic Soil*. Environmental Pollution, 158(6), 2235-2240.

OECD (Organisation for Economic Cooperation and Development). 2003. *Guidance Document on Reporting Summary Information on Environmental, Occupational and Consumer Exposure*. ENV/JM/MONO(2003)16. Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, Paris, France. http://www.oecd-ilibrary.org/environment/guidance-document-on-reporting-summary-information-on-environmental-occupational-and-consumer-exposure_9789264079113-en.

OECD (Organisation for Economic Cooperation and Development). 2015. *OECD Guidelines for the Testing of Chemicals*. Paris, France. http://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm (accessed on March 9, 2015).

Ohta, R., A. Takagi, H. Ohmukai, H. Marumo, A. Ono, Y. Matsushima, T. Inoue, H. Ono, and J. Kanno. 2012. *Ovariectomized Mouse Uterotrophic Assay of 36 Chemicals*. The Journal of Toxicological Sciences, 37(5), 879-889.

Oregon_DEQ (Department of Environmental Quality). 2010a. *Attachment 2. Priority Persistent Pollutant List (P3 List)*. http://www.deq.state.or.us/wq/SB737/ (accessed on June 19, 2014).

Oregon_DEQ (Department of Environmental Quality). 2010b. *Attachment 4. Pollutant Profiles*. http://www.deq.state.or.us/wq/SB737/docs/LegRpAtt420100601.pdf (accessed on June 19, 2014).

Oregon_DEQ (Department of Environmental Quality). 2010c. *Water Quality: Senate Bill 737 Implementation: Addressing Priority Persistent Pollutants in Oregon's Water*. http://www.deq.state.or.us/wq/SB737/#TLR (accessed on February 2, 2015).

Osako, M., Y.-J. Kim, and S. Sakai. 2004. *Leaching of Brominated Flame Retardants in Leachate from Landfills in Japan*. Chemosphere, 57, 1571-1579.

OSHA (Occupational Safety and Health Administration). 2015. *Chemical Exposure Health Data*. United States Department of Labor, Washington, DC. https://www.osha.gov/opengov/healthsamples.html (accessed on February 6, 2015).

Ozkaynak, H., J. Xue, V. G. Zartarian, G. Glen, and L. Smith. 2011. *Modeled Estimates of Soil and Dust Ingestion Rates for Children*. Risk Analysis, 31(4), 592-608.

Pellizzari, E. D., R. A. Zweidinger, and M. D. Erickson. 1978. *Environmental Monitoring near Industrial Sites: Brominated Chemicals. Part I and II*. Contract Number 68-01-1978. Research Triangle Institute, for Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.

Peltola, J. 2002. *An Environmental Screening of Four Brominated Flame Retardants in Finland*. to be published in Chemosphere. (as cited in EC, 2008).

Qu, G., A. Liu, T. Wang, C. Zhang, J. Fu, M. Yu, J. Sun, N. Zhu, Z. Li, G. Wei, Y. Du, J. Shi, S. Liu, and G. Jiang. 2013. *Identification of Tetrabromobisphenol a Allyl Ether and Tetrabromobisphenol a 2,3-Dibromopropyl Ether in the Ambient Environment near a Manufacturing Site and in Mollusks at a Coastal Region*. Environmental Science and Technology, 47(9), 4760-4767.

Qu, G., J. Shi, T. Wang, J. Fu, Z. Li, P. Wang, T. Ruan, and G. Jiang. 2011. *Identification of Tetrabromobisphenol A Diallyl Ether as an Emerging Neurotoxicant in Environmental Samples by Bioassay-Directed Fractionation and HPLC-APCI-MS/MS*. Environmental Science and Technology, 45, 5009-5016.

Quade, S. C. 2003. *Determination of Tetrabromobisphenol a in Sediment and Sludge.* (M.S. dissertation), University of Guelph, Ottawa, Canada.

Raftogianis, R., C. Creveling, R. Weinshilboum, and J. Weisz. 2000. *Chapter 6: Estrogen Metabolism by Conjugation*. Journal of the National Cancer Institute Monographs, 27.

Russo, J., and I. H. Russo. 2004. *Genotoxicity of Steroidal Estrogens*. Trends in Endocrinolology and Metabolism, 15(5), 211-214.

Saegusa, Y., H. Fujimoto, G. H. Woo, K. Inoue, M. Takahashi, K. Mitsumori, A. Nishikawa, and M. Shibatani. 2009. *Developmental Toxicity of Brominated Flame Retardants, Tetrabromobisphenol a and 1,2,5,6,9,10-Hexabromocyclododecane, in Rat Offspring after Maternal Exposure from Mid-Gestation through Lactation*. Reproductive Toxicology, 28, 456-467.

Saegusa, Y., H. Fujimoto, G. H. Woo, T. Ohishi, L. Wang, K. Mitsumori, A. Nishikawa, and M. Shibutani. 2012. *Transient Aberration of Neuronal Development in the Hippocampal Dentate Gyrus after Developmental Exposure to Brominated Flame Retardants in Rats*. Archives of Toxicology, 86(9), 1431-1442.

Samsonek, J., and F. Puype. 2013. *Occurrence of Brominated Flame Retardants in Black Thermo Cups and Selected Kitchen Utensils Purchased on the European Market*. Food Additives and Contaminants, Part A, 30(11), 1976-1986.

Schauer, U. M. D., W. Volkel, and W. Dekant. 2006. *Toxicokinetics of Tetrabromobisphenol a in Humans and Rats after Oral Administration*. Toxicological Sciences, 91, 49-58.

Schlabach, M., M. Remberger, E. Brorstrom-Lunden, K. Norstrom, L. Kaj, H. Andersson, D. Herzke, A. Borgen, and M. Harju. 2011. *Brominated Flame Retardants (BFR) in the Nordic Environment*. TemaNord 2011:528. Nordic Council of Ministers, Copenhagen, Denmark. http://www.norden.org/en/publications/publikationer/2011-528.

Shi, Z., Y. Wu, J. Li, Y. Zhao, and J. Feng. 2009. *Dietary Exposure Assessment of Chinese Adults and Nursing Infants to Tetrabromobisphenol a and Hexabromocyclododecanes: Occurrence Measurements in Foods and Human Milk*. Environmental Science and Technology, 43, 4314-4319.

Sidhu, S., A. Morgan, M. Kahandawala, K. Muddasani, B. Gullet, and D. Tabor. 2013. *Use of Cone Calorimeter to Identify Selected Polyhalogenated Dibenzo-P-Dioxins/Furans and Polyaromatic Hydrocarbon Emissions from the Combustion of Ciruit Board Laminates: Final Report*. October 22. University of Dayton Research Institute and the U.S. Environmental Protection Agency, Dayton, Ohio and Research Triangle Park, North Carolina.

Sjodin, A., D. Patterson, and A. Bergman. 2003. *A Review on Human Exposure to Brominated Flame Retardants – Particularly Polybrominated Diphenyl Ethers*. Environment International, 29, 829-839.

SLS (Springborn Life Sciences, Inc.). 1989a. *Acute Toxicity of Tetrabromobisphenol a to Eastern Oysters (Crassostrea virginica) under Flow-through Conditions*. 89-1-2898. Wareham, MA. (EC, 2008).

SLS (Springborn Life Sciences, Inc.). 1989b. *The Chronic Toxicity of Tetrabromobsiphenol a (TBBPA) to Daphnia magna under Flow-through Conditions.* SLS Study No. 89-01-2925. Wareham, Massachusettes. (as cited in ACC, 2006).

SLS (Springborn Life Sciences). 1989c. *The Toxicity of Tetrabromobisphenol a (TBBPA) to Fathead Minnow (Pimephales promelas) Embryos and Larvae*. SLS Study No. 89-2-2937. Wareham, MA. (as cited in ACC, 2006).

Stoner_Laboratories. 1978. *The Bioaccumulation of Tetrabromobisphenol A in the Bluegill Sunfish*. Project 780241. Santa Clara, CA. (as cited in EC, 2008).

Strain, G. M., M. Banasik, M. Hardy, and T. Stedeford. 2009. *Tetrabromobisphenol A (TBBPA) and Model-Derived Risks for Neurobehavioral Effects in Offspring from a One-Generation Reproduction Study*. Toxicology, 260(1-3), 155-157.

Suzuki, S., and A. Hasegawa. 2006. *Determination of Hexabromocyclododecane Diastereoisomers and Tetrabromobisphenol A in Water and Sediment by Liquid Chromatography/Mass Spectrometry*. Analytical Sciences, 22(March), 469-474.

Sverdrup, L. E., T. Hartnik, E. Mariussen, and J. Jensen. 2006. *Toxicity of Three Halogenated Flame Retardants to Nitrifying Bacteria, Red Clover (Trifolium pratense), and a Soil Invertebrate (Enchyraeus crypticus)*. Chemosphere, 64, 96-103.

Tada, Y., T. Fujitani, N. Yano, H. Takahashi, K. Yuzawa, H. Ando, Y. Kubo, A. Nagasawa, A. Ogata, and H. Kamimura. 2006. *Effects of Tetrabromobisphenol a, a Brominated Flame Retardant, in ICR Mice after Prenatal and Postnatal Exposure*. Food and Chemical Toxicology, 44(8), 1408-1413.

Thomas, R. G. 1982a. Volatilization from Soil. In Lyman, W. J., *Handbook of Chemical Property Estimation Methods* (Chapter 16, pp. 16.11-16.39). McGraw-Hill Book Company, New York, NY.

Thomas, R. G. 1982b. Volatilization from Water. In Lyman, W. J., *Handbook of Chemical Property Estimation Methods* (Chapter 15, pp. 15.11-15.33). McGraw-Hill Book Company, New York, NY.

Tobe, M., Y. Kurokawa, Y. Nakaji, H. Yoshimoto, A. Takagi, Y. Aida, J. Monna, K. Naito, and M. Saito. 1986. *Subchronic Toxicity Study of Tetrabromobisphenyl-A: Report to the Ministry of Health and Welfare*. (as cited in IPCS, 1995).

UL_IDES (Underwriter Laboratories IDES). n.d. *UL 94 Flame Rating*. http://www.ides.com/property_descriptions/UL94.asp (accessed on June 23, 2014).

United_Kingdom. 2008. *Annex Xv Restriction Report - November 30 2008*. http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=1&ved=0CB0QFjAA&url=http%3A%2F%2Fecha.europa.eu%2Fdocuments%2F10162%2F13630%2Ftrd_uk_bisphenol_a_en.rtf&ei=t-iqU8ODMcuysQTG54CwAw&usg=AFQjCNEIbrGxxYSbZhuaErjWBvEKeHffDw&sig2=cj6NndGPjwC9LVWwaLCR6A&bvm=bv.69620078,d.cWc.

van Bergen, S., and A. Stone. 2014. *Flame Retardants in General Consumer and Children's Products*. 14-04-021. Department of Ecology, State of Washington, Olympia, WA. https://fortress.wa.gov/ecy/publications/SummaryPages/1404021.html.

Van der Ven, L. T., T. Van de Kuil, A. Verhoef, C. M. Verwer, H. Lilienthal, P. E. Leonards, U. M. Schauer, R. F. Canton, S. Litens, J. F. H. De, T. J. Visser, W. Dekant, N. Stern, H. Hakansson, W. Slob, d. B. M. Van, J. G. Vos, and A. H. Piersma. 2008. *Endocrine Effects of Tetrabromobisphenol-a (TBBPA) in Wistar Rats as Tested in a One-Generation Reproduction Study and a Subacute Toxicity Study*. Toxicology, 245(1-2), 76-89.

VCC (Velsicol Chemical Corporation). 1978a. *Acute Toxicity of Tetrabromobisphenol A (Unpublished)*. 8EHQ-0678-0185. (as cited in EC/HC, 2013).

VCC (Velsicol Chemical Corporation). 1978b. *Pilot Teratology Study in Rats with Tetrabromobisphenol a with Cover Letter Dated 04/17/78*. Study conducted by. 0200479.

Veldhoen, N., A. Boggs, K. Walzak, and C. C. Helbing. 2006. *Exosure to Tetrabromobisphenol-a Alters Th-Associated Gene Expression and Tadpole Metamorphosis in the Pacific Tree Frog Pseudacris regilla*. Aquatic Toxicology, 78, 292-302.

Viberg, H., and P. Eriksson. 2011. *Differences in Neonatal Neurotoxicity of Brominated Flame Retardants, PBDE 99 and TBBPA, in Mice*. Toxicology, 289(1), 59-65.

Waaijers, S. L., J. Hartmann, A. M. Soeter, R. Helmus, S. A. E. Kools, P. de Voogt, W. Admiraal, J. R. Parsons, and M. H. S. Kraak. 2013. *Toxicity of New Generation Flame Retardants to Daphnia magna*. Science of the Total Environment, 463, 1042-1048.

Walsh, G. E., M. J. Yoder, L. L. McLaughlin, and E. M. Lores. 1987. *Responses of Marine Unicellular Algae to Brominated Organic Compounds in Six Growth Media*. Ecotoxicology and Environmental Safety, 14, 215-222.

Washington_State_DEC (Washington State Department of Ecology). 2014. *Overview of the Law*. http://www.ecy.wa.gov/programs/swfa/cspa/ (accessed on September 18, 2014).

Wichmann, H., F. T. Dettmer, and M. Bahadir. 2002. *Thermal Formation of PBDD/F from Tetrabromobisphenol A - a Comparison of Polymer Linked TBBPA with Its Additive Incorporation in Thermoplastics*. Chemosphere, 47, 349-355.

Wollenberger, L., L. Dinan, and M. Breitholtz. 2002. *Effects of Brominated Flame Retardants on Two Marine Copepod Species, Acartia tonsa and Nitocra spinipes, and on the Ecdysteroid-Responsive Drosophila melanogaster BII-Cell-Line*. Organohalogen Compounds, 57, 451-454.

WSDE (Washington State Department of Ecology). 2011. *Rationale for Reporting List of Chemicals of High Concern to Children*. http://www.ecy.wa.gov/programs/swfa/cspa/pdf/79947.pdf (accessed on June 19, 2014).

WSDE (Washington State Department of Ecology). 2013. *Reporting Guidance - Product Categories and Scope*. http://www.ecy.wa.gov/programs/swfa/cspa/pdf/cspaguide_category.pdf (accessed on March 9, 2015).

WSDE (Washington State Department of Ecology). 2014a. *Children's Safe Product Act Reports*. https://fortress.wa.gov/ecy/cspareporting/Reports/ReportViewer.aspx?ReportName=ChemicalReportByCASNumber (accessed on June 19, 2014).

WSDE (Washington State Department of Ecology). 2014b. *The Reporting List of Chemicals of High Concern to Children (CHCC)*. http://www.ecy.wa.gov/programs/swfa/cspa/chcc.html (accessed on February 2, 2015).

Yager, J. D. 2014. *Mechanisms of Estrogen Carcinogenesis: The Role of E2/E1-Quinone Metabolites Suggests New Approaches to Preventive Intervention - a Review*. Steroids, August 24, 2014; Epub ahead of print.

Yang, S., S. Wang, F. Wu, Z. Yan, and H. Liu. 2012. *Tetrabromobisphenol A: Tissue Distribution in Fish, and Seasonal Variation in Water and Sediment of Lake Chaohu, China*. Environmental Science and Pollution Research, 19, 4090-4096.

Zalko, D., D. Prouillac, A. Rui, E. Perdu, L. Dolo, I. Jouanin, C. Canlet, L. Debaruwer, and J.-P. Cravedi. 2006. *Biotransformation of the Flame Retardant Tetrabromobisphenol a by Human and Rat Sub-Cellular Liver Fractions*. Chemosphere, 64, 318-327.

Zatecka, E., L. Ded, F. Elzeinova, A. Kubatova, A. Dorosh, H. Margaryan, P. Dostalova, and J. Peknicova. 2013. *Effect of Tetrabrombisphenol a on Induction of Apoptosis in the Testes and Changes in Expression of Selected Testicular Genes in CD1 Mice*. Reproductive Toxicology, 35, 32-39.

Zweidinger, R. A., S. D. Cooper, M. D. Erickson, L. C. Michael, and E. D. Pellizzari. 1979. Sampling and Analysis for Semivolatile Brominated Organics in Ambient Air. In Schuetzle, D., *Monitoring Toxic Substances* (ACS Symposium Series 94 ed., Chapter 13, pp. 217-231). American Chemical Society, Washington, DC.

Zweidinger, R. A., S. D. Cooper, and E. D. Pellizzari. 1979. Identification and Quantitation of Brominated Fire Retardants. In Hall, C. E. V., *Measurement of Organic Pollutants in Water and Wastewater, ASTM STP 686* (pp. 234-250). American Society for Testing and Materials, Philadelphia, PA.

Appendix A Data Available for TBBPA-bis(dibromopropyl ether), TBBPA-bis(allyl ether) and TBBPA-bis(methyl ether)

Although EPA decided not to conduct assessments for the three cluster members other than TBBPA, there are some data available for these compounds. Table_Apx A-1 presents an overview of the data available for all cluster members, to show the comparison of the other cluster members with the index chemical TBBPA. The ability to use TBBPA data to characterize these other chemicals (i.e. the ability to read-across) is also discussed for environmental and human health endpoints.

Table_Apx A-1: Data Availability and Read Across for Cluster Members

Endpoint	Chemical			
	TBBPA	**TBBPA-bis(dibromo propyl ether)**	**TBBPA-bis(allyl ether)**	**TBBPA-bis(methyl ether)**
Production Volume and Uses				
Production Volume (2010 or 2011)	X	X	X	ND
Industrial Uses	X	X	ND	ND
Consumer Uses	X	X	ND	ND
Physical-Chemical Properties				
Melting Point	X	X	X	X
Boiling Point	X	X	X	X
Vapor Pressure	X	X	X	X
Water Solubility	X	ND	ND	ND
Octanol-Water Partition Coefficient	X	ND	ND	X
Fate Properties				
Biodegradation	**X**	**X**	ND	ND
Experimental Bioconcentration Data	**X**	ND	ND	ND
Exposure (Monitoring Data)				
Environmental media	X	X	X	X
Biota	X	X	X	X
Environmental Effects				
Acute fish	X	X	ND	ND
Chronic fish	X	ND	ND	ND
Acute invertebrate	X	X	ND	ND
Chronic invertebrates	X	ND	ND	ND
Algae	X	X	ND	ND
Sediment toxicity	X	ND	ND	ND
Earthworms	X	X	ND	ND

Table_Apx A-1: Data Availability and Read Across for Cluster Members

Endpoint	Chemical			
	TBBPA	**TBBPA-bis(dibromo propyl ether)**	**TBBPA-bis(allyl ether)**	**TBBPA-bis(methyl ether)**
Potential for read across from TBBPA?	NA	No; Physical-chemical properties differ	No; Physical-chemical properties differ	No; Physical-chemical properties differ
Human Health				
Acute Oral	X	X	X	ND
Acute Dermal	X	X	X	ND
Acute Inhalation	X	X	ND	ND
Repeated-Dose	X [oral and limited dermal/inhalation]	X [oral]	ND	ND
Developmental	X	ND	ND	ND
Reproductive	X	ND	ND	ND
Genetic Toxicity	X [gene mutations, chromosomal aberrations, other]	X [gene mutations, chromosomal aberrations, other]	X [gene mutations]	ND
Neurotoxicity/ neurobehavioral	X	ND*	ND	ND
Skin Irritation	X	X	ND	ND
Eye Irritation	X	X	ND	ND
Sensitization	X	X	ND	ND
Carcinogenicity	X	ND	ND	ND
Potential for read across from TBBPA?	NA	No; This compound has alkylating potential [high mw, low solubility limit toxicity]	No; This compound has alkylating/epoxide forming potential [high mw, low solubility limit toxicity]	Yes; Structurally and mechanistically similar to TBBPA

NA = not applicable; X = data available; ND = no data available

**in vitro* only

The data for each of these endpoints are described in the following sections:

A-1. Exclusion from Further Assessment
A-2. Chemical Structures
A-3. Physical-Chemical Properties
A-4. Production Volumes
A-5. Uses
A-6. Fate Properties
A-7. Exposure
A-8. Ecological Hazard
A-9. Human Health Hazard

A-1 Exclusion from Further Assessment

EPA/OPPT does not propose to conduct risk assessments for the three cluster members other than TBBPA for reasons detailed below.

A-1-1 TBBPA-bis(dibromopropyl ether)

Regarding ecological toxicity, the only adequate data for this compound are for earthworms, and the results indicate low toxicity (ECHA, 2013). The toxicity estimation program EcoSAR v. 1.11 (EPA, 2012b) is not well suited for use with this compound to fill additional endpoints because log K_{OW} values are expected to be higher than those used to develop the algorithms used within EcoSAR. Yet, TBBPA-bis(dibromopropyl ether) is likely to have low water solubility and a high octanol-water partition coefficient and no toxic effects are expected in aquatic and other organisms when considering quantitative structure activity relationships (QSARs) (Lipnick, 1995).

For human health, a toxicokinetics study in rats shows low absorption by TBBPA-bis(dibromopropyl ether) (Knudsen et al., 2007), which limits its ability to reach target cells. Lack of absorption is expected given the compound's high molecular weight and log K_{OW} and low water solubility. Low toxicity has been indicated in available studies and is likely to be due to its limited absorption (ECHA, 2013; GLCC, 1982; IPCS, 1995).

Due to differences in physical-chemical properties compared with TBBPA and its potential to act as an alkylating agent, EPA/OPPT has determined that TBBPA toxicity studies should not be used as surrogate data for this compound for either ecological or human health toxicity endpoints. Therefore, EPA/OPPT will not assess risks to this compound for these reasons as well as the limited toxicity data available. The expected low toxicity of the compound also suggests that gathering additional data on this compound is not a high priority.

A-1-2 TBBPA-bis(allyl ether)

No adequate ecological toxicity data were found for TBBPA-bis(allyl ether) and it is not expected to exhibit effects in aquatic and other organisms due to physical-chemical properties and QSARs (Lipnick, 1995).

Regarding the potential to result in human health effects, absorption is likely to be limited as is the ability to reach target cells. Limited toxicity information suggests low toxicity (Abbott et al., 1981; Brusick, 1977; EC/HC, 2013; Qu et al., 2011).

Similar to the dibromoether, differences in physical-chemical properties and reactivity due to TBBPA-bis(allyl ether)'s alkylating potential preclude using TBBPA toxicity data to read across to this compound. EPA/OPPT does not propose to assess risks from this compound due to these differences and the limited toxicity information. Again, the expected low toxicity indicates that this compound is not a high priority for obtaining data in order to conduct a risk assessment.

A-1-3 TBBPA-bis(methyl ether)

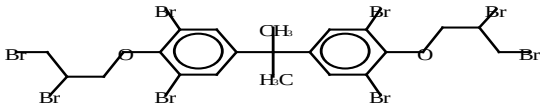
No adequate ecological toxicity data were found for this compound, and like the other two cluster members, it is not expected to exhibit effects in aquatic and other organisms due to physical-chemical properties and QSARs (Lipnick, 1995). Also, differences in physical-chemical properties compared with TBBPA suggest that TBBPA cannot be used as a surrogate for ecological toxicity.

No human health toxicity data were found for TBBPA-bis(methyl ether). Unlike the ecological toxicity endpoints, TBBPA could be used as a surrogate compound for TBBPA-bis(methyl ether) to estimate human health hazards based on enough similarity in the chemicals' structures. However, TBBPA-bis(methyl ether) is found only as a transformation byproduct of TBBPA; EC (2008) indicates that it may be a minor degradation product. In addition, its concentrations in the environment are usually lower than TBBPA concentrations (see Supplemental File 2 for environmental concentrations). Furthermore, scenarios of concern for TBBPA are not relevant for TBBPA-bis(methyl ether) because it is not manufactured or found in consumer products. Therefore, EPA/OPPT does not propose conducting a risk assessment on this compound.

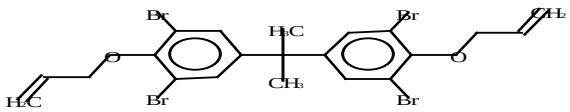
A-2 Chemical Structures

Individual compound structures for the three cluster members are given in the sections below.

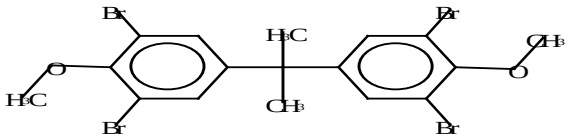
A-2-1 TBBPA-bis(dibromopropyl ether)



A-2-2 TBBPA-bis(allyl ether)



A-2-3 TBBPA-bis(methyl ether)



A-3 Physical-Chemical Properties

TBBPA-bis(methyl ether), TBBPA-bis(allyl ether) and TBBPA-bis(dibromopropyl ether) are solids with low vapor pressure and low water solubility. Table_Apx A-2 identifies the physical-chemical properties, which are only available for some cluster members. Estimation program values (EPA, 2013a) for vapor pressure and water solubility were unrealistically low and log K_{OW} values were unrealistically high. Therefore, estimated values are not reported in Table_Apx A-2. However, compared with TBBPA, the other cluster members are expected to have lower water solubility and vapor pressures and higher octanol-water partition coefficients (log K_{OW}s) given their larger size and higher molecular weights.

Table_Apx A-2: Physical-Chemical Properties

Chemical Name	CASRN	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg @ 25°C)	Water Solubility (mg/L)	Octanol-Water Partition Coefficient (log K_{OW})
TBBPA-bis(dibromopropyl ether)	21850-44-2	95	> 200°C (dec)	< 1x 10^{-6}	ND	ND
TBBPA-bis(allyl ether)	25327-89-3	120	> 200°C (dec)	< 1 x 10^{-6}	ND	ND
TBBPA-bis (methyl ether)	37853-61-5	ND	> 200°C (dec)	< 1 x 10^{-6}	ND	> 6.4

ND: no measured data
Source: IPCS (1995)

A-4 Production Volumes

A-4-1 TBBPA-bis(dibromopropyl ether)

According to the 2012 CDR, the production volume of TBBPA-bis(dibromopropyl ether) is between 1 and 10 million pounds per year, as shown in

Table**_Apx A-3**. The CDR database identifies ICL-IP America, Inc., ICC Chemical Corporation and one company that claimed CBI as manufacturers/importers of TBBPA-bis(dibromopropyl ether) (EPA, 2014b).

Trade names for TBBPA-bis(dibromopropyl ether) include ICL-IP's FR-720 and Dover Chemical Corporation's (a subsidiary of ICC Industries, Inc.) Doverguard 68 (Dover_Chemical, 2013; ICL-IP, 2013a).

CDR data do not indicate whether this chemical is imported (EPA, 2014b). All companies listed in the 2012 CDR database exported 0 pounds and did not report import volumes or claimed the data as CBI.

A-4-2 TBBPA-bis(allyl ether)

CDR data identifies ICC Chemical Corporation as a manufacturer/importer of TBBPA-bis(allyl ether). The national production volume for TBBPA bis(allyl ether) is withheld from the 2012 CDR to protect CBI claims. However, one of the two ICC sites reported a past production volume (for the year 2010) of 124,575 pounds (EPA, 2014b), as shown in

Table_Apx **A-3**.

CDR data do not indicate whether this chemical is imported (EPA, 2014b). All companies listed in the 2012 CDR database exported 0 pounds and did not report import volumes or claimed the data as CBI.

A-4-3 TBBPA-bis(methyl ether)

There are no reports for TBBPA-bis(methyl ether) in the 2012 CDR database (EPA, 2014b).

Table_Apx A-3: 2012 CDR Production Volume Data (Pounds/Year) for TBBPA-bis(dibromopropyl ether), TBBPA-bis(allyl ether) and TBBPA-bis(methyl ether)

Chemical Name	Company Site	2012 Domestic Manufacturing	2012 Imported	2012 Exported	2012 Used on Site[1]	2010 Past Production (import and manufacture)	2011 National Production
TBBPA-bis(dibromo-propyl ether)	ICL-IP America, Inc. 622 Emerson Road, Suite 500 St. Louis, MO 63141	ND	CBI	0	N/A	426,480	1 million to 10 million
	ICC Chemical Corporation 460 Park Avenue New York, NY 10022	ND	CBI	0	N/A	CBI	
	CBI	ND	CBI	0	N/A	CBI	
TBBPA-bis(allyl ether)	ICC Chemical Corporation 460 Park Avenue New York, NY 10022	ND	CBI	0	N/A	CBI	Withheld
	ICC Chemical Corporation 3676 Davis Rd NW Dover, OH 44622	79,640	ND	0	0	124,575	Withheld
TBBPA-bis(methyl ether)	NR	NR	NR	NR	NR	NR	NR

[1]The total volume (domestically manufactured and imported) of the chemical used at the reporting site without leaving the site.
ND = No Data; the company did not provide the requested information.
NR = No Reports; "No Reports" in the CDR public database indicates that production volume was not reported for the IUR/CDR for a given year. This does not necessarily indicate that a chemical was not manufactured in the United States, but rather indicates that a chemical, if manufactured, had a production volume below the reporting threshold.
N/A = Not Applicable; the imported chemical was never physically at the site.
"Withheld" in the CDR public database indicates that the national production volume of a chemical was unable to be aggregated in order to protect to CBI claims.
Source: **EPA (2014b)**

A-5 Uses

The 2012 CDR data are minimal for industrial and consumer uses of TBBPA-bis(dibromopropyl ether) and TBBPA bis(allyl ether), as shown in Table_Apx A-4.

The CDR database does not contain records for TBBPA-bis(methyl ether) (EPA, 2014b). In 1995 the IPCS Environmental Health Criteria for TBBPA and derivatives stated that as of 1994 TBBPA-bis(methyl ether) was not used for commercial purposes based on the personal communications from a Great Lakes Chemicals representative (IPCS, 1995). Instead, it was noted that this compound was a product of environmental biotransformation.

The Environmental Health Criteria for flame retardants (IPCS, 1997) listed TBBPA-bis(methyl ether) as a flame retardant for expandable polystyrene, but no references were provided. Furthermore, under EPA's Design for the Environment Program, companies that produce polystyrene foam did not report using any TBBPA-based products, including TBBPA-bis(methylether), in flame retardant applications.

Although there is one report of TBBPA-bis(methyl ether)'s use as a flame retardant, multiple other sources indicate that it is not used in products. Thus, for purposes of this assessment it is assumed that TBBPA-bis(methyl ether) appears in the environment solely as a transformation product of TBBPA.

Table_Apx A-4: Industrial and Consumer Use Data for TBBPA-bis(dibromopropyl ether), TBBPA-bis(allyl ether) and TBBPA-bis(methyl ether)

Chemical Name	Manufacturing Site	Type of Processing	Industrial Use Data			Consumer Use Data		
			Sector	Industrial Use	Percent of Production Volume	Consumer Use Product Category	Commercial or Consumer Use	Percent of Production Volume
TBBPA-bis(dibromo propyl ether)	ICL-IP America, Inc. 622 Emerson Road, Suite 500 St. Louis, MO 63141-6742	Processing-incorporation into formulation, mixture or reaction product	Plastics Product Manufacturing	Flame retardants	100	Plastic and Rubber Products not covered elsewhere	Commercial	100
	ICC Chemical Corporation 460 Park Avenue New York, NY 10022-1906	ND	ND	ND	ND	ND	ND	ND
	CBI	Processing-incorporation into article	Plastics Material and Resin Manufacturing	Flame retardants	100	Plastic and Rubber Products not covered elsewhere	Commercial	100
TBBPA-bis(allyl ether)	ICC Chemical Corporation 460 Park Avenue New York, NY 10022-1906	ND	ND	ND	ND	ND	ND	ND
	Dover Chemical Corp 3676 Davis Road North West Dover, OH 44622-9771	ND	ND	ND	ND	ND	ND	ND
TBBPA-bis(methyl ether)	NR	NR	NR	NR	NR	NR	NR	NR

ND = No Data; the company did not provide the requested information.
NR = No Reports; "No Reports" in the CDR public database indicates that production volume was not reported for the IUR/CDR for a given year. This does not necessarily indicate that a chemical was not manufactured in the United States, but rather indicates that a chemical, if manufactured, had a production volume below the reporting threshold.
Source: EPA (2014b)

A-6 Fate Properties

If released to air, degradation of these substances by sunlight and reactants in the atmosphere to less brominated simpler substances is expected to be slow. If released to water, sediment or soil, the fate of these cluster members may be influenced by partitioning to suspended solids, soil and sediment, respectively. Microbial biodegradation to less brominated substances can occur in the absence of oxygen (anaerobic conditions). The biodegradation of these substances in the environment is dependent on a number of factors including the presence of acclimated microorganisms capable of biodegrading the chemicals in those media and oxygen levels in the media (anaerobic conditions promote reductive debromination). A range of degradation rates is possible (from minutes to years). TBBPA-bis(methyl ether), TBBPA-bis(allyl ether) and TBBPA-bis(dibromopropyl ether) have high estimated bioaccumulation factors.

Table_Apx A-5 lists fate endpoints that are available for the three cluster members and information is discussed in subsequent sections.

Table_Apx A-5: Environmental Fate Endpoints for Three Cluster Members

Endpoint	TBBPA-bis (dibromopropyl ether)	TBBPA-bis(allyl ether)	TBBPA-bis(methyl ether)
Photo-degradation Half-life	1 day (estimated, 1.5×10^6 hydroxyl radicals per cm^3; 12-hour day)[a]	1.9 hours (estimated, 1.5×10^6 hydroxyl radicals per cm^3; 12-hour day)[a]	2.2 days (estimated, 1.5×10^6 hydroxyl radicals per cm^3; 12-hour day)[a]
Hydrolysis Half-life	Stable	Stable	Stable
Biodegra-dation	1% after 28 days (not readily biodegradable, OECD 301C)[b]	No data	No data
Bioconcen-tration	BAF = 1.2×10^4 (estimated)[a]	BAF = 3.9×10^5 (estimated)[a]	BAF = 8.6×10^6 (estimated)[a]
Log K_{OC}	6.8 (estimated)[a]	5.8 (estimated)[a]	4.8 (estimated)[a]
Fugacity[a] (Level III Model)			
Air (%)	<0.1	<0.1	<0.1
Water (%)	4.9	5.9	4.4
Soil (%)	94.8	93.0	92.3
Sediment (%)	0.2	1.1	3.2
Persistence[c]	P3 (high)	P3 (high)	P3 (high)
Bioaccumu-lation[c]	B3 (high)	B3 (high)	B3 (high)

[a] EPA (2013a)
[b] NITE (2010a)
[c] Criteria specified in: EPA (1999a)

A-6-1 Fate in Environmental Media

A-6-1-1 Air

TBBPA-bis(methyl ether) and TBBPA-bis(dibromopropyl ether) are expected to undergo relatively slow atmospheric hydroxy radical oxidation with estimated atmospheric half-lives of a few days. TBBPA-bis(allyl ether) is expected to have a much shorter half-life (approximately 2 hours) (EPA, 2013a). However, the relatively low vapor pressures of these substances suggest that they will not exist in the vapor phase under environmental conditions so atmospheric photo-oxidation is likely to be a slow process.

A-6-1-2 Fate in Water

Hydrolysis is expected to be relatively unimportant based on the chemical structures of these compounds. TBBPA-bis(dibromopropyl ether) is not readily biodegradable (NITE, 2010a). Volatilization from water surfaces will be a relatively unimportant fate process for these compounds based upon an estimated Henry's law constant of $<1.0 \times 10^{-10}$ atm-m^3/mole (EPA, 2013a).

A-6-1-3 Fate in Soil, Sediment and Groundwater

These cluster members are expected to have low mobility in soil based on estimated log K_{OC} values ranging from 4.8 – 6.8 (EPA, 2013a).

A-6-2 Bioconcentration/Bioaccumulation and Persistence

Persistence and bioconcentration potential are qualitatively characterized according to the criteria set forth in EPA/OPPT's New Chemicals Program (EPA, 1999a). These cluster members lack experimental bioconcentration and bioaccumulation data. However, based on the estimated BCF and BAF values for the substances they are expected to have high bioconcentration potential.

A-7 Exposure

There are a variety of monitoring data for the three cluster members. For the current assessment, EPA/OPPT consulted data adequacy guidance available for the High Production Volume (HPV) Program and specific guidance on using exposure data developed by the Organisation for Economic Cooperation and Development (OECD) (OECD, 2003). Table_Apx A-6 presents a summary table of available monitoring data, and more detailed information is in Supplemental Files 2 and 3.

Table_Apx A-6: Availability of Exposure Data for Three Cluster Members

CAS NUMBER	21850-44-2	25327-89-3	37853-61-5
CHEMICAL NAME	**TBBPA-bis(dibromo propyl ether)**	**TBBPA-bis(allyl ether)**	**TBBPA-bis(methyl ether)**
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			●
wastewater	●	●	●

Table_Apx A-6: Availability of Exposure Data for Three Cluster Members

CAS NUMBER	21850-44-2		25327-89-3	37853-61-5
CHEMICAL NAME	TBBPA-bis(dibromopropyl ether)		TBBPA-bis(allyl ether)	TBBPA-bis(methyl ether)
AIR AND WATER				
deposition				
BIOTA				
avian	●	●		
fish	●	●	●	●
aquatic animals (including shellfish)	●	●	●	●
terrestrial animals	●	●		
vegetation	●			

● = some data available, US or international

A-8 Ecological Hazard

A-8-1 TBBPA-bis(dibromopropyl ether)

There are a few studies for TBBPA-bis(dibromopropyl ether). Algae, fish and aquatic invertebrates were exposed to TBBPA-bis(dibromopropyl ether) in different water accommodation fraction (WAF) toxicity studies (ECHA, 2013). However, the compound was tested at 100 mg/L or higher, which is significantly above its water solubility (ECHA, 2013). In addition to testing above the water solubility, the researchers did not measure the test concentrations. As a result, these studies were not acceptable and were not included in this review.

A 56-day reproduction study is available for the earthworm *Eisenia fetida.* The study was conducted using OECD test guideline 207. A chronic value of 724 mg/kg was determined (ECHA, 2013).

No chronic aquatic toxicity studies using fish or aquatic invertebrates (either water column or sediment) were found for TBBPA-bis(dibromopropyl ether).

A-8-2 TBBPA-bis(allyl ether)

EPA/OPPT did not locate standard ecotoxicity studies that evaluated the effects of TBBPA-bis(allyl ether) on organisms in the environment.

A-8-3 TBBPA-bis(methyl ether)

EPA/OPPT did not locate standard ecotoxicity studies that evaluated the effects of TBBPA-bis(methyl ether) on organisms in the environment.

A-9 Human Health Hazard

A-9-1 TBBPA-bis(dibromopropyl ether)

EPA/OPPT estimates that TBBPA-bis-(dibromopropyl ether) would not be absorbed through the skin as a neat material, would have poor skin absorption when in solution and would have poor absorption via the lungs and gastrointestinal tract.

Following single or repeated (5 or 10 days) oral administrations of 20 mg/kg [^{14}C]-TBBPA-bis(dibromopropyl ether) to male F-344 rats, the compound was poorly absorbed from the gastrointestinal tract and uptake to the systemic circulation was considered slow. Distribution to the tissues accounted for <1% of the dose at 96 hours. Ninety-five percent of the dose was excreted in the feces within 36 hours of administration after conjugation via glucuronidation and/or sulfation. Elimination in the urine accounted for <0.1% of the administered dose and 1% of the dose was excreted in the bile after 24 hours (ECHA, 2013; Knudsen et al., 2007).

Based on oral and dermal LD_{50} values >2, 000 mg/kg and an inhalation LC_{50} value >20 mg/L in rats, the acute mammalian toxicity of TBBPA-bis(dibromopropyl ether) is considered low (ECHA, 2013). Oral and dermal LD_{50} values were >20,000 mg/kg in mice (IPCS, 1995). These data indicate that this compound has low acute toxicity.

Mice administered TBBPA-bis(dibromopropyl ether) in their diet at 200 or 2,000 mg/kg-bw/day for 90 days showed no mortality or abnormal symptoms upon gross pathological examination. The NOAEL was determined to be 2,000 mg/kg-bw/day (highest dose tested) (ECHA, 2013; IPCS, 1995).

TBBPA-bis(dibromopropyl ether) is not an eye or skin irritant in rabbits. The compound was not a skin sensitizer in a guinea pig maximization test (ECHA, 2013).

Although the compound was reported to be mutagenic to *Salmonella typhimurium* strains TA100 and TA1535 in one assay, it was negative in two other bacterial reverse mutation assays. In the assay that was positive for genotoxicity, the compound was slightly less pure (95.1 vs. 99.8%) than the batch used in one of the negative assays that used a very similar method. The test substance purity was not stated in the third bacterial assay. In an assay using mouse lymphoma cells, the compound was also negative for mutagenicity (ECHA, 2013; GLCC, 1982). TBBPA-bis(dibromopropyl ether) did not cause chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary (CHO) cells, was

negative in an *in vivo* micronucleus assay in mice and did not produce unscheduled DNA synthesis in rats (IPCS, 1995).

The dibromopropyl groups in TBBPA-bis-(dibromopropyl ether) have alkylating potential. However, it is unlikely that this compound can act as an alkylating agent due to its large molecular weight, low water solubility and high log K_{OW}. These properties all reduce the bioavailability of the compound. This is supported by the genotoxicity data of TBBPA-bis(dibromopropyl ether), which are predominantly negative. TBBPA-bis(dibromopropyl ether) appears to inhibit sulfation of estradiol (E2), but does not exhibit estrogenic activity via interference with estrogen receptors (ER). TBBPA bis (2,3-dibromopropyl) ether also does not appear to interfere with AhR-mediated, androgenic or progestrogenic pathways (Canton et al., 2006). TBBPA-bis(dibromopropyl ether) competed with thyroid hormone precursor thyroxine (T4) for binding to human transthyretin (TTR), but did not exhibit thyroid hormone (T3) mimicking activity (Hamers et al., 2006).

A-9-2 TBBPA-bis(allyl ether)

TBBPA-bis(allyl ether) has low acute oral and dermal toxicity. The oral LD_{50} in rats was > 5000 mg/kg bw, and the dermal LD_{50} in rabbits was > 2000 mg/kg (Abbott et al., 1981; EC/HC, 2013).

TBBPA-bis(allyl ether) was negative in *Salmonella* and *Saccharomyces* when tested with and without metabolic activation (Brusick, 1977; EC/HC, 2013).

Environmental fractions of TBBPA-bis(allyl ether) induced high cytotoxicity in neuronal cells of primary cultured cerebellar granule cells. However, the cytotoxic effect was not confirmed by studies in human liver carcinoma Hep G2, human breast cancer MCF-7 and mouse leukemic monocyte macrophage RAW 264.7 cell lines (EC/HC, 2013; Qu et al., 2011).

A-9-3 TBBPA-bis(methyl ether)

No toxicity data were found for TBBPA-bis(methyl ether). Replacement of the hydrogen atom of the two hydroxy groups in TBBPA by methyl groups slightly increases the size of the compound. There are no structural alerts for genotoxicity and carcinogenicity of TBBPA-bis(methyl ether). The overall toxicity of TBBPA-bis(methyl ether) is not expected to be higher than TBBPA based on structure-activity relationship analysis.

Appendix B Literature Searches and Data Quality

B-1 Literature Available for the Cluster Members

During background, scoping and problem formulation, EPA/OPPT reviewed other recently performed assessments and searched published and unpublished literature. The literature review included the cluster members' chemistry, uses, sources (including industrial releases), fate, exposure and hazard to humans and ecological receptors.

First, EPA/OPPT reviewed previous risk assessments to determine whether various scenarios could result in risks within the United States. The primary sources of information were human health and environmental risk assessments for TBBPA conducted by the EU (EC, 2006, 2008) and health and environmental risk assessments conducted by Canada for TBBPA and TBBPA-bis(allyl ether) (EC/HC, 2013). Other assessments included several predictions of the intake of TBBPA from its presence in food (de Winter-Sorkina et al., 2003; Driffield et al., 2008; EFSA, 2011; FSAI, 2010; Shi et al., 2009).

In addition, EPA/OPPT reviewed hazard profiles prepared under EPA's Design for the Environment Program for two members of the TBBPA cluster. The hazard profile for TBBPA is contained within *Flame Retardants in Printed Circuit Boards: Updated Draft Report (EPA, 2014e).* A recent profile is available for TBBPA-bis(2,3-dibromopropyl ether) in the final document *An Alternatives Assessment for the Flame Retardant Decabromodiphenyl Ether (DecaBDE)* (EPA, 2014a) and was consulted for the current TBBPA cluster assessment.

Another source of hazard and exposure information along with physical-chemical and fate properties for both TBBPA and TBBPA-bis(dibromopropyl ether) is the public data available for chemicals submitted to the European Chemicals Agency under REACH (ECHA, 2014).

In addition to reviewing these sources, EPA/OPPT conducted a review of toxicology and exposure studies published through June 2013. EPA/OPPT searched Toxline and Pubmed from the US National Library of Medicine for toxicology, biomedical and health literature. EPA/OPPT also searched the Chemical Abstracts Service from the American Chemical Society for chemical information. Other sources of information reviewed were the publicly available databases such as EPA's Chemical Data Reporting (CDR) and Inventory Update Reporting (IUR) databases.

EPA/OPPT also searched for additional exposure information in other databases for the time period of 2007 through August 2013. The Web of Science includes multidisciplinary science information from Thomson Reuters; the BIOSIS Citation Index contains life sciences information and is also from Thomson Reuters; CAB Abstracts contains life sciences literature from CABI; and Medline contains biomedical literature from the US National Library of Medicine. Search terms included the chemical CAS number and chemical abbreviation as well as concentration, environmental, monitoring, human, exposure, urine, blood, air, water, soil and sediment.

EPA/OPPT's summary of the environmental hazard of TBBPA is based in part on experimental studies previously summarized in the 2013 Canadian Assessment (EC/HC, 2013) and the final European Risk

Assessment Report (EC, 2008), study reports from EPA's TSCATS database, public literature searches and confidential sources. Although all data identified in confidential sources were evaluated, only information already made public (either in published risk assessments or journal articles) is included in this risk assessment. In addition, EPA/OPPT searched the ECOTOX database to identify peer-reviewed articles (EPA, 2014c). Source articles from these searches were retrieved and reviewed.

In some cases (e.g., when a significant pathway was identified), more recent literature (after August or June 2013) was also consulted.

B-2 Data Adequacy

Data was acceptable if it met standard quality criteria, which varies according to the type of information reviewed. Most toxicity or exposure monitoring studies referenced in previous risk assessments, such as those conducted by the European Union (EU) or Canada, were considered to be adequate if the previous assessment indicated that the studies were valid. However, EPA/OPPT reviewed selected studies referenced in such assessments when either the interpretation and description of results or the adequacy of the study was not clearly stated.

For the studies described in previous assessments that EPA/OPPT evaluated further and for recently published studies, EPA/OPPT followed data adequacy guidance developed for the High Production Volume (HPV) Chemicals Program (EPA, 1999b). The guidance generally suggests that EPA use studies conducted according to accepted testing guidelines such as EPA harmonized guidelines for pesticides and industrial chemicals or Organisation for Economic Cooperation and Development (OECD) test guidelines. Scientific quality criteria established for the HPV Program include: a clear description of the endpoints, inclusion of appropriate controls, identification of test substance and test organism, stated exposure duration and administration route, transparent reporting of effect concentrations and adherence to recommended tests strategies (EPA, 1999b). These criteria are based on guidelines developed and used by EPA's Office of Chemical Safety and Pollution Prevention and OECD (EPA, 2014g; OECD, 2015). The guidance also allows EPA/OPPT to use data that don't strictly follow such guidelines, primarily when less acceptable data can support the conclusions from a larger body of studies for a particular endpoint using a weight–of–evidence approach.

EPA/OPPT also used study reliability criteria presented in a 2003 OECD *Guidance Document on Reporting Summary Information on Environmental, Occupational and Consumer Exposure* (OECD, 2003) to evaluate studies that reported environmental and residential (indoor dust, etc.) monitoring data and biomonitoring studies.

Finally, EPA/OPPT used scientific judgment based on an understanding of TBBPA's unique physicochemical and fate characteristics to judge data quality and whether a particular study can contribute to TBBPA's overall hazard identification. This scientific evaluation allowed EPA/OPPT to consider whether any identified study deficiencies would detract from the results or would be minor enough so that EPA/OPPT could still rely on the study conclusions for hazard identification.

Appendix C Fate and Transport

The environmental transport and transformation of TBBPA is strongly influenced by its low volatility, low water solubility and its slow degradation by biotic and abiotic processes in the environment. Where particulate TBBPA is released to air its oxidation by OH radicals is expected to be slow. TBBPA may be subject to photolysis in air but the rates and products are unknown. Ultimately air releases of TBBPA would be expected to undergo deposition to terrestrial and aquatic environments. TBBPA tends to partition to soil and sediment where it can undergo microbial O-methylation to form TBBPA-bis(methyl ether). It can also undergo debromination under anaerobic conditions to form bisphenol A (BPA). Although these transformations have been observed, the overall environmental persistence of TBBPA is expected to be moderate to high. Measured bioconcentration factors indicate that TBBPA has a low potential for bioconcentration.

The rate of loss of the substance, typically due to degradation, may be less than its rate of entry to the environment. Therefore, levels of the compound in the environment may increase over time, leading to greater potential for exposure. EPA/OPPT will assume that loss is slow and that levels will increase over time when estimating exposure in the proposed assessment.
Table_Apx **C-1** summarizes environmental fate data for TBBPA.

Table_Apx C-1: Environmental Fate

Endpoint	Results
Photodegradation half-life	3.6 days (estimated, 1.5×10^6 hydroxyl radicals per cm^3; 12-hour day)[a]
Hydrolysis Half-life	Stable
Biodegradation	18.1 – 25.7% after 64 days (Massachusetts sandy loam, aerobic conditions)[b]; 59.9 – 64.1% after 64 days (Arkansas silty loam, aerobic conditions)[b]; 56.8 – 58.9% after 64 days (California clay loam, aerobic conditions)[b]; 43 – 56.3% after 64 days (Massachusetts sandy loam, anaerobic conditions)[c]; 35 – 46.6% after 64 days (Arkansas silty loam, anaerobic conditions)[c]; 9.4 – 10.5% after 64 days (California clay loam, anaerobic conditions)[c]; 0% after 14 days (not readily biodegradable, OECD 301C)[d]
Bioconcentration	BCF = 720 (measured in eastern oysters)[e] BCF = 1,200-1,300 (measured in fathead minnows)[h]; BCF = 30 – 341 (measured in carp based on a water concentration of 0.08 mg/L)[d]; BCF = 52 – 485 (measured in carp based on a water concentration of 0.008 mg/L)[d]; BCF = 20 – 170 (measured in bluegill for water concentrations of 0.0098 – 0.0014 mg/L)[f] BAF = 717.5 (estimated)[a]
Log K_{OC}	5.4 (estimated)[a] 4.8 (measured)[g] 6.0 (measured)[g] 5.2 (measured)[g] 5.0 (measured)[g]

Table_Apx C-1: Environmental Fate

Endpoint	Results
Fugacity[a] (Level III Model)	
Air (%)	<0.1
Water (%)	1.8
Soil (%)	69.1
Sediment (%)	29.1

[a] EPA (2013a); [b] GLCC (1989c); [c] GLCC (1989d); [d]NITE (2010b); [e] GLCC (1989b); [f] Stoner_Laboratories (1978); [g] GLCC (1989e); [h] GLCC (1989a)

C-1 Fate in Environmental Media

C-1-1 Fate in Air

TBBPA is expected to undergo relatively slow atmospheric hydroxy radical oxidation. Estimated atmospheric half-lives of a few days were predicted using Version 4.10 of EPISuite (EPA, 2013a). However, the relatively low vapor pressure of TBBPA suggests that it will not exist in the vapor phase under environmental conditions. Therefore, atmospheric photo-oxidation is likely to be a slow process. TBBPA has been shown to undergo direct photolysis in water when irradiated with UV light in the environmental spectrum (300 – 390 nm) and may be subject to photolysis in the atmosphere (Eriksson et al., 2004).

C-1-2 Fate in Water

TBBPA released to water will sorb to suspended solids and sediments due to its low water solubility and high log K_{OC} value. Hydrolysis of TBBPA is expected to be relatively unimportant due to the absence of structural components that hydrolyze under environmental conditions. Volatilization from water surfaces will be a relatively unimportant fate process based upon an estimated Henry's law constant of $<1.0 \times 10^{-10}$ atm-m^3/mole (Thomas, 1982b).

In studies of photolysis, TBBPA was irradiated in water with the range of solar UV wavelengths that are encountered in the environment. Photolysis half-lives ranged from 16 minutes at pH 10 to 350 minutes at pH 5.5. TBBPA was shown to photodegrade via cleavage between the tertiary carbon and one of the benzene rings. The main decomposition products were 4-(2- hydroxyisopropyl)-2,6-dibromophenol; 4-isopropylene-2,6-dibromophenol; and 2,6-dibromo-4-isopropylene (Eriksson et al., 2004).

TBBPA is not readily biodegradable. It achieved 0% of its theoretical oxygen demand over a 14-day incubation period using an activated sludge inoculum and the modified MITI (OECD 301C) test (NITE, 2010b). In an aerobic river water and sediment biodegradation study TBBPA degraded with half lives in the range of 48-84 days (Fackler, 1989).

C-1-3 Fate in Soil and Sediment

TBBPA is expected to have low mobility in soil based on both estimated and measured log K_{OC} values. Larsen et al. (2001) investigated the leaching potential of TBBPA applied to soil and sand columns and found no TBBPA leached from the bottom of the soil column with much of it retained in the upper 1 cm of the soil. The adsorption of TBBPA to sediment was determined during a toxicity study on sediment-dwelling midge larvae (GLCC, 1989e). The solid-phase concentrations were not measured during the study and are based on the nominal amount of substance added. The mean value for the organic carbon-water partition coefficient (K_{OC}) that was estimated from the data was 68,753 l/kg (log K_{OC} 4.8). In addition, as part of the 14-day toxicity study, sediment-solids and sediment pore water concentrations were measured allowing estimates of the value of Koc to be made. The mean values of K_{OC} obtained were 1,008,730, 141,980 and 94,830 l/kg (log K_{OC} 6.0, 5.2 and 5.0) for sediments with organic carbon contents of 0.25, 2.7 and 6.8% respectively.

Hydrolysis of TBBPA in soil and sediments is expected to be relatively unimportant due to the absence of structural components that hydrolyze under environmental conditions. Volatilization of TBBPA from moist soil surfaces is not expected to be an important fate process given its low Henry's law constant ($<1.0 \times 10^{-10}$ atm-m^3/mole) (Thomas, 1982a). TBBPA is not expected to volatilize from dry soil surfaces based upon its low vapor pressure.

The biodegradation potential of TBBPA under aerobic and anaerobic conditions in a 64-day test was investigated using three soils. Under aerobic conditions, TBBPA was degraded 18– 64% (GLCC, 1989c). Under anaerobic conditions, the degradation range was 9 – 56 % (GLCC, 1989d). Two main biodegradation products were noticed in each soil. However, these were not positively identified and did not appear to be the dimethyl derivative TBBPA-bis(methyl ether) or the diethyl derivative (GLCC, 1989c, 1989d). In another study, biodegradation half-lives of 65 days, 93 days and 430 days were reported for TBPPA in an aerobic activated sludge, aerobic digested sludge and anaerobic activated sludge, respectively (Nyholm et al., 2010).

TBBPA has been shown to degrade to BPA under anaerobic conditions and form the intermediates tribromobisphenol A (Tri BBPA), dibromobisphenol A (DiBBPA) and monobromobisphenol A, which were rapidly consumed (Arbeli and Ronen, 2003). TBBPA has also been demonstrated to undergo microbial O-methylation by bacterial isolates and sediments to form the TBBPA derivative, TBBPA-bis(methyl ether) (Allard et al., 1987). Conversions to the methylated derivative of approximately 60% in 24 hours were observed with pure culture bacterial isolates. In sediments, conversion rates ranged from 10% in 60 days to 50% in 80 days (George and Haggblom, 2008).

C-2 Persistence

Biotic and abiotic degradation studies have shown TBBPA to degrade very slowly under most environmental conditions with half-lives greater than 2 months in water, soil and sediment (Fackler, 1989; GLCC, 1989c, 1989d; NITE, 2010b).

The persistence of TBBPA is influenced by a number of factors. These include the environmental media to which the substance partitions; the presence of acclimated microorganisms capable of biodegrading

the chemical in those media; oxygen levels in the media (anaerobic conditions promote degradation of TBBPA by reductive debromination) and prolonged direct exposure to sunlight leading to photolysis of the molecule. When microorganisms are not acclimated, oxygen levels are high and direct exposure to sunlight is limited, TBBPA has been shown to be resistant to environmental degradation processes.

C-3 Bioaccumulation/Bioconcentration

The majority of bioconcentration studies in fish and mollusks indicate that TBBPA has a low bioconcentration potential. However, a single study using fathead minnows reported a BCF value of 1200-1300 (GLCC, 1989a). In this study that used ^{14}C-TBBPA, radioactivity was eliminated from the tissues with a half life of less than 24 hours. In further analysis of the data, as discussed in EC (2008), the BCF was calculated in terms of a ratio of parent TBBPA to the total body burden of radioactivity, resulting in a BCF of approximately 160 for just TBBPA and not its degradates. This recalculated value is consistent with the results of other fish bioconcentration studies.

Based upon the experimental evidence and expert opinion, TBBPA is expected to have low bioaccumulation potential.

C-4 Exclusion of Degradation Products from Further Assessment

For a full consideration of possible risks from the manufacture, use and disposal of TBBPA, EPA/OPPT identified the most likely compounds that could result from combustion, biodegradation or photolysis of TBBPA. Based on data available for these compounds, EPA/OPPT determined whether the compounds might result in risks to human health or the environment and whether it would be feasible to assess risks from these compounds in the current assessment. As a result of this scoping analysis, EPA/OPPT concluded that data on degradation are limited, uncertain or both. Therefore, EPA/OPPT will not assess risks from TBBPA's degradation products in a risk assessment.

C-4-1 Combustion Products

Incineration of TBBPA can result in polybrominated dibenzo-*p*-dioxins (PBDDs) and polybrominated dibenzofurans (PBDFs) as well as polyaromatic hydrocarbons (PAHs).

A recent study found that PBDDs, PBDFs and PAHs were emitted from incineration of TBBPA epoxy laminates. PAHs were emitted at higher levels from this laminate than from non-flame retardant laminates (Sidhu et al., 2013). In another study, Wichmann et al. (2002) found that PBDDs and PBDFs were emitted at similar magnitudes when comparing emissions from TBBPA used in reactive applications to those in additive flame retardant applications with PBDFs released in higher amounts that PBDDs.

An accurate estimate of the amount of TBBPA within electronic waste is not available. Furthermore, EPA/OPPT doesn't have robust information on the amount of electronic waste that is incinerated in the

United States. Finally, compounds other than TBBPA can result in similar combustion products when incinerated. Therefore, the contribution of TBBPA to combustion byproducts is not possible to determine with enough accuracy to include in EPA/OPPT's proposed risk assessment.

C-4-2 Biodegradation Products

Bisphenol A (BPA; CAS 80-05-7) is a possible product of reductive debromination of TBBPA, primarily under anaerobic conditions. Thus TBBPA could be a source of BPA in the environment (EC, 2008). Overall, biodegradation data are considered to be too limited to predict, with confidence, the rate at which TBBPA degrades to BPA in the environment. This is because the majority of the studies use microorganisms that have been collected from environments contaminated with TBBPA, exposed to TBBPA over extended periods to induce adaptation to degrade the substance and are conducted under laboratory conditions that are not necessarily representative of the environment.

C-4-3 Photodegradation Products

TBBPA may photodegrade to form a range of bromophenols and dibromoisopropylphenol derivatives. Overall there appears to be limited to no human health toxicity data for dibromophenols. Some ecotoxicity data are available for 2-bromophenol (CAS 95-56-7) (NLM, 2009). Due to uncertainties in extrapolation from laboratory to the field, it is not certain how much of these products would be formed in the environment (Eriksson et al., 2004).

Appendix D Toxics Release Inventory Emissions

This appendix describes EPA/OPPT's approach to assessing exposure surrounding manufacturing facilities. For both the environment and human health, EPA/OPPT modeled the impact of TBBPA deposition from TRI-reported air releases from two manufacturing facilities that emitted the highest amounts of TBBPA.

D-1 TRI Releases from Manufacturers

In this assessment, EPA/OPPT used data from the Toxics Release Inventory (TRI) to characterize environmental releases of TBBPA. The TRI is a database that contains detailed information on releases and transfers of certain listed toxic chemicals from industrial facilities. The database is maintained by the Agency and is updated annually (EPA, 2012e).

In 2012, a total of 52 facilities across 7 industries reported releases of TBBPA to TRI (EPA, 2012e). This information is reported in Table_Apx D-1. See Table_Apx D-2 for a more detailed account of these disposals and releases.

Based on data from the 2012 TRI, the chemicals industry accounted for ~97% of all reported TBBPA disposal and releases. Two facilities from the chemicals industry accounted for ~94% of these disposal and releases. Of the total disposal and releases, 94.5% were to land and 4.5% to air.

Table_Apx D-1: Disposal and Releases of TBBPA by Industry as Reported in the 2012 TRI

Industry	NAICS[a] Code	Number of Facilities	Disposal and Releases (pounds per year)			
			On-site	Off-site	Total	Percent of Total
Chemicals	325	23	75,786	48,174	123,960	97.0%
Textiles	313/314	5	143	1,557	1,700	1.3%
Hazardous Waste/Solvent Recovery	562	4	662	762	1,425	1.1%
Transportation Equipment	336	8	8	560	567	0.4%
Plastics and Rubber	326	6	33	154	187	0.1%
Paper	322	1	5	0	5	<0.1%
Computers/Electronics Products	334	5	1	1	2	<0.1%
Total		**52**	**76,637**	**51,208**	**127,845**	**100%**

a – North American Industry Classification System (NAICS)
Source: EPA (2012e)

Table_Apx D-2: Disposal and Releases of TBBPA by Industry as reported in the 2012 TRI

Industry	NAICS Code	Total On-site Disposal and Releases						Total Off-site Disposal and Releases			Total On- and Off-site Disposal and Releases
		Under-ground Injection Class I Wells	RCRA Subtitle C Landfills	Other On-Site Landfills	Fugitive Air Emissions	Stack Air Emissions	Surface Water Discharges	RCRA Subtitle C Landfills	Other Landfills	Other Land Disposal	
Chemicals	325	100	0	70,182	44	5,453	6	44,205	3,969	0	123,960
Textiles	313/314	0	0	0	141	2	0	0	1,557	0	1,700
Hazardous Waste/Solvent Recovery	562	0	656	0	0	7	0	0	762	0	1,425
Transportation Equipment	336	0	0	0	1	6	0	0	29	531	567
Plastics and Rubber	326	0	0	0	33	0	0	0	154	0	187
Paper	322	0	0	0	5	0	0	0	0	0	5
Computers / Electronics Products	334	0	0	0	0	1	0	0	1	0	2
Total		**100**	**656**	**70,182**	**224**	**5,469**	**6**	**44,205**	**6,471**	**531**	**127,845**

Source: EPA (2012e)

The two top-releasing facilities in the 2012 TRI are shown in Table_Apx D-3. In 2012, the Dow Chemical facility in Freeport, Texas was one of the two highest emitters. However, historical emissions have been highest from Great Lakes Chemical (El Dorado, Arkansas) and Albemarle (Magnolia, Arkansas), as indicated in Table_Apx D-4.

Table_Apx D-3: Disposal and Releases of TBBPA by Manufacturing Facility as Reported in the 2012 TRI

Facility	NAICS Code	Disposal and Releases (pounds per year)			
		On-site	Off-site	Total	Percent of Total
Dow Chemical (Freeport, TX)	325	68,882	0	68,882	53.9%
Albemarle (Magnolia, AR)	325	6,410	44,176	50,586	39.6%
Remaining 50 facilities	N/A	1,345	7,032	8,377	6.6%
Total		**76,637**	**51,208**	**127,845**	**100%**

Source: EPA (2012e)

Over the past 13 years, disposal and releases of TBBPA, as reported in TRI, have decreased by ~84%. During this time, two facilities from the chemicals industry were, on average, responsible for ~90% of all TBBPA disposal and releases (see Table_Apx D-4). These disposal and releases were primarily to land or air.

Table_Apx D-4: TBBPA TRI Release Trends from 2001 to 2012

Year	Disposal and Releases from All Facilities (pounds per year)			Disposal and Releases from Great Lakes Chemical and Albemarle
	On-site	Off-site	Total	Percent of Total
2000	257,134	537,846	794,981	94%
2001	250,689	625,651	876,340	96%
2002	190,326	863,971	1,054,297	98%
2003	145,766	497,653	643,419	98%
2004	113,779	466,078	579,857	98%
2005	106,737	253,070	359,807	98%
2006	114,902	210,464	325,367	92%
2007	83,124	261,016	344,139	98%
2008	48,962	153,536	202,497	95%
2009	46,906	113,089	159,995	95%
2010	64,801	180,459	245,260	96%
2011	58,837	157,583	216,420	88%
2012	76,637	51,208	127,845	40%

Source: EPA (2012e)

The stack air emissions data for the two facilities modeled in this assessment are outlined in Table_Apx D-5. On average, from 2000 to 2012, these two manufacturing plants have accounted for 97% of all TBBPA emitted to air in the United States. The Great Lakes facility produced the majority of these emissions from 2000 to 2011. In 2012, this facility reported no emissions to air (EPA, 2012e).

Table_Apx D-5: Air Emissions for Facilities Modeled in the Current Assessment

Year	Stack Air Emissions (pounds per year)	
	Great Lakes Chemical	**Albemarle**
2000	41,824	15,403
2001	40,455	11,000
2002	45,030	6,000
2003	61,724	6,000
2004	59,989	6,042
2005	52,933	5,982
2006	55,900	4,938
2007	49,156	5,557
2008	38,724	1,684
2009	40,821	1,689
2010	48,692	1,590
2011	32,987	1,590
2012	0	5,000

Source: EPA (2012e)

Appendix E TBBPA and other Dust Particle Concentrations in Occupational Settings

Workers may be exposed primarily by ingesting TBBPA dust from the air at work sites. Limited data are available for TBBPA at manufacturing and processing sites. These data are described below along with data for particles not otherwise regulates (PNOR) at the same types of facilities that would manufacture and process TBBPA. EPA/OPPT will consider all of these data to estimate risks to workers.
Manufacturing

During bagging or loading operations, dust may be generated within facilities that manufacture TBBPA and workers may be exposed by ingesting particles that are inhaled from the air. To consider potential workplace exposures within facilities, EPA/OPPT examined Chemical Exposure Health Data (CEHD) from the Occupational Safety and Health Administration (OSHA, 2015). Because TBBPA is not specifically listed in OSHA's database, data for particulates not otherwise regulated (PNOR) were used to develop estimates of TBBPA exposures. This exposure data represents the NAICS codes listed below, which were reported in the 2012 TRI and are judged to be representative of facilities that accounted for approximately 97% of TBBPA releases reported in the 2012 TRI:

- 3251 Basic Chemical Manufacturing
- 3252 Resin, Synthetic Rubber and Artificial Synthetic Fibers and Filaments Manufacturing
- 3255 Paint, Coating and Adhesive Manufacturing
- 3259 Other Chemical Product and Preparation Manufacturing

Potential dust exposures related to TBBPA manufacturing (NAICS Code 3251) are summarized in Table_Apx E-1. EPA/OPPT will evaluate risks of ingesting dust after inhalation by workers inside these types of facilities.

Table_Apx E-1: Potential Occupational Exposures from Manufacture of TBBPA*

Exposure Type	Potential Dust Exposures (mg/m^3)**		Comments
PNOR (Total Dust)	Range:	0.47 to 195	▪ 30 data points; personal samples; ten years of data (2002 to 2011); not specific to TBBPA ▪ OSHA PEL for PNOR (Total Dust): Time-Weighted Average (TWA) 15 mg/m^3 ▪ NAICS Code: 3251
PNOR (Respirable Fraction)* **	Range:	0.07 to 19	▪ 21 data points; personal samples; ten years of data (2002 to 2011); not specific to TBBPA ▪ OSHA PEL for PNOR (Respirable Fraction): TWA 5 mg/m^3 ▪ NAICS Code: 3251

Source: OSHA (2015)
* Dust concentrations are used as surrogates for TBBPA from similar industry sectors as TBBPA sectors.
**These exposure estimates are not TWA values; thus they cannot be compared directly to the OSHA PELs.
*** < 10 µm based on particle sampling methods (see: https://www.osha.gov/dsg/topics/silicacrystalline/dust/chapter_1.html)

E-1 Processing

During loading and unloading operations, dust may be generated within facilities that process or compound TBBPA. Dust generated from unloading operations is expected to be pure TBBPA. However, dust generated from compounding and loading operations is not expected to be pure TBBPPA. These two types of dust (pure vs. mixture) may have different bioavailabilities. Potential exposures from processing TBBPA are summarized in Table_Apx E-2. EPA/OPPT will evaluate occupational risk from exposure in processing plants to TBBPA as/in dust after ingestion from air.

Table_Apx E-2: Potential exposures from processing of TBBPA*

Data Source	Potential TBBPA Exposures (mg/m^3)		Comments
EU TBBPA RA (EC, 2006)	0.2 to 12 2 to 50	▪ Personal Samples (n=13) ▪ Model estimates based on EASE (Estimation and Assessment of Substance Exposure)	▪ Monitoring data is for compounding operations; represents unloading of powder; specific to TBBPA.
ACC BFR End User Survey (ACC, 2000)	0.1 to 15 0.1 to 2 0.0007 to 79	▪ Total dust, personal samples (n=52) ▪ Total dust, personal samples (n=11); BFR identified as TBBPA ▪ Bromine content; personal samples (n=34)	▪ Monitoring data represents BFR end user sites. ▪ Most measurements are for total dust samples (not TBBPA specific).*
OSHA CEHD (OSHA, 2015)**	0.02 to 268 0.05 to 169	▪ Total dust; Personal Samples (n=146) ▪ Respirable dust; Personal Samples (n=63)	▪ Ten years of data (2002 to 2011) ▪ Targeted to represent processing facilities (NAICS Codes: 3252, 3255, 3259) ▪ Data is not specific to TBBPA.*

* Data are for dust concentrations that could be used as a surrogate for TBBPA concentrations based on similarities in industry sectors where the dust is generated.

**These exposure estimates are not TWA values; thus they cannot be compared directly to the OSHA PELs.

Appendix F Ecological Hazard Study Summaries

The following sections describe standard toxicity studies that were considered for use in the proposed TBBPA risk assessment for environmental organisms.

The test species, test conditions and toxicity endpoints were summarized and evaluated for data quality. Data quality inclusion criteria included: use of appropriate analytical and test controls, identification of test substance and test organism, stated exposure duration, a clear description of the effect endpoints and transparent reporting of effect concentrations. Guideline studies as well as studies using other protocols were included if they met data quality criteria.

Available toxicity information on representative test species are used to denote toxicity to a wider group of organisms within individual taxa or species groups such as aquatic plants, aquatic invertebrates (both water column and sediment), fish and soil invertebrates.

Because only limited experimental data are available to characterize toxicity to these species and taxa, acute and chronic uncertainty factors that account for both differences in species sensitivities and variability among laboratories that conducted the studies can be applied to toxicity values to calculate lower bound levels on the concentration associated with toxicity to organisms in the species or taxa described above. These lower bound values are referred to as concentrations of concern (COCs).

The uncertainty factors are based on established EPA/OPPT methods (EPA, 2012d, 2013b) These factors are dependent upon the availability of datasets that can be used to characterize relative sensitivities across multiple species within a given taxa or species group, but are often standardized in risk assessments conducted under TSCA because the data available for most industrial chemicals is limited (Ahlers et al., 2008).

F-1 Toxicity to Aquatic Organisms

Studies considered to be of sufficient quality are summarized in Table_Apx F-1. Some effects were observed in other acute aquatic studies, but those values were considerably above the reported water solubility for TBBPA. EPA found a few acceptable studies to characterize chronic toxicity to aquatic organisms.

F-1-1 Aquatic Plant Toxicity

Toxicity was observed, with 72-hr EC_{50} values ranging from 0.09 to >5.6 mg/L, when algae were exposed to TBBPA (GLCC, 1988b; Walsh et al., 1987).

F-1-2 Aquatic Invertebrate Toxicity

F-1-2-1 Water Column

Acute exposure to TBBPA by freshwater aquatic invertebrates (*Daphnia magna*) resulted in 48-hour EC_{50} values[15] of 0.60 and 0.96 mg/L (GLCC, 1978c; Waaijers et al., 2013). In addition, TBBPA was toxic to several marine invertebrates at low concentrations. The Eastern oyster (*Crassostrea virginica*) exhibited a 96-hour EC_{50} value of 0.098 mg/L based on shell deposition (GLCC, 1989b). In an acute mysid shrimp (*Mysidopsis bahia*) marine ecotoxicity study, adverse effects from TBBPA were observed with 96-hour EC_{50} values ranging from 0.86 to 1.2 mg/L (Goodman et al., 1988). A TBBPA concentration of 0.40 mg/L caused lethality in the marine invertebrate species *Acartia tonsa* under static conditions (Wollenberger et al., 2002). In addition, *Chironomus tentans* were exposed to TBBPA in a 14-day toxicity study (GLCC, 1989e). Adverse effects (lethality) were observed at 0.13 mg/L (14-day LC_{50}).

Adverse effects from TBBPA have been observed in chronic invertebrate studies at concentrations of less than 1 mg/L. Chronic exposure of aquatic invertebrates to TBBPA resulted in a 21-day MATC of 0.540 mg/L based on reproductive effects (SLS, 1989b). In addition, shell length reduction in the common mussel (*Mytilus edulis)* was observed in a 70-day GLP study, with a MATC of 0.023 mg/L (ACC, 2005).

F-1-2-2 Sediment

The available sediment toxicity studies for sediment-dwelling worms, emergent insects and amphipods indicate that observed effects exhibited sediment toxicity in the range of 117 - 500 mg/kg for the species tested.

Wildlife International (Krueger, 2002a, 2002b) studied survival and reproduction in a repeated 28-day study using the blackworm *Lumbriculus variegates,* exposed to TBBPA. For total organic carbon (TOC) contents of 2 and 5%, the MATCs were 117 and 329 mg/kg sediment dry weight, respectively.

In another 28-day study using the midge *Chironomus riparius* exposed to TBBPA, a MATC for emergence was determined to be 177 mg/kg. In this same study, a 28-day EC_{50} of 235 mg/kg dry weight was derived based on midge emergence (ACC-BFRIP, 2005b). In another sediment toxicity test, amphipods (*Hyalella azteca*) were exposed to TBBPA, resulting in a 28-day NOEC and LOEC of 250 and 500 mg/kg dry weight, respectively, based on the survival endpoint (ACC-BFRIP, 2006). The MATC for *H. azteca* was 354 mg/kg dry weight.

[15] Similar to the LC_{50}, the EC_{50} is the effect concentration at which 50% of the test organisms show a specific effect other than lethality. The value is calculated using the % of organisms affected at the concentrations used in the toxicity study.

F-1-3 Fish Toxicity

For a variety of fish species, acute toxicity studies resulted in 96-hour LC_{50} values[16] ranging from 0. 40 to 1.1 mg/L under static and flow-through conditions with measured and nominal concentrations (GLCC, 1978b, 1988a).

Adverse effects from TBBPA have been observed in chronic fish studies at concentrations of less than 1 mg/L. A 35-day fish maximum acceptable toxicity concentration (MATC) [17] for *Pimephales promelas* was 0.22 mg/L for hatching (SLS, 1989c). A zebrafish embryo toxicity test was conducted with TBBPA, but considered unacceptable for the purposes of this hazard assessment due to a lack of replicates and difficulties with study interpretation (only body burden concentrations presented) (Kuiper et al., 2007). Chronic exposure of aquatic invertebrates to TBBPA resulted in a 21-day MATC of 0.540 mg/L (SLS, 1989b). In addition, shell length reduction in the common mussel (*Mytilus edulis)* was observed in a 70-day GLP study, with a MATC of 0.023 mg/L (ACC, 2005).

F-1-4 Concentrations of Concern

The most sensitive species is expected to be protective of a wider variety of species that are not specifically represented by the available experimental data. These were used for both water column and sediment species, with application of uncertainty factors, to calculate acute and chronic COCs.

F-1-4-1 Water Column

Considering data from acute studies of fish, aquatic invertebrates and algae, the *C. virginica* 96-hour EC_{50} of 0.098 mg/L resulted in the lowest value and EPA/OPPT divided this 96-hour EC_{50} value by an uncertainty factor (UF) of 5 for acute tests using invertebrates, as per established EPA/OPPT methods (EPA, 2012d, 2013b) to give an acute COC of 0.02 mg/L (or 20 µg/L).

Although a value of 0.090 mg/L using *Skeletonema costatum* is the single most sensitive acute toxicity value, the resulting value (0.0225 mg/L) is not the most sensitive COC when divided by the standard aquatic plant uncertainty factor of 4.

For chronic concerns, the *Mytilus edulis* 70-day chronic value of 0.023 mg/L based on growth rate is the most sensitive value. When divided by an uncertainty factor (UF) of 10 for chronic effects, as per established EPA/OPPT methods (EPA, 2012d, 2013b), the resulting chronic COC is 0.002 mg/L (or 2 µg/L).

F-1-4-2 Sediment

The *L. variegates* 28-day MATC of 117 mg/L, based on reproduction, was divided by an uncertainty factor (UF) of 10 for chronic effects, as per established EPA/OPPT methods (EPA, 2012d, 2013b), to give a chronic COC of 11.7 mg/L (or 11,700 µg/L).

[16] LC_{50} is the lethal concentration at which 50% of the test organisms die. It is calculated using the % of organisms that die at the concentrations in the toxicity study and is not necessarily a concentration that was used in the study.
[17] The MATC is calculated as the geometric mean of the NOEC and LOEC from the study.

Table_Apx F-1: Toxicity from TBBPA to Aquatic Organisms

Test Organism	Fresh/ Salt Water	Test Guideline/ Study Type	Duration	Endpoint	Concentration (mg/L)	Chemical Analysis	Effects	Reference
Aquatic Plants								
Green algae *Pseudo-kirchneriella subcapitata*	Fresh	USEPA 40 CFR 797.1050	72-hr	EC_{50}	>5.6	Measured Static	Biomass	GLCC (1988b)
Green algae *Chlorella sp.*	Salt	USEPA 40 CFR 797.1050	96-hr	EC_{50}	>1.5	Measured Static	Growth	Walsh et al. (1987)
Diatom *Skeletonema costatum*	Salt	USEPA 40 CFR 797.1050	72-hr	EC_{50}	0.09	Measured Static	Growth	Walsh et al. (1987)
Diatom *Thalassiosira pseudonana*	Salt	USEPA 40 CFR 797.1050	72-hr	EC_{50}	0.13	Measured Static	Growth	Walsh et al. (1987)
Aquatic Invertebrates: Water Column								
Water flea *Daphnia magna*	Fresh	OECD TG 202	48-hr	LC_{50}	0.96	Nominal Static	Mortality	GLCC (1978c)
Water flea *Daphnia magna*	Fresh	OECD TG 202, 2004	48-hr	LC_{50}	0.60	Nominal Static	Mortality	Waaijers et al. (2013)
Eastern oyster *Crassostrea virginica*	Salt	USEPA CFR 40 TG 797.1800	96-hr	EC_{50}	0.098	Measured Flow- through	Shell deposition	SLS (1989a)
Mysid shrimp *Mysidopsis bahia*	Salt	_a	96-hr	LC_{50}	0.86	Measured Flow-through	Mortality	Goodman et al. (1988)
Marine copepod *Acartia tonsa*	Salt	Draft ISO/DIS 14669	48-hr	LC_{50}	0.40	Nominal Semi-static	Mortality	Wollenberger et al. (2002)
Midge *Chironomus tentans*	Fresh	ASTM, 1987 E1706-05	14-day	LC_{50}	0.13	Measured Flow-through	Mortality	GLCC (1989e)

Table_Apx F-1: Toxicity from TBBPA to Aquatic Organisms

Test Organism	Fresh/ Salt Water	Test Guideline/ Study Type	Duration	Endpoint	Concentration (mg/L)	Chemical Analysis	Effects	Reference
Water flea *Daphnia magna*	Fresh	USEPA CFR 40 797.1330	21-day	LOEC	0.98	Flow-through Measured	Reproduction	SLS (1989b)
				NOEC	0.30			
				MATC	0.54			
Blue mussel *Mytilus edulis*	Salt	_a	70-day	LOEC	0.032	Flow-through Measured	Growth rate, shell length	ACC (2005)
				NOEC	0.017			
				MATC	0.023			
Aquatic Invertebrates: Sediment								
Blackworm *Lumbriculus variegatus*	Fresh	USEPA OPPTS 850.1735, ASTM E1706/95b	28-day Tested in 2.5% OC content	LOEC	151	Measured	Reproduction	Krueger (2002a)
				NOEC	90			
				MATC	117			
Blackworm *Lumbriculus variegatus*	Fresh	USEPA OPPTS 850.1735, ASTM E1706/95b	28-day Tested in 5.9% OC content	LOEC	426	Measured	Reproduction	Krueger (2002b)
				NOEC	254			
				MATC	329			
Harlequin fly *Chironomus riparius*	Fresh	OECD TG 218	28-day	LOEC	250	Nominal	Emergence development	ACC-BFRIP (2005b)
				NOEC	125			
				MATC	177			
Amphipod crustacean *Hyalella azteca*	Fresh	USEPA OPPTS 850.1735	28-day	LOEC	500	Nominal	Survival	ACC-BFRIP (2006)
				NOEC	250			
				MATC	354			
Fish								
Rainbow trout *Oncorhynchus mykiss*	Fresh	OECD TG 203, 1984	96-hr	LC_{50}	0.40	Nominal	Mortality	GLCC (1978b)
Bluegill sunfish *Lepomis macrochirus*	Fresh	OECD TG 203, ASTM, 1975	96-hr	LC_{50}	0.51	Nominal	Mortality	GLCC (1978a)
Fathead minnow *Pimephales promelas*	Fresh	OECD TG 203, 1984	96-hr	LC_{50}	0.54	Measured Flow-through	Mortality	GLCC (1988a)

Table_Apx F-1: Toxicity from TBBPA to Aquatic Organisms

Test Organism	Fresh/ Salt Water	Test Guideline/ Study Type	Duration	Endpoint	Concentration (mg/L)	Chemical Analysis	Effects	Reference
Rainbow trout *Oncorhynchus mykiss*	Fresh	OECD TG 203	96-hr	LC_{50}	1.1	Measured Flow-through	Mortality	ACC (2003)
Zebra fish *Danio rerio*	Fresh	OECD TG 202	96-hr	LC_{50}	1.1	Nominal Static	Mortality	Chow et al. (2013)
Fathead minnow *Pimephales promelas*	Fresh	USEPA CFR 40 797.1600	35-day	LOEC	0.31	Flow-through Measured	Early Life Stage Survival, Hatching	SLS (1989c)
				NOEC	0.16			
				MATC	0.22			

Note: The shaded rows indicate the principal study used for assessing acute / chronic risks to aquatic organisms.

[a] Test guideline/type not reported

LOEC = Lowest Observed Effect Concentration

NOEC = No Observed Effect Concentration

MATC = Maximum Acceptable Toxicant Concentration

OC = Organic Carbon

F-2 Toxicity to Terrestrial Organisms

F-2-1 Terrestrial Plant Toxicity

The effect of tetrabromobisphenol-A (purity: 99%) on 21-day emergence and growth of six species of plants (ACC-BFRIP, 2002) was determined using OECD Guideline 208 (proposed version), US EPA OPPTS 850.4100 (1996) and US EPA OPPTS 850.4225 (1996).

The following six plant species were tested: Monocots - corn (*Zea mays*), onion (*Allium cepa*), ryegrass (*Lolium perenne*); Dicots - cucumber (*Cucumis sativa*), soybean (*Glycine max*) and tomato (*Lycopersicon esculentum*). Overall, treatment-related effects on seedling growth were seen in five out of the six species tested (soybean was the exception). In contrast, no treatment-related effects were seen on seedling emergence or condition of seedling in any of the species tested. The MATCs for corn, cucumber, onion, ryegrass and tomato are 518, 32, 518, 127 and 518 mg/kg dry soil, respectively (ACC-BFRIP, 2002).

Terrestrial plants were not considered for the proposed TBBPA risk assessment. For perspective, TBBPA is two to three orders of magnitude less toxic to terrestrial plants than to soil-dwelling organisms.

F-2-2 Soil Invertebrate Toxicity

EPA considered three studies evaluating potential toxicity to soil-dwelling organisms to be of sufficient quality to support hazard characterization of TBBPA. These studies are summarized in Table_Apx F-2.

In 2003, earthworms (*Eisenia fetida*) were exposed to TBBPA in a 56-day reproductive study (ACC-BFRIP, 2003). The experimentally-derived and analytically-measured 56-day NOEC, LOEC and MATC values were 2.1, 4.5 and 3.1 mg/kg soil (dry weight), respectively. In 2005, results from a 56-day reproductive study with soil-dwelling worms (*E. fetida)* indicated that adverse effects from TBBPA were observed at nominal concentrations as low as 0.63 mg/kg (LOEC) (ACC-BFRIP, 2005a). The reported nominal NOEC is 0.31 mg/kg dry weight soil and the MATC was determined to be 0.44 mg/kg dry weight soil. Furthermore, an additional earthworm study was conducted in 2006 using reproduction as the endpoint of concern (Sverdrup et al., 2006). Sverdrup et al. (2006) exposed *Enchytraeus crypticus* to TBBPA for 21 days. Based on reproduction, the experimentally-derived and analytically-measured 21-day NOEC, LOEC and MATC values were 3, 10 and 5.5 mg/kg soil (dry weight), respectively.

Table_Apx F-2: Soil Invertebrate Toxicity Data for TBBPA (mg/kg)

Test Organism	Test Guideline/ Study Type	Duration (day)	Endpoint	Value (mg/kg)	Test Analysis	Effect	Reference
Terrestrial Organisms							
Earthworm (Enchytraeus crypticus)	ISO, 2002	21-day	LOEC	10	Measured	Reproduction	Sverdrup et al. (2006)
			NOEC	3			
			MATC	5.5			
Earthworm (*Eisenia fetida*)	USEPA OPPTS 850.6200, OECD TG 207	56-day	LOEC	4.5	Measured	Reproduction	ACC-BFRIP (2003)
			NOEC	2.1			
			MATC	3.1			
Earthworm (*Eisenia fetida*)	USEPA OPPTS 850.6200, OECD TG 207/222	56-day	EC_{50}	0.91	Nominal	Reproduction	ACC-BFRIP, 2005a
			LOEC	0.63			
			NOEC	0.31			
			MATC	0.44			

Note: The shaded row indicates the principal study used for assessing acute risks to aquatic organisms.
LOEC = Lowest Observed Effect Concentration
NOEC = No Observed Effect Concentration
MATC = Maximum Acceptable Toxicant Concentration

The most sensitive species is expected to be protective of a wider variety of species that are not specifically represented by the available experimental data. The *E. fetida* 56-day MATC of 0.44 mg/kg, based on reproduction, was the lowest endpoint, and it was divided by an uncertainty factor (UF) of 10 for chronic effects, as per established EPA/OPPT methods (EPA, 2012d, 2013b), to give a chronic COC of 0.044 mg/kg or 44 µg/kg.

F-2-3 Avian Toxicity

Under EPA's High Production Volume (HPV) Chemical Challenge program, data on birds have been submitted for TBBPA (ACC, 2006) and are described below.

Several experiments have been conducted on distribution and effects of TBBPA in birds. ^{14}C-TBBPA was injected into quail eggs (1.9 µg/g egg) on day 3 of incubation, and uptake and distribution of ^{14}C-TBBPA was studied in 6- and 9- day-old quail embryos. TBBPA was also administered to adult females (single oral or intravenous doses, 250 µg/bird) to investigate its distribution. In addition, the potential for certain reproductive and endocrine effects were evaluated in adult birds after embryonic exposure (15 µg/g egg). The embryonic uptake of TBBPA was low (< 1% of the radiolabel) after yolk injection on day 3 and was distributed in the yolk, although metabolism was detected based on labeling in the liver, bile and allantoic fluid. Thus, TBBPA's transfer to the embryo from the yolk was low with rapid metabolism and excretion (Halldin et al., 2001).

In laying quail, TBBPA was rapidly eliminated via bile and excreted in feces, and transfer to egg yolks was low. This effect was seen after oral and intravenous administration. *In ovo* exposure to TBBPA (15 µg/g egg) did not cause estrogen-like effects in the adult quail. Egg-laying was not affected in female

birds, and no effect in male quail on sexual behavior, testis weight or plasma testosterone was detected (Halldin et al., 2001).

A previous study by the same group of investigators after 45 µg TBBPA /g was injected in quail eggs also did not find estrogenic-like effects (Berg et al., 2001).

Given the lack of effects observed in these studies and method of exposure (egg injection) for some studies, EPA/OPPT doesn't plan to evaluate these effects in the proposed risk assessment.

F-3 Toxicity to Amphibians

Data on amphibians have also been submitted to EPA for TBBPA (ACC, 2006) and have been evaluated by EC/HC (2013).

In the frog embryo teratogenesis assay: *Xenopus* (FETAX) bioassay, TBBPA was evaluated for potential hormonal activity in the tadpole (*Xenopus*) embryo during the first 96 hours of development. Mortality, malformation rate and growth inhibition/acceleration were evaluated by measuring changes in embryo length and the presence of features indicative of earlier/later life stages. At 0.1, 1, 10 100 or 500 µg/L, TBBPA had no effect on *Xenopus* development when using either standard or minimal levels of sodium and potassium (Garber et al., 2001).

TBBPA was also evaluated in the tadpole (*Xenopus*) tail regression assay to determine possible effects on thyroid hormones. At developmental stage 58[18], TBBPA was microinjected into tadpoles at doses up to 60 µg/tadpole. Although positive controls showed delayed tail resorption, TBBPA showed no effects on tail resorption (Balch and Metcalfe, 2001).

TBBPA was found to decrease functioning of the thyroid hormone, triiodothyronine (T3), which is critical to the triggering and control of metamorphosis in amphibians (Brown et al., 1996; Hanada et al., 2003; Kashiwagi et al., 1999). Veldhoen et al. (2006) studied pre-metamorphic tadpoles of the Pacific tree frog (*Pseudacris regilla*) and found that normal thyroid hormone-mediated gene expression profiles were significantly altered at both TBBPA concentrations (5.4 µg/L and 54 µg/L) evaluated. The results show changes in endocrine-regulated gene expression at a sensitive life stage of the frog can occur within hours of exposure to low concentrations (EC/HC, 2013).

The possible adverse effects of tetrabromobisphenol A exposure on the endocrine system in amphibians have shown mixed results. Furthermore, the effect of changes in gene expression is not clear. For these reasons, EPA/OPPT has not considered these results further for inclusion in a risk assessment of TBBPA.

[18] Normal growth at this stage would be the following: hind limbs emerged and forelimbs formed but not emerged.

F-4 Summary of Environmental Hazard

Ecotoxicity studies for TBBPA have been conducted in aquatic plants, aquatic invertebrates (water column and sediment), fish, terrestrial plant species, soil invertebrates and birds. Four COCs were derived for the assessment, as summarized in Table_Apx F-3. The first COC in the table was determined by dividing the acute effect level by an uncertainty factor of 5; the three chronic COCs were calculated using a chronic uncertainty factor of 10.

Table_Apx F-3: Ecotoxicity Concentrations of Concern

Environmental Toxicity	Concentration of Concern (COC)	Species and Effect	Reference
Acute toxicity, aquatic water column organisms	0.02 mg/L	Eastern oyster; shell deposition	SLS (1989a)
Chronic toxicity, aquatic water column organisms	0.002 mg/L	Blue mussel; Growth rate, shell length	ACC (2005)
Chronic toxicity, aquatic/sediment-dwelling organisms	11.7 mg/kg	Blackworm; reproduction	Krueger (2002a)
Chronic toxicity, terrestrial organisms	0.044 mg/kg	Earthworm; reproduction	ACC-BFRIP (2005)

Appendix G Human Health Hazard Study Summaries

The toxicological effects of TBBPA have been extensively reviewed and evaluated by the European Union (EC, 2006) and Health Canada (EC/HC, 2013). EPA/OPPT's Design for the Environment and the National Toxicology Program (EPA, 2014e; NTP, 2014a) have also provided toxicity reviews. Therefore, most of the sections below that describe available toxicokinetics and toxicodynamics studies as well as mode of action data rely heavily on previous assessments. The reader is referred to these previous reviews and original articles for more detailed information. A more recent study, the NTP (2014a) cancer bioassay, is described in more detail.

Most studies using TBBPA have been rodent studies, primarily conducted via the oral route. In a recent NTP cancer bioassay, TBBPA was associated with more than one tumor type in rodents. Also, some developmental/newborn rodent studies resulted in effects. However, many of the subchronic, reproductive and developmental toxicity studies conducted in rodents found no effects at the highest doses tested.

G-1 Epidemiology

In a cross-sectional study on 515 high school students in Belgium, TBBPA measured in serum was not consistently associated with changes in neurobehavioral function in these adolescents, as assessed by several types of tests (Kicinski et al., 2012).

G-2 Toxicokinetics

There are no *in vivo* toxicokinetics data via the dermal route for TBBPA. However, *in vitro* data show that TBBPA applied as 2 mg/cm^2 to human skin for 24 hours results in limited absorption (< 1%) (ECHA, 2013). This information, combined with TBBPA's low water solubility, high molecular weight and high log K_{OW} suggest that the compound will have limited absorption through the skin (EC, 2006).

Data are also lacking on TBBPA's toxicokinetics after inhalation. TBBPA has a median particle size of approximately 31.81 to 52.20 µm. Approximately 4% of the particles are <15 µm in diameter (EC, 2006). The particle size distribution indicates that only a small amount of TBBPA is expected to be respirable (< 10 µm) and an even smaller amount of this respirable fraction is expected to deposit in the alveolar region of the lungs after inhalation. Another amount will deposit in the nasopharyngeal region and be either exhaled or swallowed/absorbed through the GI tract. The EU assumed that approximately 75% of inhaled particles will be absorbed; 70% of this was assumed to be from swallowing/GI tract absorption and 5% from absorption through the lung (EC, 2006).

Several oral toxicokinetics studies have been conducted in rodents. An oral study of Sprague Dawley rats shows that considerable amounts (e.g., > 70%) of TBBPA can be absorbed by the gastrointestinal tract (Hakk et al., 2000). TBBPA can undergo Phase II metabolism directly, primarily conjugation via glucuronidation and/or sulfation. The conjugated forms are then excreted primarily via the feces after oral exposure (Hakk et al., 2000; Kuester et al., 2007; Schauer et al., 2006).

Approximately 95% of TBBPA or its metabolites were excreted in the feces within 72 hours after a single oral administration and only about 1% was excreted in the urine (Hakk et al., 2000). There was limited retention of TBBPA or metabolites in the blood and tissues (liver: 0.4%, muscle: 0.12%, skin: 0.12%, fat: 0.7%, blood: 0.01%). Rapid elimination and low tissue retention of TBBPA were also reported in Fischer 344 rats following oral or intravenous routes of exposure. Rates of elimination and tissue retention were comparable for single doses or for repeated daily doses of 20 mg/kg-bw for 5 or 10 consecutive days (Kuester et al., 2007). One study in pregnant rats found limited transfer of TBBPA or its metabolites to the fetus; tissues in the pregnant rats and fetuses contained about 1.2% and 0.34%, respectively, of radioactivity 48 hours after exposure to ^{14}C ring-labeled TBBPA (Meerts et al., 1999).

Similar to results of rat studies, TBBPA-glucuronide and TBBPA-sulfate were identified as the major metabolites in humans after oral administration of TBBPA (Schauer et al., 2006; Zalko et al., 2006). The half-life of TBBPA in humans has been estimated to be about 2 days (Hagmar et al., 2000; Sjodin et al., 2003).

G-3 Acute Toxicity

Acute oral, dermal and inhalation studies have been performed with TBBPA. These studies show that TBBPA has low acute toxicity by all routes of exposure. The oral LD_{50}s are > 50,000 mg/kg-bw in rats and 3200 mg/kg-bw in mice; the dermal LD_{50} is > 10,000 mg/kg-bw in rabbits; and inhalation LC_{50}s are > 10.92 mg/L in rats and > 50 mg/L in mice (GLCC, 1967; Gustafsson and Wallen, 1988; HTRI, 1966; IBRI, 1967; VCC, 1978a).

Nakajima et al. (2009) evaluated neurobehavioral changes in an open-field test 3 hours after gavage exposure using 0.1, 5 or 250 mg/kg-bw/day TBBPA. Some behavioral effects were seen at 0.1 and 5.0 but not at 250 mg/kg-bw/day. TBBPA was found in the striatum at the two lowest doses and showed non-specific accumulation in the brain at 250 mg/kg-bw/day. Given the lack of a dose response, it is difficult to make a conclusion regarding acute neurobehavioral effects from this study.

G-4 Repeated-Dose Toxicity

The chronic and subchronic toxicity of TBBPA was investigated in an inhalation study, a dermal study and several oral repeated-dose studies. The inhalation and dermal studies are discussed. Oral studies of 90 days or longer are also summarized.

G-4-1 Inhalation

In a 14-day inhalation study in rats (IRDC, 1975), the EU concluded that no adverse systemic effects were reported at 2, 6 and 18 mg/L, with the exception of signs of mechanical irritation in all treatment groups due to the high dust levels (EC, 2006).

G-4-2 Dermal

In a 21-day dermal study, TBBPA was administered to rabbits at doses up to 2,500 mg/kg-bw/day for 6 hours/day, 5 days/week. No toxicologically significant effects were identified (IRDC, 1979).

G-4-3 Oral – Gavage

In a 90-day oral gavage study, rats were administered TBBPA at doses of 0, 100, 300 or 1,000 mg/kg-bw/day (MPI_Research, 2002a). No neurobehavioral effects were observed during the weekly functional observational battery evaluations. Slight changes in hematological evaluations and clinical chemistry were reported; however, the EU concluded that these effects were not toxicologically significant. Statistically significant decreases in serum T_4 were reported in males and females, but no accompanying change in serum T_3, thyroid stimulating hormone (TSH) or histopathology of the liver, thyroid, parathyroid or pituitary was reported. The EU again concluded that the decreases in serum T_4 were not adverse. Absolute spleen weight was decreased in males in the top two dose groups; no histopathological findings were noted. An increase in relative epididymis weight was reported in the middle dose group; however, no changes in relative epididymis weight or histopathology were identified in the high dose group. Again, the EU concluded that these findings were of no toxicological significance (EC, 2006).

In a recent subchronic toxicity study, groups of 10 male and 10 female F344/NTac rats and B6C3F1 mice were administered 0, 10, 50, 100, 500 or 1,000 mg/kg-bw/day TBBPA in corn oil by gavage, 5 days per week for up to 14 weeks (NTP, 2014a). In the rats, dose-related decreases in serum T_4 levels occurred on day 4 and at week 14 in 500 and 1,000 mg/kg-bw/day males and females. These effects occurred less consistently at 100 mg/kg-bw/day. Significant increases occurred in liver weights of 500 and 1,000 mg/kg-bw/day rats (males and females) and significant decreases occurred in spleen weights of 500 and 1,000 mg/kg-bw/day males. No treatment-related histopathologic lesions were observed.

In the mice, liver weights of 500 mg/kg-bw/day males and 1,000 mg/kg-bw/day males and females were significantly greater than those of the vehicle controls. Kidney weights were significantly decreased and spleen weights were significantly increased in 1,000 mg/kg-bw/day males. At 500 and 1000 mg/kg-bw/day, males exhibited increased incidences of renal tubule cytoplasmic alterations. No additional treatment-related histopathologic lesions were observed in mice in this 14-week study (NTP, 2014a).

Administration of TBBPA in corn oil to Wistar Han rats at 0, 250, 500 or 1,000 mg/kg-bw/day 5 days per week by gavage for up to 105 weeks resulted in decreased body weight (by at least 10% lower than vehicle controls after week 25) at 500 and 1,000 mg/kg-bw/day. At three months, thymus weights in the 1,000 mg/kg-bw/day dose group were significantly lower and liver weights were higher than vehicle controls. Females at all doses exhibited increased incidences of nonneoplastic lesions of the uterus (NTP, 2014a).

B6C3F1 mice (50/sex/dose) were also administered TBBPA via gavage in corn oil at 0, 250, 500 or 1,000 mg/kg-bw/day for 5 days/week for up to 105 weeks. Mice at 1,000 showed decreased body weights

(by more than 10% after week 25) and decreased survival compared with vehicle controls. In male mice, nonneoplastic lesions were seen in the liver and kidney at 250 and 500 mg/kg-bw/day. Male mice at 500 mg/kg-day and female mice at 250 and 500 mg/kg-bw/day exhibited forestomach lesions (NTP, 2014a).

G-4-4 Oral – Dietary

Rats were fed a diet for 3 months that included approximately 0, 0.3, 3, 30 or 100 mg/kg-bw/day TBBPA. No changes were observed in clinical signs, body weights, hematology, clinical chemistry, urinalysis, organ weights, gross or microscopic pathology (Dow_Chemical, 1975).

TBBPA was given to B6C3F1 mice at 0, 500, 4900, 15,600 or 50,000 ppm (approximately 0, 71, 700, 2,200 or 7,100 mg/kg-bw/day) for 3 months. All mice at 7,100 mg/kg-bw/day died but no mice died at lower doses. Body weight gains were decreased at 2,200 and 7,100 mg/kg-bw/day and red blood cells, hemoglobin, hematocrit, serum triglycerides and total serum proteins were decreased at 2,200 mg/kg-bw/day. Increased spleen weights were also observed (Tobe et al., 1986).

G-5 Reproductive and Developmental Toxicity

G-5-1 Multigenerational Studies

No effects on reproduction, fertility or developmental toxicity including neurobehavioral abnormalities (*e.g.*, motor activity, learning and memory, auditory response) were observed in an OECD compliant two-generation study in Sprague-Dawley rats using gavage doses of 0, 10, 100 or 1,000 mg/kg-bw/day (MPI_Research, 2002b, 2003). In this study, there were significant decreases in serum thyroxine (T_4) levels in F_0 and F_1 offspring at 100 and 1,000 mg/kg-bw/day. Mean serum T_3 levels were also significantly lower in F_0 males at the highest dose (1,000 mg/kg-bw/day), but no changes were found in the F_0 females or in the male or female F_1 offspring. There were also no effects on TSH levels or microscopic changes in the liver or pituitary gland; the thyroid was not examined histopathologically. There was no dose-response relationship in T_4 levels; following the 30-day recovery period, the levels were similar to controls. The European Union concluded that the thyroxine effects were not toxicologically significant (EC, 2006).

Van der Ven et al. (2008) reported the results of a one-generation reproduction dietary study in Wistar rats using TBBPA doses of ~ 0, 3, 10, 30, 100, 300, 1,000 or 3,000 mg/kg-bw/day. In this study, exposure lasted 11 weeks (males) and 2 weeks (females) prior to mating and during mating (both sexes). For females, dosing continued throughout gestation and lactation. After weaning, dosing of offspring were 10 weeks old. Dams exhibited decreased body weight at the highest dose along with reduced food consumption. However, benchmark doses calculated at the lower 95% confidence limit for an associated 10% decrease in body weight were close to the highest dose and sometimes higher than 3000 mg/kg-bw/day. There were no effects on the reproduction parameters examined, including sperm count or morphology.

In offspring, decreased plasma T_4 levels were associated with lower bounds on benchmark doses ($BMDL_{10}$s) of 30.8 and 16.1 mg/kg-bw/day in males and females, respectively. Modeling of the increased T_3 levels in female offspring resulted in a $BMDL_{10}$ of 2.3 mg/kg-bw/day; this effect was not seen in males. The authors also report $BMDL_{10}$s of 0.5 and 0.6 mg/kg-bw/day, respectively, for increased testicular and pituitary gland weights in male offspring. The testes, pituitary gland and thyroid gland did not exhibit histopathological changes to accompany the increased organ weights or hormone changes. Other effects in offspring (decreased anogenital distance in females at day 7 but not day 4 or 21; number of days to vaginal opening) were observed. However, BMDLs for these effects were calculated as 2736 and 2745 mg/kg-bw/day, respectively (Van der Ven et al., 2008). Review of data by dose level as presented in this publication didn't always reveal clear dose-response relationships.

The possible neurobehavioral effects in offspring from the above one-generation reproduction study were investigated from PND 50 to 140 after being exposed *in utero* and after direct dosing of TBBPA. The authors examined auditory responses by measuring brainstem auditory evoked potentials (BAEPs), which are electrophysiologic responses elicited by auditory stimuli and recorded from the scalp or brain surface as waveform with a series of positive and negative peaks (Lilienthal et al., 2008).

The authors reported that BAEP thresholds and wave IV latency were increased in exposed female offspring in the low sound frequency range. In the males, absolute latency of wave IV and interpeak latencies II-IV were also increased at low frequencies of sound. The authors reported a $BMDL_{10}$ of 8 mg/kg-bw/day for wave IV latency. BMDLs for increased BAEP thresholds in females ranged from 1 to 40 mg/kg-bw depending on the sound frequency at which they were measured (Lilienthal et al., 2008).

Both of the above studies have been criticized for various reasons. Banasik et al. (2009) expressed concerns about Van der Ven et al. (2008) regarding the use of modeling software, methodology and conduct of the study. Also, the effects identified by Van der Ven et al. (2008) were not considered critical endpoints by Health Canada (EC/HC, 2013). Some of the methods and statistical analyses of the findings presented by Lilienthal et al. (2008) were also called into question by Strain et al. (2009).

Other limitations or deficiencies of Lilienthal et al. (2008) were identified by comparing the study with EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) Test Guidelines on Neurophysiology: Sensory Evoked Potentials (870.6855, August 1998). According to these EPA test guidelines, a pigmented strain of rat is the preferred animal species to be tested because albino strains of animals have known abnormalities of the visual and auditory systems. Furthermore, at least 10 nulliparous and nonpregnant rats per group should be used, and positive control groups exhibiting functional changes in the sensory systems to be tested are recommended. Instead, the study of Lilienthal et al. (2008) used groups of 5-6 pregnant Wistar rats (which are albino rats) and did not include positive controls.

In a separate review of Lilienthal et al. (2008) by an EPA neurotoxicologist, it was noted that although the criticisms by Strain et al. (2009) have some merit, they are not sufficient to completely dismiss the findings (Herr, 2013). EPA/OPPT believes that this study suggests the potential for auditory effects but will not use this study in a quantitative risk assessment given some concerns (one being the use of albino rats) and the difficulty determining what exposures may lead to the effects (e.g., whether exposure by the dams/parents or direct exposure to the offspring experiencing the effects is most relevant).

Zatecka et al. (2013) conducted a 2-generation drinking water study in CD1 outbred mice. In the parental generation, TBBPA was administered only to pregnant dams during gestation (at 0 or 0.035 mg/kg-bw/day) and not to fathers. F_1 offspring were then dosed during pre-pubescence, pubescence and up to adulthood and evaluated at 70 days of age. In the F_1 offspring, there was an increased incidence of apoptotic cells in testes and increased expression of genes encoding proteins important during spermatogenesis. The F_1 generation was then bred in a cross-over fashion using four patterns (both parents exposed; neither exposed; mother exposed; father exposed). The F_2 offspring were then evaluated at 70 days of age; it is not clear from the study description whether the F_2 rats had access to TBBPA in the drinking water or from dam's milk or both. In the F_2 offspring with both parents exposed to TBBPA, testicular weights were reduced ($p < 0.01$), prostate weights were increased ($p < 0.05$) and seminal vesicle weights were increased ($p < 0.01$). The F_2 generation with only fathers exposed showed increased epididymis weights ($p < 0.01$). No visible abnormalities or pathological changes in seminiferous tubule morphology were seen. The significance in these effects is unclear because only one dose was used and histopathological, sperm and other reproductive effects were not observed.

G-5-2 Prenatal and Postnatal Developmental Toxicity Studies

There were no significant dose-related effects on T_4, T_3 or TSH in offspring at PND 20 or postnatal week 11 after pregnant Sprague-Dawley rats were fed TBBPA at dietary levels of 0, 100, 1,000 or 10,000 ppm (~ 17, 149 or 1472 mg/kg-bw/day) from gestation day (GD) 10 to PND 20. However, offspring exhibited slight decreases in T_3 on PND 20 that were not dose-related. TBBPA did not alter brain development or other reproductive parameters. The study did not state whether offspring had direct access to TBBPA in the food (Saegusa et al., 2009).

In a pilot range-finding study (VCC, 1978b), no developmental effects were observed in offspring of dams administered TBBPA up to 10,000 mg/kg-bw/day from GD 6-15. In a standard developmental toxicity study (Noda et al., 1985), pregnant Wistar rats were administered TBBPA via gavage from GD 0 to 20 at doses up to 2,500 mg/kg-bw/day. No effects were seen in dams or in offspring evaluated up to PND 21. In another developmental toxicity study (MPI_Research, 2001), pregnant rats were administered TBBPA via gavage up to 1,000 mg/kg-bw/day from GD 0 to 19 and again, no effects were observed in dams or offspring.

No differences in various neurobehavioral measures in a study of NMRI mice administered 0.75 and 11.5 mg TBBPA/kg-bw orally on PND 10 (Eriksson et al., 2001; Eriksson et al., 1998).

Viberg and Eriksson (2011) report biochemical changes related to cholinergic effects in neonatal NMRI mice treated with 11.5 mg TBBPA/kg-day. Radioactivity from TBBPA dosing was highest (at 3.7%) in the brain at 3 hours, decreased to 0.9% at 24 hours and was 0.3% by 7 days after dosing. It is not entirely clear whether the study controlled for possible litter effects. Although some evaluations were done with equal numbers of animals per litter, methods of litter culling were less clear for other assessments (Viberg and Eriksson, 2011).

In a study in which TBBPA was administered at 0%, 0.01%, 0.1% or 1% in the diet to pregnant ICR mice (6/dose) from the first day of gestation to weaning at postnatal day 27, no effects on average litter size, litter weight, total number of offspring, average male or female offspring weights or dam weights

were reported (Tada et al., 2006). The offspring drank the dam's milk while the dams were being treated. Also, offspring had access to dam's food from PND 22 to 27; it is not known how much was ingested. Changes in total cholesterol, triglycerides and organ weights (liver, brain, spleen) were seen primarily at the highest dose ($p < 0.05$) in the dams. Female offspring exhibited an increased incidence of renal tubule atrophy at the highest dose. Based on enlargement of hepatocytes and very slight focal necrosis of hepatocytes in female offspring, Health Canada considered the LOAEL to be 0.1% (~140.5 mg/kg-bw/day during gestation), with a NOAEL of 0.01% (~15.7 mg/kg-bw/day during gestation).[19] Littermates were used as independent variables for the experimental and statistical analyses. Thus, the tendency of littermates to respond more similarly to one another than non-litter mates was not fully taken into account. However, the authors chose the same number (4 offspring of each sex) randomly from each litter to partially account for such effects (Tada et al., 2006).

In a dietary developmental toxicity study, Saegusa et al. (2012) administered TBBPA to Sprague Dawley rats from GD 10 through PND 12. The highest concentration (10,000 ppm or ~ 800 mg/kg-bw/day) resulted in increased interneurons in the dentate hilus-expressing reelin; this effect suggests alterations in neuronal migration. It is not clear from this study whether offspring had direct access to TBBPA in the diet of the dams after birth.

In a study of newborn rats directly dosed by gavage from days 4 to 21 after birth, an effect on the kidneys (polycystic lesions associated with the dilation of tubules) was noted at 200 and 600 mg/kg-bw/day but not at 40 mg/kg-bw/day. Effects at 600 mg/kg-bw/day were considered moderate in females and severe in males whereas the lesions seen in the two males that exhibited effects at 200 mg/kg-bw/day were of slight severity. At 85 days of age, nephrotoxic lesions were still seen at 200 and 600 mg/kg-bw/day. There were no neurobehavioral effects as assessed by testing reflexes on PND 21 (Fukuda et al., 2004). Based on the slight effects in the kidney at 200 mg/k-bw/day, the LOAEL is considered to be 200 and the NOAEL 40 mg/kg-bw/day.

In comparison, no similar effect was found in 5-week old rats dosed via gavage with 2,000 or 6,000 mg/kg-bw/day for 18 days (Fukuda et al., 2004). The EU suggested that the kidney effects observed in the newborn rats are likely due to the immature metabolic capability and/or immature kidneys (EC, 2006).

G-6 Irritation and Sensitization

The European Union and Canada concluded that TBBPA is not a skin, eye or respiratory irritant and is not considered to be a skin or respiratory sensitizer in animals or humans (EC, 2006; EC/HC, 2013; GLCC, 1967; Gustafsson and Wallen, 1988; HTRI, 1966; IBRI, 1967; VCC, 1978a).

G-7 Genotoxicity and Carcinogenicity

The following sections present the finding of the NTP (2014a) cancer bioassay and discuss conclusions from the Office of Pesticide Program's (OPP's) Cancer Assessment Review Committee (CARC) about

[19] The LOAEL and NOAEL during lactation are associated with doses of 379.9 and 42.1 mg/kg-bw/day, respectively.

TBBPA-related tumors and human relevance. Mode of action is also discussed along with EPA/OPPT's overall classification regarding human relevance.

G-7-1 Genotoxicity

Both *in vitro* and *in vivo* assays discussed in available reviews have found that TBBPA is not genotoxic. These studies include multiple bacterial reverse mutation assays with and without metabolic activation, an *in vitro* test for intragenic recombination in mammalian cells, an *in vitro* mammalian chromosomal aberration test using human peripheral blood lymphocytes (with and without metabolic activation) and a mouse micronucleus study(EC, 2006; NTP, 2014a).

G-7-2 NTP Carcinogenesis Bioassays

NTP recently published a report of the results of carcinogenesis studies of TBBPA in rats and mice (NTP, 2014a). Groups of Wistar Han rats and $B6C_3F_1$ mice were administered 0, 250, 500 or 1,000 mg/kg-bw/day TBBPA in corn oil by gavage, 5 days per week for up to 105 weeks. At 0 and 1,000 mg/kg-bw/day, 60 rats/sex/dose were used and at 250 and 500 mg/kg-bw/day, 50 rats/sex/dose were used. Fifty mice/sex/dose were used for all doses.

G-7-2-1 Findings in Rats

Males

In males, mean body weights were at least 10% lower than controls after week 25. There were no clinical findings and survival did not differ between dosed groups and controls. At three months, there were no treatment-related lesions. After two years, the incidences of interstitial cell adenoma of the testis were slightly increased at 500 (1/50) and 1,000 mg/kg-bw/day (3/50) compared to controls (0/50) ($p \leq 0.05$ for the trend test). Pairwise comparisons were not statistically significant.

Females

Body weights were similar in all groups, including controls. There were no clinical findings and survival was similar among all groups. No treatment-related lesions were seen at the three-month evaluation.

For the uterus only (not other tissues), NTP first evaluated the tissues transversely and later evaluated them longitudinally. According to the original transverse evaluation, there were increases in both neoplastic and non-neoplastic lesions of epithelial origin. Cystic endometrial hyperplasia of the endometrium was increased at 1,000 mg/kg-bw/day ($p \leq 0.05$ by the Poly-3 test). NTP found positive dose-response trends in the incidences of 1) adenoma ($p = 0.001$) and 2) adenocarcinoma (epithelial origin) ($p < 0.05$; Poly-3 test). When tumors were combined, the incidences of adenoma, adenocarcinoma or malignant mixed Müllerian tumors of the uterus showed a positive trend ($p < 0.05$ by the Poly-3 test). By pairwise comparison, the incidences were significantly increased in the 500 and 1,000 mg/kg-bw/day groups ($p < 0.05$ and < 0.01 by the Poly-3 test). The combined incidences of these three tumor types in control, low-, mid- and high-dose groups were: 3/50, 7/50, 11/50 and 13/50, respectively.

More nonneoplastic and neoplastic lesions of epithelial origin were identified after longitudinal evaluation of residual uterine tissue. When the original and residual evaluations were combined, atypical endometrial hyperplasia was significantly higher than controls at all doses ($p \leq 0.01$; Poly-3 test). However, cystic endometrial hyperplasias were no longer significantly higher than controls. There were positive trends (Poly-3 test) in the incidences of 1) adenocarcinoma alone ($p < 0.01$) and 2) the combined incidences of adenoma, adenocarcinoma or malignant mixed Müllerian tumor ($p < 0.001$) for the combination of original and residual sections. For both adenocarcinomas alone and for the combined tumor types, pairwise comparisons showed that incidences were increased in the 500 and 1,000 mg/kg-bw/day groups ($p < 0.01$; Poly-3 test). The combined incidences of the three tumor types in the control, low-, mid- and high-dose groups were: 6/50, 11/50, 16/50 and 19/50, respectively.

In the ovaries, incidences of rete ovarii cysts were significantly greater at 500 and 1,000 mg/kg-bw/day compared with controls ($p \leq 0.05$; Poly-3 test).

G-7-2-2 Findings in Mice

Both Sexes – Decreased Survival

Survival of mice at 1,000 mg/kg-bw/day (577 days for males; 413 days for females) was lower than controls (687 days for males; 711 days for females) ($p < 0.001$). Decreased survival was seen as early as 6 months. Although (NTP, 2014a) reports numbers of 1,000 mg/kg-bw/day mice that had neoplasms, the incidence is lower than the 500 mg/kg-bw/day group and the decreased survival at 1,000 mg/kg-bw/day was not attributed to the tumors. Instead, decreased survival was associated with decreased body weight gain and may have been due to gastrointestinal toxicity. Because of the decreased survival at the highest dose, NTP (2014a) evaluated tumors only for the 0, 250 and 500 mg/kg-bw/day dose groups.

Males

Several non-neoplastic lesions were observed in the kidney and forestomach. Renal tubule cytoplasmic alterations were observed at 250 and 500 mg/kg-bw/day (≤ 0.01; Poly-3 test) and increased in severity by dose. In the forestomach, the 500 mg/kg-bw/day males exhibited ulcers, mononuclear cell infiltration, inflammation and epithelium hyperplasia ($p \leq 0.05$ or ≤ 0.01).

Both nonneoplastic and neoplastic lesions were observed in the liver. Compared with the control group, the number of male mice with clear cell foci was increased at 500 mg/kg-bw/day; eosinophilic foci were significantly increased at 250 and 500 mg/kg-bw/day ($p \leq 0.01$ for all). The incidence of multiple hepatocellular adenoma was significantly increased at 500 mg/kg-bw/day compared with controls ($p < 0.05$; Poly-3 test). In addition, the incidences of hepatoblastoma (11/50) and the combined incidence of hepatocellular carcinoma or hepatoblastoma (24/50) in 250 mg/kg-bw/day males (11/50) were significantly greater than those in the vehicle controls (2/50 or 12/50, respectively) ($p < 0.01$; Poly-3 test). Differences were not statistically significant at 500 mg/kg-bw/day or by trend tests.

Other increased incidences of tumors were observed in the intestines or in all organs. The combined incidences (0/50, 0/50 and 3/50 at 0, 250 and 500 mg/kg-bw/day) of adenoma or carcinoma of the large intestine (cecum or colon) occurred with a significant positive trend (< 0.05 by the Poly-3 test). The incidences of 1) hemangiosarcomas or 2) combined hemangiomas/hemangiosarcomas (3/50, 5/50 and 9/50 at 0, 250 and 500 mg/kg-bw/day) when summing tumors for all organs occurred with significant positive trends ($p < 0.05$ by the Poly-3 test). By pairwise comparison, hemangiosarcomas were higher than controls at 1,000 mg/kg-bw/day ($p < 0.05$; Poly-3 test).

Females

Females exhibited ulcers, mononuclear cell infiltration, inflammation and epithelium hyperplasia in the forestomach at 250 and 500 mg/kg-bw/day (females). No increased incidences of tumors were found in female mice.

G-7-2-3 NTP Conclusions Regarding Tumors Related to TBBPA Treatment

Under the condition of these studies, NTP concluded that there was *clear evidence of carcinogenic activity* of TBBPA in female Wistar Han rats based on increased incidences of uterine epithelial tumors, which primarily included uterine adenocarcinomas. There was *some evidence of carcinogenic activity* of TBBPA in male B6C3F1/N mice based on the increased incidences of hepatoblastoma. NTP concluded that there was *equivocal evidence of carcinogenic activity* of TBBPA in male Wistar Han rats based on slightly increased incidences of testicular adenoma. The large intestine neoplasms and hemangiosarcoma (all organs) are considered equivocal findings. There was *no evidence of carcinogenic activity* of TBBPA in female B6C3F1/N mice (NTP, 2014a).

G-7-3 CARC Conclusions Regarding Weight of Evidence for TBBPA-Related Tumors

The results of independent reviews of cancer bioassays/carcinogenicity, often of pesticides, are often subsequently peer-reviewed by EPA's Cancer Assessment Review Committee (CARC), which reviews data and recommends a cancer classification. This classification will then determine how the Agency regulates pesticides or other reviewed compounds. The committee also recommends methods to quantify human health risk (http://www.epa.gov/pesticides/health/cancerfs.htm). During the problem formulation of TBBPA, EPA's OPPT asked the CARC to provide an independent review of the newly available NTP study to help inform the cancer assessment.

The CARC conclusions are based on whether clear statistically significant dose-response trends and pairwise statistical comparisons can be seen, whether precursor lesions were observed and whether tumors are clearly within historical control ranges.

Similar to the NTP conclusions, the CARC considered uterine tumors in rats to be clearly related to TBBPA treatment. However, in contrast to NTP's conclusions, the CARC made the following conclusions:

- TBBPA treatment is not associated with testicular tumors in male rats and intestinal tumors (other than the hemangiosarcomas
- TBBPA is associated with hemangiomas and hemangiosarcomas in male mice
- TBBPA is not related to hepatoblastomas in male mice based on the lack of either statistical significance or a dose trend. Despite statistical significance at the highest dose, the liver adenomas in male mice are not of concern from TBBPA exposure because incidences were within the historical control range and there were no precursor lesions.

The CARC's conclusions for each tumor type is further delineated in Supplemental File 4 (CARC, 2014).

The CARC concluded that there is not enough evidence regarding the mode of action (MOA) to meet the International Programme on Chemical Safety (IPCS) 2007 Human Relevance Framework. This lack of clear MOA and unknown human relevance resulted in CARC deferring to the default science position of the 2005 EPA Cancer Guidelines (EPA, 2005) that tumors are relevant to humans. More information on the CARC's overall weight of evidence specifically regarding relevance to humans is discussed in Section 2.6.4.5G-7-5.

G-7-4 Mode of Action Considerations for Cancer

TBBPA's possible MOAs for induction of tumors are not clearly understood. Although not an evaluation of all available data, some considerations as to TBBPA's possible cancer MOAs are discussed here, with an emphasis on MOAs related to uterine tumors.

Based on the toxicokinetics data, it is possible that liver effects (*i.e*., enlargement of hepatocytes, increased liver weight and slight focal necrosis of hepatocytes) observed in adult rats and/or mice after exposures to high doses of TBBPA for extended periods could be due to saturated metabolic capability and diminished elimination/excretion of the compound.

Negative genotoxicity studies suggest that a direct genotoxic MOA is not considered likely for tumorigenesis. The CARC also concluded that there is no likely concern for mutagenicity for TBBPA (CARC, 2014).

Uterine tumors can arise in response to endogenous estrogen overstimulation in aged rats, which can be exacerbated by administration of exogenous chemicals through direct and indirect pathways (Alison et al., 1994; Lax, 2004). After binding directly to estrogen receptors (ERs) in a cell, endogenous estrogen and estrogen agonists can activate hormone-responsive genes that promote DNA synthesis and cell proliferation. Therefore, estrogen and estrogen agonists can act as tumor promoters by inducing proliferation of cells with pre-existing mutations and eventually lead to tumor formation. Estrogen (as a result of excessive exposure) has been recognized as a known human carcinogen (IARC group 1 carcinogen) (NTP, 2014b).

The ER binding activity of TBBPA has been investigated in a number of *in vitro* screening assays. Review of the overall weight-of-evidence from *in vitro* assays has indicated that there is no significant estrogenic potential for TBBPA. A recent study in mice has shown that TBBPA was negative for estrogenic responses by both subcutaneous injection and oral routes of exposure up to 1,000 mg/kg-

bw/day (Ohta et al., 2012). Because *in vitro* and *in vivo* studies showed that TBBPA has no significant estrogenic potential, TBBPA is unlikely to operate directly by the ER-mediated pathway for the induction of uterine tumors.

Conjugations (glucuronidation and sulfation) are the major biotransformation pathways for excretion of TBBPA in rats, and these pathways are shared by estrogen (Raftogianis et al., 2000). Competition for glucuronosyl-transferases and/or sulfotransferases by TBBPA could indirectly result in higher levels of estrogen and increased formation of estrogen-derived reactive radicals following exposure to high concentrations of TBBPA (NTP, 2014a).

In addition to competing with enzymes that metabolize estrogen, a recent crystallographic analysis of TBBPA and a related brominated compound suggests that TBBPA, in addition to being a weak agonist, may bind to and actually inhibit sulfotransferases (e.g., SULT1E1) that metabolize estrogen (Gosavi et al., 2013) thereby causing possible buildup of estrogen.

Besides the promotional and indirect genotoxic effects, estradiol (and its interconvertible metabolite estrone) can also exert genotoxic effects after being metabolized to catechols and then to reactive quinones that can form DNA adducts and contribute to oxidative DNA damage by reactive oxygen species (Bansal et al., 2009; Chen et al., 2008; Russo and Russo, 2004; Yager, 2014). If unrepaired, these mutations may lead to tumor formation. There are data that suggest that both estrogen activity and oxidative stress are required to induce cancer (Conova, 2003).

The *Tp53* tumor suppressor gene is responsible for cell cycle checkpoint maintenance and genomic stability, and loss of cell cycle checkpoint control due to *Tp53* mutations can result in the development of various tumor types in rodents and humans (Blagosklonny, 2000; Muller and Vousden, 2013). In the NTP bioassays (NTP, 2014a), a statistically significant increase in the incidence of mutations of the *Tp53* tumor suppressor gene was noted in uterine adenocarcinomas from TBBPA treated rats (60%) compared to the incidences in mutations associated with spontaneous tumors from control rats (20%). It is possible that increased incidence of *Tp53* mutations may be caused by the reactive oxygen radicals or metabolites produced after metabolism of the high levels of circulating estrogens due to competitive binding/inhibition of high doses of TBBPA to sulfotransferases or glucuronosyl-transferases. However, with the exception of multiple mutations in uterine tumors of two rats treated with TBBPA, there was no difference between the mutation spectra of spontaneous tumors and those from TBBPA-treated rats. Therefore, it may be more likely that increased estrogen levels due to competitive inhibition of estrogen conjugations by high doses of TBBPA may cause uterine tumors by promoting pre-existing *Tp53* mutations in the uterus by turning on hormone-responsive genes that promote DNA synthesis and cell proliferation.

Uterine/endometrial cancer is one of the most common cancers in women with over 54,000 new cases estimated for 2015 (ACS, 2015).There are two types of uterine carcinoma with respect to histology, MOA and molecular genetic pathways. Type I carcinoma (the most common type), is associated with expression of ER, estrogen overstimulation, endometrial hyperplasia and *Tp53* mutations in only about 10-20 % of the carcinoma. Type II carcinoma is unrelated to estrogen and frequent lack of estrogen receptor activities. It is associated with atrophic endometrium, and *Tp53* mutations (90%) are the most frequent genetic alterations (Lax, 2004). In light of the high incidence of *Tp53* mutations in the uterine

adenocarcinomas, weak ER binding potential and the lack of increased levels of circulating estrogen in TBBPA-treated rats, it is likely that TBBPA induced type II carcinoma in the rats (rather than type I carcinoma). This notion is supported by the findings that there was no increase in endometrial hyperplasia (which is associated with type I carcinoma) in all dosed groups of female rats in the NTP bioassays when the original and residual tissues evaluations were combined; instead a new atypical hyperplasia was identified (NTP, 2014a). The two types of uterine/endometrial carcinomas seen in the rat study are similar to those observed in humans (e.g, Bansal et al., 2009) suggesting that the rat model is relevant to humans.

Another possible MOA for TBBPA's association with uterine tumors deserves consideration. An *in vitro* study investigating the effects of TBBPA on the uptake of neurotransmitters into isolated rat brain synaptosomes showed a mixed concentration-dependent competitive/non-competitive mode of inhibiting dopamine uptake (Mariussen and Fonnum, 2003). Uterine tumors can be induced by dopamine receptor agonists in the rat through such an indirect estrogen pathway. Dopamine serves as a key regulator of serum prolactin by activating dopamine receptors on the pituitary to inhibit the secretion of prolactin. Chronic administration of dopamine receptor agonists to rats can result in decreased serum prolactin levels after competitively binding to the dopamine receptors on the pituitary, leading to estrogen dominance. Such dominance is due to increased estrogen synthesis after luteolysis of the persistent corpora lutea and the formation of new follicles. This estrogen dominance then leads to estrogen activity (*i.e*., expression of hormone-responsive genes that promote cell proliferation) and oxidative stress, which may induce hyperplasia and tumors of the uterus. This carcinogenic effect has not been demonstrated in other species including humans because prolactin is the luteotrophic hormone in rodents but not in primates (Alison et al., 1994; Neumann, 1991). Although the data above demonstrate TBBPA antagonism of dopamine uptake, it is unknown if TBBPA can also act as a dopamine agonist.

NTP is now conducting additional studies that evaluate treatment-related molecular changes in the uterus (NIEHS, 2015).

As noted in Section G-7-3, the CARC concluded that available mode of action data were not adequate to meet the International Programme on Chemical Safety (IPCS) Human Relevance Framework (IPCS, 2007). The CARC did not discuss the specific information that was lacking to establish an MOA. However, there are several important considerations identified by the Human Relevance Framework in determining an MOA for any compound. The Framework specifies that the postulated key events critical to the induction of tumors should be measured consistently. Concordance of dose-response relationships between the key events and tumors is also needed, with consideration of Bradford Hill criteria and whether differences in biological response (such as dose transitions) may occur at different sections of the dose-response curve. Temporally, postulated key events for a mode of action should be observed before the tumors are seen. There should be enough information to suggest some strength, consistency and specificity when associating key events with tumor incidence. Biological plausibility is important, as is the consideration of whether alternate modes of action occur (IPCS, 2007).

G-7-5 Classification of Carcinogenic Potential for Humans

The weight of evidence for whether TBBPA is associated with tumors *in rodents* was presented in 2.6.4.5G-7-3. This section (G-7-5) specifically discusses conclusions regarding the relevance of these data to humans.

The CARC classified TBBPA as *likely to be carcinogenic to humans* according to criteria described in EPA's 2005 Cancer Guidelines. Some criteria that can influence a classification decision include the presence of: 1) tumors in more than one species and sex, 2) more than one tumor type, 3) uncommon tumors, 4) dose-response relationships, 5) tumors known to occur in humans and 6) the presence of non-neoplastic lesions.

The CARC based their conclusion on the presence of uterine epithelial tumors (combined adenoma, adenocarcinoma or malignant mixed Müllerian tumors) in female Wistar Han rats and hemangiomas and hemangiosarcomas in male B6C3F1 mice.

In separate comments, the NTP also agreed with the CARC that TBBPA is *likely to be carcinogenic to humans* (NIEHS, 2015).

G-8 Studies Proposed for Risk Assessment

Data on tumor incidences are available from the NTP cancer bioassay (NTP, 2014a). Based on EPA's CARC and the NTP conclusions that TBBPA is likely to be carcinogenic to humans and because MOA information is limited, EPA/OPPT will evaluate risks using data on uterine tumors (females) and hemangiomas and hemangiosarcomas (males) from this study Appendix J describes the method used to determine slope factors from a linear low-dose extrapolation. EPA/OPPT will use these slope factors in a risk assessment of TBBPA.

EPA/OPPT will also use a study of developmental effects to assess risk for children in scenarios discussed in Chapter 0. Although EPA/OPPT may consider other studies further, the study by Fukuda et al. (2004) is likely to be the most appropriate study for several reasons. The study directly dosed young animals so that matching results with exposure data is easier than studies that dosed both dams and offspring. It is possible that TBBPA causes adverse effects primarily as a result of exposure to TBBPA by young rodents. This is a plausible conclusion based on the breadth of studies that appear to suggest effects are more likely when young animals are dosed directly. The European Union suggested that the kidney effects observed in the newborn rats could be due to immature metabolic capability and/or the immature kidneys of such young animals (EC, 2006).

G-9 Uncertainties

G-9-1 Carcinogenesis Bioassay Methods

NTP (2014a) administered TBBPA to rodents via oral gavage throughout their lifetime. It is not known whether similar adverse effects would result if humans are exposed to TBBPA associated with dust particles or as other forms for less than a lifetime (or even a full lifetime).

The doses used in NTP (2014a) ranged from 250 to 1000 mg/kg-bw/day. It is possible that at lower exposures likely to be experienced by humans, TBBPA would be excreted before it could exert adverse effects. Yet, the available toxicokinetics data are limited in their ability to answer this question. Lower-dose toxicokinetics studies show similar rates of excretion as higher doses via the oral route and the longest toxicokinetics studies are 10 days (Kuester et al., 2007). Therefore, TBBPA's toxicokinetic behavior after longer exposure durations, lower concentrations and exposure via dust (vs. gavage) is not known.

G-9-2 Developmental Toxicity Data

The studies evaluating reproductive and developmental toxicity show a wide variety of results from no effects up to very high doses to some subclinical effects at low doses. Also, it is not clear whether dosing dams and offspring or just dosing offspring results in effects of TBBPA treatment. Thus, there is uncertainty in choosing any developmental toxicity study for evaluation in a quantitative risk assessment of TBBPA.

Appendix H Parameters Needed for Estimating Fish Ingestion

Bioconcentration factors and fish ingestion rates are needed to estimate risks from TBBPA intake through eating fish from one water body identified near one of the Arkansas manufacturing facilities.

Chapter 0 presents bioconcentration factors (BCFs) that can be used to estimate the concentration of TBBPA in fish from the predicted water concentrations. For this assessment, EPA/OPPT will consider using 720 L/kg, measured using eastern oysters (GLCC, 1989b). The values of 1200-1300 L/kg from GLCC (1989a) are higher, but they are based on measuring total radioactivity and reflect measurement of the parent compound and metabolites rather than the parent compound only; thus, this value is not being considered. The lowest measured BCF is 20 L/kg (EC, 2000).

For this assessment, EPA/OPPT plans to use a fish consumption rate of 22 g/day for the recreational fishers who may fish from this water body and the adult members of their family. This value is the default fish consumption rate for adults recommended for the protection of human health in EPA's Office of Water (OW) 2014 draft ambient water quality criteria (AWQC). This value represents the 90th percentile consumption rate of freshwater and estuarine finfish and shellfish for the US adult population 21 years and older as summarized in Table 9a of EPA (2014d). The estimate is based on data from the 2003-2004 National Health and Nutrition Evaluation Survey (NHANES). Statewide studies of freshwater recreational fish intake are summarized in the *Exposure Factors Handbook* (EPA, 2011b) for a number of states. However, there is no study available from Arkansas. Mean intake from statewide surveys, as reported in EPA (2011b), range from 5 to 51 g/day and 95th percentile values range from 14-61 g/day.

For children, EPA/OPPT is considering using 90th percentile consumption rates of freshwater and estuarine finfish and shellfish, also using NHANES data, for specific age groups as detailed in Table 20a of EPA (2014d). For children age 1 to <3 years the value is 4.7 g/day; for children 3 to <6 year the value is 5.8 g/day; and for children age 6 to <11 year the value is 7.7 g/day.

Children < 11 is the age range most relevant for considering effects of developing cancer given that this is a bit more than one tenth of the human life span (EPA, 2005). A shorter age range, from one < three years, could be an appropriate age range for developmental effects based on toxicity studies suggesting effects in newborns vs. a lack of effects in somewhat older rodents (Fukuda et al., 2004).

The body weight used in estimating intake of TBBPA via fish ingestion will correspond to the receptor and toxicological endpoint of interest. For estimating risks of developing uterine tumors, EPA/OPPT proposes to use the body weight of 74.8 kilograms, which is the average weight of female adults aged 30 to <40 years old as presented in the *Exposure Factors Handbook* (EPA, 2011b). For estimating risks of developing hemangiomas or hemangiosarcomas, EPA proposes using a value of 87.0, the average weight for males aged 30 to <40 (EPA, 2011b). For children aged 1 to <2 years the recommended mean body weight is 11.4 kg; for 2 to <3 year the weight is 13.8 kg; for 3 to <6 years the weight is 18.6 kg; and for 6 to <11 years the weight is 31.8 kg (EPA, 2011b).

Exposure can be estimated using these parameters in the following equation:

$X = (WC * BCF * FC)/(1000 * BW)$

Where:

X = Intake of TBBPA via fish ingestion, µg/kg-bw/day
WC = TBBPA water concentration, µg/L
BCF = Bioconcentration factor, L/kg
FC = Fish consumption, g/day
1000 = Conversion factor for fish weight, g/kg
BW = Body weight of human receptors being assessed, kg

Appendix I Draft Approach for Estimating Exposure from Mouthing of TBBPA

TBBPA flame retardants in this cluster are either additive or reactive components used in plastic articles and may or may not be chemically bonded to the polymers. Thus, TBBPA may migrate from the polymer matrix to the surface of the article and have the potential for exposures through direct contact. The presence of TBBPA in a variety of products indicates the potential for consumer exposure via object to mouth contact and hand to mouth contact with articles. EPA/OPPT will consider the methods and parameters discussed below to estimate mouthing exposures.

Table_Apx I-1: Plan for Evaluating Risk to Children from Ingestion of TBBPA from Products in the Home

Exposure Scenario	Rationale	Assessment Approach
Mouthing of products (object-to-mouth) as well as hand-to-mouth transfer by young children in the home	Exposures are expected to be highest in children; younger children are expected to have longer duration of mouthing activity when compared to older children and adults. Sufficient data to quantify exposure and toxicity	Concentrations of TBBPA in products and surface loadings will be combined with age-specific activity patterns and exposure factors to estimate an exposure in mg/kg-bw/day for children. Measured or estimated migration rates in saliva can also be considered if available. To estimate developmental risk, exposure for 1-year olds will be compared with a toxicity value from a developmental study in a margin of exposure (MOE) evaluation. For cancer risk, exposure for children in a wider age range (0 to 7) will be multiplied by cancer slope factors to estimate cancer risk. EPA/OPPT will consult with CPSC and conduct additional literature searches to identify whether migration data specific to TBBPA are available. Data from published and unpublished literature as well as previous assessments will be considered.

I-1 TBBPA Concentrations in Products and Product Surfaces

Recent studies have shown that TBBPA is present in many different types of consumer products and articles as well as on the surfaces of many products. These products include electronic appliances, electronic devices, plastic toys, plastic jewelry and tents (Di Napoli-Davis and Owens, 2013; Gallen et al., 2014; Keller et al., 2014; Samsonek and Puype, 2013; van Bergen and Stone, 2014). Gallen et al. (2014) evaluated the TBBPA content of many different products using X-ray fluorescence, wipe

sampling and destructive methods to estimate concentrations. Di Napoli-Davis and Owens (2013) used wipe sampling on the surface of electronic products. van Bergen and Stone (2014) used destructive methods (cryogenic milling and gas chromatography/mass spectrometry) to estimate concentrations for a wide range of products and product components. Within the Washington State database (WSDE, 2014a), TBBPA concentrations within products are reported as ranges; in the proposed TBBPA risk assessment, EPA/OPPT could use the mid-point of these ranges with conversion factors to estimate loading on the surface of various products. Keller et al. (2014) used wipe sampling to estimate TBBPA loading on the surface of a tent. Samsonek and Puype (2013) measured TBBPA on the surface of black coffee mugs. The results of these studies show that the range of TBBPA concentrations and surface loadings in and on a variety of products span several orders of magnitude.

EPA/OPPT may use these data to estimate a range of TBBPA surface loadings (TBBPA/cm^2) potentially available for transfer to hands and into saliva.

I-2 Migration Rates into Saliva

The migration from the surface of a product into human saliva can be measured through *in vivo* or *in vitro* testing. Results of these tests are expressed as the mass of a chemical per surface area per unit time. For example, values could be expressed as pg, µg or mg per either cm^2 or 10 cm^2 per minute.

In an *in vivo* study, central tendency migration rates for polybrominated diphenyl ethers (PBDEs) ranged from 0.000003 to 0.0026 to µg/10 cm^2-minute and high-end migration rates ranged from 0.00004 to 0.03 µg/10 cm^2-minute (Chen et al., 2009). Babich (2014) summarized available *in vitro* testing of phthalates; central tendency migration rates ranged from 1.1 µg/10 cm^2-mintue to 4.4 µg/10 cm^2-minute while high-end migration rates ranged from 1.9 µg/10cm^2-minute to 11.4 µg/10 cm^2-minute (Babich, 2014).

In vitro and *in vivo* estimates can vary over several orders of magnitude for a given chemical and product combination. PBDEs have very low water solubility (and lower migration rates) while phthalates have moderate water solubility. While many other physical-chemical properties may influence migration potential into saliva, water solubility is likely to be one of the most important factors. Thus, because TBBPA's water solubility is between the values reported for PBDEs and phthalates, it is possible that the migration rate of TBBPA into saliva could be between the ranges reported in Babich (2014) and Chen et al. (2009).

I-3 Children's Activity Patterns

Based on the type of product sampled in the above studies, an object may be handled routinely by a child, resulting in TBBPA transfer from the object to the child's hand and then subsequently to his or her mouth. An article could also be directly placed in a child's mouth. Thus, EPA/OPPT will assign these objects as having the potential for either "hand to mouth" transfer or "object to mouth" transfer.

Because children have higher hand–to-mouth and object-to-mouth activity than adults and adult exposure is expected to be minimal, EPA/OPPT will evaluate exposure for only for children.

Furthermore, mouthing behaviors are typically more prevalent among the youngest children. Thus, to estimate developmental toxicity risks, EPA/OPPT will evaluate exposure for 1-year olds, which is the age with the highest exposure potential as a result of mouthing behavior.

However, to estimate cancer risk, a wider age range is recommended because a longer exposure duration is thought to be required before tumors develop. EPA/OPPT proposes evaluating exposures for children from age 0 through 7 years old to estimate cancer risks.

EPA will use data on the frequency and duration of touching objects and placing them in mouths; this information will be adapted from the Exposure Factors Handbook (EPA, 2011b).

I-4 Other Parameters Being Considered

Additional default parameters used in EPA's Standard Operating Procedures for Residential Pesticide Exposure Assessment (EPA, 2012c), EPA's SHEDS model (EPA, 2008b), or contained within the Transfer Efficiency Database (Gorman, 2012) could also be considered. Measured data is preferred over defaults.

I-5 Method to Combine Exposure Data

The variables used to estimate exposures could be considered in a deterministic way, assigning a fixed variable representative of high-end or central-tendency exposures (EPA, 2012c). These variables could also be considered in a probabilistic manner by sampling from distributions (EPA, 2008b; Ozkaynak et al., 2011).

I-6 Confidence and Uncertainty in the Available Data

A variety of the parameters to be included in any modeling are highly variable and some may be data poor.

The potential for exposure may increase under the following circumstances: (1) if routine contact and close proximity with the product is expected; (2) if the product contacts liquid; (3) if the product is often warm or hot; or (4) if very young children use or are frequently near such products (Gallen et al., 2014).

Appendix J Dose-Response Assessment for Cancer Endpoints

The data from NTP (2014a) described in Appendix G were used to develop a dose-response relationship using linear low-dose extrapolation.

J-1 Choice of Model, Points of Departure and Oral Slope Factors

The CARC recommended a model that uses low dose linear extrapolation[20] for quantification of human risk from TBBPA (CARC, 2014). EPA/OPPT agrees that using a linear low-dose model is most appropriate because there are limitations that preclude a clear understanding of TBBPA's MOA in relation to the observed tumors. If TBBPA acts via a non-linear/threshold mechanism, the use of linear low dose extrapolation will over-predict cancer risk.

EPA/OPPT modeled the dose response for uterine tumors and for hemangiomas and hemangiosarcomas using a cancer multistage model (EPA, 2012a), with linear extrapolation at low doses as recommended by EPA (2005) to determine the point of departure — the 90% lower bound benchmark dose (BMDL). Using the BMDL, two slope factors were calculated for females using the following data: 1) combined incidence of all uterine tumors of epithelial origin (adenocarcinomas, adenomas and malignant mixed Müllerian tumors); and 2) uterine adenocarcinomas only. Likewise, two slope factors were calculated for males: 1) the combined incidence of hemangiomas or hemangiosarcomas; and 2) hemangiosarcomas only (Hummel, 2013b, 2014). Table_Apx J-1 lists BMDs, BMDLs and slope factors.

Based on recommendations from EPA (2005) and EPA (2012a), EPA/OPPT used the dose associated with a 10% extra cancer risk as the point of departure to model the TBBPA tumor data.

The oral slope factor, which approximates a 95% confidence limit, is the upper bound on increased cancer risk from a lifetime of oral exposure to a chemical and is usually expressed as a proportion of the population affected per mg of the chemical per kg-bw/day (EPA, 2011c). The oral slope factor can also be used to determine the extra lifetime risk that an individual may develop cancer. In the TBBPA assessment, EPA/OPPT will use the slope factor to calculate individual risk.

The slope factor for the risk of developing tumors was calculated using the following equation:

Equation 1 $SF_{(human, daily)} = 0.1/(BMDL_{(animal, 10\% extra risk)} * DAF * 5/7)$

Where:

$SF_{(human, daily)}$ = slope factor expressing the extra lifetime risk (mg TBBPA/kg-bw/day)$^{-1}$
0.1 = benchmark response level (10%)
BMDL = lower 90% confidence bound on the benchmark dose
DAF = dosimetric adjustment factor = $(BW_{animal}/BW_{human})^{(1/4)} = 0.24$

[20] The CARC recommended the Q1* for modeling (CARC, 2014), but EPA/OPPT used a multistage model according to more recent EPA recommendations (EPA, 2012a).

5/7 = conversion from NTP (2014a) dosing of 5 days/week to 7 days/week exposure (this factor is used only for the general population exposures)

Table_Apx J-1: Parameters Used in Dose-Response Equations

	$BMDL_{(animal, 10\% extra risk)}$ mg/kg-bw/day	$BMDL_{(10HED)}$[a] mg/kg-bw/day	$SF_{(human, daily)}$ $(mg/k\text{-}bw/day)^{-1}$
Tumors in Females			
Uterine tumors (combined)	177	42.6	0.00329
Uterine adenocarcinomas	191	45.9	0.00305
Tumors in Males			
Hemangiosarcomas and hemangiomas	216	51.8	0.00270
Hemangiosarcomas	200	48.0	0.00292

Sources: Hummel (2013b); Hummel (2014)

$BMDL_{(10HED)} = BMDL_{(animal, 10\% extra risk)} * DAF$

Further work will be needed to determine factors to account for the amount of inhaled particulates that might be swallowed/absorbed. The European Union suggested that 70% of inhaled particulates might be swallowed (EC, 2006). EPA/OPPT has not yet determined a value for the proposed assessment.

J-2 Calculation of Target Risk Levels

The slope factor can be used to calculate a TBBPA dose associated with three target risk levels:

Equation 2 $$\frac{\mathrm{SF(human,daily)}}{(1\ mg\ TBBPA\ per\ kg\ per\ bw\ per\ day)} = \frac{RL}{x}$$

Where:

$SF_{(human, daily)}$ = extra lifetime risk per 1 mg TBBPA/kg-bw/day from Eq. 1

RL = target risk level (1/10,000; 1/100,000; or 1/1,000,000)

x = the daily dose associated with the chosen target risk level (mg/kg-bw/day)

The relationship can be rearranged to solve for x for any target risk level:

$$x = \frac{RL * 1\ mg\ TBBPA\ per\ kg\ per\ bw}{\mathrm{SF(human,daily)}}$$

Resulting doses associated with the three risk levels are listed in Table_Apx J-2.

Table_Apx J-2: Doses (in mg/kg-bw/day) Associated with Three Target Risk Levels

	Target Risk Level		
	1×10^{-6}	**1×10^{-5}**	**1×10^{-4}**
Uterine tumors (combined)	0.000304	0.00304	0.0304
Uterine adenocarcinomas	0.000328	0.00328	0.0328
Hemangiosarcomas and hemangiomas	0.000370	0.00370	0.0370
Hemangiosarcomas	0.000343	0.00343	0.0343

J-3 Key Sources of Uncertainty

J-3-1 Tumors Modeled

NTP concluded that for hepatoblastomas in male mice, there is some evidence of carcinogenic activity that can be attributed to TBBPA. Thus, EPA/OPPT investigated possible dose-response relationships using the cancer multistage model and other models. The effects at 250 and 500 mg/kg-bw/day were statistically significantly different from controls using pairwise comparisons ($p < 0.05$). Furthermore, the data showed a statistically significant dose-related trend using the one-sided Cochran-Armitage trend test ($p < 0.05$). However, the data did not provide a good fit using the cancer multistage model (Hummel, 2013b), and none of the other models available in the benchmark dose response modeling software resulted in goodness of fit p-values at acceptable levels of > 0.1 when considering the full shape of the dose-response curve (Hummel, 2013a). Thus, this tumor type cannot be considered in a quantitative risk assessment of TBBPA.

J-3-2 Use of Linear Low-Dose Extrapolation

The CARC noted that according to the IPCS MOA framework (IPCS, 2007), data are not adequate to draw conclusions about the mode(s) of action for the tumor incidence associated with TBBPA. Therefore, as recommended by EPA (2005), linear low dose extrapolation was used as the default option for modeling tumor data.

There are several reasons that a non-linear mode of action could explain the relationship between TBBPA and tumor incidence. EPA/OPPT and the CARC determined that a direct genotoxic MOA for tumorigenesis is unlikely. In addition, uterine tumors might be a result of TBBPA's competitive binding of enzymes involved in the conjugation of endogenous estrogens or TBBPA's enzyme inhibition; any resulting higher estrogen levels might lead to tumors only after a threshold dose of TBBPA is achieved. Furthermore, if damage to DNA occurs from the generation of reactive oxygen species (e.g., as a result of metabolism of TBBPA), such damage may also lead to tumor formation via a non-linear MOA.

J-3-3 Choice of Dose-Response Model

Cancer multistage models were chosen for modeling based on adequate fits for two tumor types and biological considerations even though other models also resulted in adequate fits of the data.

Appendix K EU and Canada Risk Assessments: Specific Evaluations Consulted for Current Assessment

Some of the more detailed evaluations of the EU and Canadian risk assessments that were considered during problem formulation are described below.

K-1 EU Calculations of TBBPA Uptake from Soil Near Manufacturing and Processing Sites

The European Union (EU) human health risk assessment of TBBPA (EC, 2006) estimated risks used a log K_{OW} of 5.9 and a K_{OC} of 49,726 L/kg to calculate uptake of TBBPA from soil to plants and livestock for several manufacturing (and processing) scenarios. Resulting estimates of dietary intake ranged from 1.7×10^{-5} to 2.92 mg/kg-bw/day, with the highest value estimated at sites where TBBPA is used as an intermediate in the production of TBBPA derivatives. The next highest estimate was 2.33 mg/kg-bw/day for individuals living near manufacturing facilities.[21] EPA/OPPT does not plan to use log Kow or Koc values based on the potential for predict uptake that is higher than actual uptake to plants/livestock.

K-2 EU Environmental Assessment at Processing Sites

The EU risk assessment for the environment evaluated processing sites and a discussion of their analysis and applicability to the current TBBPA assessment is described below.

K-2-1 Acrylonitrile Butadiene Styrene (ABS) Compounding Sites

Although the EU found risks at processing sites, the generic scenarios used in the EU risk assessment for ABS compounding facilities would not readily apply to United States facilities that process TBBPA because reported release information from TRI differs from the release assumptions used by the EU.

Using two approaches, the EU concluded that environmental risks are possible at ABS (plastic) compounding sites that use TBBPA as an additive flame retardant (EC, 2008):

- a generic scenario evaluation based on flame retardant use in polymers with some TBBPA-specific data using certain worst-case assumptions and
- a site-specific evaluation using monitored emissions data from a single site.

For the generic approach, the EU used default release estimates and several worst-case assumptions. The largest releases were TBBPA dust losses from raw materials handling and other particulate releases, which eventually went to wastewater.

[21]These two highest values reported in the EU risk assessment were used only as examples because the EU doesn't produce TBBPA or its derivatives (EC, 2006).

In addition to these more generic scenarios, the EU monitored TBBPA emissions from one ABS compounding site and identified risks for aquatic, sediment- and soil-dwelling organisms. The EU specifically stated that air emissions led to risks for soil-dwelling organisms. The site-specific monitoring information is confidential, however. Therefore, the amount of TBBPA emitted and the types of emissions (i.e. whether there were also releases to land and water in addition to air releases) are not known (EC, 2008).

For all years of TBBPA reporting to TRI, the largest amount transferred to WWTPs occurred in 2003, when 152 pounds (all facilities) were released to wastewater. In nine of the reporting years (2000-2002; 2007-2012), 10 or fewer pounds of TBBPA were sent to wastewater treatment plants (WWTPs). Facilities reported minimal direct releases to surface water. The highest value was 71 pounds in 2003 (EPA, 2012e). Thus, assumptions related to releases differ significantly between the European Union and the United States.

In the United States during 2012, six facilities were identified in the category of plastics and rubber facilities (NAICS code 326), the category that would include ABS compounding sites. One of these facilities reported 33 pounds as fugitive air emissions. Four of the facilities disposed a total of 154 pounds of TBBPA to "other landfills." No other releases (including stack air releases) were reported for these facilities. Similar emissions were reported for facilities within this industry category in previous years. Between 2000 and 2012, the highest fugitive air emissions for a single facility was 37 pounds, in 2010 (EPA, 2012e). Thus, for similar types of processing plants as those evaluated by the EU, only limited emissions have been reported to TRI for US facilities.

Overall, both the types and amounts of emissions reported for these facilities differ between the EU and the United States. Unlike the releases reported in the EU analysis for the ABS compounding sites, releases reported by US plastics and rubber facilities to TRI are not expected to result in environmental risks.

K-2-2 ABS Conversion Sites and Epoxy Resin Manufacturing Facilities

The EU risk assessment also found risks for soil-dwelling organisms surrounding facilities that manufacture epoxy and/or polycarbonate resins and at ABS conversion sites. However, these risks were found for situations where sludge is generated/applied to agricultural land. The EU notes that when these activities were taken into account, risks were not identified for these generic scenarios. Furthermore, the EU did not identify environmental risks when using actual site-specific data at eight epoxy resin manufacturers and at two sites using TBBPA in reactive flame retardant applications (EC, 2008).

US facilities have reported minimal TBBPA releases to surface water and WWTPs as stated above. Also, no releases were reported to land treatment (EPA, 2012e).

K-2-3 EPA's Conclusion for Processing Sites

When considering ABS compounding sites (reactive uses), TRI reporting shows that plastics and rubber facilities reported minimal air emissions and no other releases of note.

Other processing sites in the United States have reported higher stack air releases. However, given that these are a small proportion of the air emissions from the top manufacturing site, EPA/OPPT did not further evaluate these releases.

For manufacturing epoxy and polycarbonate resins and ABS conversion sites, measured data for the ten surveyed sites in the EU risk assessment showed low risks. Although some risks were identified in generic scenarios in the EU risk assessment, TRI data indicate minimal or no releases from such processing sites in the United States.

K-2-4 Canada's Fugacity-Based Model of Sludge Applied to Land

The Canadian government (EC/HC, 2013) ran a fugacity-based model to estimate risks from TBBPA in sludge applied to land. Using different assumptions from those used in EPA/OPPT's preliminary calculation (but similarly using a high-end TBBPA sludge concentration), risks to soil organisms were determined to be low (EC/HC, 2013). Although EPA/OPPT doesn't use these fugacity-based models when estimating exposure, these results support EPA/OPPT's preliminary calculation for this pathway.