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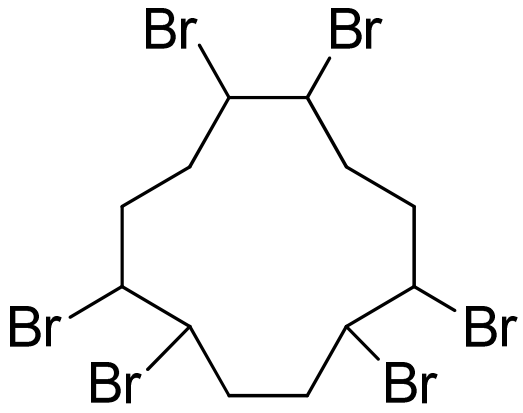
Office of Chemical Safety and
Pollution Prevention

TSCA Work Plan Chemical
Problem Formulation and Initial Assessment

Cyclic Aliphatic Bromides Cluster
Flame Retardants



CASRN	NAME
25637-99-4	Hexabromocyclododecane
3194-55-6	1,2,5,6,9,10-Hexabromocyclododecane
3194-57-8	1,2,5,6-Tetrabromocyclooctane

August 2015

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AUTHORS / CONTRIBUTORS / ACKNOWLEDGEMENTS

This report was developed by the United States Environmental Protection Agency (US EPA), Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (OPPT). The Work Plan Chemical Problem Formulation for the cyclic aliphatic bromides cluster was prepared based on currently available data. Mention of trade names does not constitute endorsement by EPA.

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Docket
Please visit the public docket (Docket: EPA-HQ-OPPT-2015-0081) to view supporting information.

ABBREVIATIONS

BFR	Brominated Flame Retardant
CASRN	Chemical Abstract Service Registry Number
CBI	Confidential Business Information
CDR	Chemical Data Reporting
CEC	Commission for Environmental Cooperation
CPSC	Consumer Product Safety Commission
EC	European Commission
ECHA	European Chemicals Agency
EFAST	Exposure and Fate Assessment Screening Tool
EPA	Environmental Protection Agency
EPS	Expanded Polystyrene
EU	European Union
FR	Flame Retardant
GD	Gestation Day
GLP	Good Laboratory Practices
HBCD	Hexabromocyclododecane
HIPS	High Impact Polystyrene
HPV	High Production Volume
HQ	Hazard Quotient
IRIS	Integrated Risk Information System
IUR	Inventory Update Reporting Rule
kg	Kilogram(s)
K_{ow}	Octanol:Water partition coefficient
lb	Pound
LOEL	Lowest Observed Effect Level
Log K_{ow}	Logarithmic Octanol:Water partition coefficient
mg	Milligram(s)
MOE	Margin of Exposure
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NKRA	Not Known or Reasonably Ascertainable
NOAEL	No-observed-adverse-effect level
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
PBT	Persistent, Bioaccumulative and Toxic
pg	picogram
PMN	Premanufacturing Notice
PS	Polystyrene

PV	Production Volume
PVC	Polyvinylchloride
RA	Risk Assessment
RAR	Risk Assessment Report
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SNUR	Significant New Use Rule
SVOCs	Semi-volatile organic chemicals
TSCA	Toxic Substances Control Act
TG	Test Guideline
US	United States
WHO	World Health Organisation
WWTP	Wastewater Treatment Plant
XPS	Extruded polystyrene
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 and initial assessment for the cyclic aliphatic bromides cluster as part of the TSCA Work Plan.

EPA/OPPT has identified a cluster of cyclic aliphatic bromide flame retardant chemicals, including, hexabromocyclododecane (HBCD; CASRN 25637-99-4), 1,2,5,6,9,10-hexabromocyclododecane (1,2,5,6,9,10-HBCD; CASRN 3194-55-6) and 1,2,5,6-tetrabromocyclooctane (CASRN 3195-57-8), for risk assessment. These three chemicals have similar physical and chemical properties, and environmental fate characteristics. Uses for 1,2,5,6-tetrabromocyclooctane have not been identified; the remaining two members of the cluster are used as flame retardants in polystyrene foams. HBCD and 1,2,5,6,9,10-HBCD have similar toxicological properties: known effects on the liver and reproductive system.

For the purposes of this assessment, the use of "HBCD" refers to either CASRN (25637-99-4 or 3194-55-6), or both. In addition, the conclusions drawn for this assessment will be applicable to both CASRNs.

The conclusions from this problem formulation and initial assessment are that EPA/OPPT will evaluate current risk assessments, and if needed, conduct additional analyses as follows:

- Workers: Evaluate the applicability of data from published risk assessments to US occupational exposure scenarios to determine if further assessment is needed. If the available data are not applicable, develop estimates of occupational exposures based on modeling and assumptions (e.g. approaches used in the new chemicals program).
- General population and biota (aquatic, terrestrial and avian): Estimate releases to the environment in the US to evaluate potential exposure of general population and biota (aquatic, terrestrial and avian) to HBCD. The estimation approach may be based on information in available assessments, coupled with US specific information and/or estimation methods and assumptions.
- Consumers: Use available or modeled data relevant to US exposure scenarios to estimate consumer exposure using available or modeled data relevant to US exposure scenarios with particular emphasis on sensitive populations.

Several scenarios were identified where exposure to HBCD is expected to be low or unknown and further analysis is not recommended by EPA/OPPT under TSCA:

- General population and environmental exposure from HBCD in landfills is not being assessed due to uncertainties in release from these sites.

- General population exposure from HBCD in drinking water is not being assessed because drinking water monitoring data for the US are not available and conclusions from available risk assessments indicate a low concern from this exposure pathway (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012).

- Consumer exposure to HBCD in High Impact Polystyrene (HIPS) is not being assessed because the level of HBCD in HIPS in the US is unknown, it is not used in typical consumer products (e.g. computer or TV chassis), its use in other consumer products (e.g. electrical appliances) is enclosed limiting potential exposure and a low risk to consumers was indicated in available risk assessments.

- Consumer exposure to HBCD in textile finishings is not being assessed because it was considered low risk by the CPSC in upholstered furnishings (CPSC, 2001), it was not reported to be used in consumer fabrics or textiles in the 2012 CDR (EPA, 2012a) and the extent of institutional (e.g. prisons), military or aviation use is unknown.

- There are no adequate toxicological data based on inhalation or dermal exposures, nor is there a PBPK model readily available for route-to-route extrapolation. Therefore EPA/OPPT will not assess inhalation or dermal contact in this assessment. However, EPA is considering the quantification of incidental ingestion of particulates that would result from exposure to HBCD dust in occupational settings. A similar approach will be used to address consumer exposure to HBCD in dust.

- There are no adequate lifetime exposure or carcinogenicity studies for HBCD.

- Inhalation, dermal and lifetime exposure assessments are data gaps that add uncertainty to EPA's risk assessment of HBCD.

Hexabromocyclododecane (HBCD) has been used as a flame retardant in plastics (additive) and textiles (backcoating) since the 1980s. Evidence suggests that HBCD is bioaccumulative, environmentally persistent and toxic. Consequently, risk to human health and the environment have been assessed by several countries and global organizations. In 2010, OPPT prepared an action plan for HBCD. Subsequently, HBCD has been nominated for listing on the Toxic Releases Inventory (TRI; in review 2014) and EPA proposed a significant new use rule (SNUR) for use in consumer textiles (EPA, 2012e).

During problem formulation, EPA/OPPT identified available fate, exposure and hazard data, and characterized potential exposures, receptors and effects. Data adequacy was determined by

following published EPA/OPPT criteria[1]. EPA/OPPT reviewed the public literature (nominally to September 2014) and Agency information sources (public and confidential) to explore the sources, pathways, receptors and effects for consideration in the assessment. EPA also identified areas of data uncertainty and assumptions.

Likely sources and pathways considered for analysis include: use of HBCD as a flame retardant in expanded polystyrene foam (EPS) and extruded polystyrene foam (XPS) in the building and construction industry accounting for 95% of HBCD use mainly in the form of insulation boards. The remaining uses are for high impact polystyrene (HIPS), mainly used for electronics, appliances and possible HBCD-containing textiles for institutional (e.g. prisons), military and aviation uses only (EPA, 2012e). HBCD is not used in consumer textiles that are manufactured in or imported into the US except for limited uses in certain automotive textiles.

As outlined in the Conceptual Model for HBCD (Figure 2-1) EPA/OPPT identified the relevant TSCA use of HBCD for this assessment as its use as flame retardants in EPS and XPS products found in commercial and residential environments. EPA/OPPT determined that the major source of exposure to HBCD for human health and the environment was via HBCD dust and/or HBCD in dust generated during the manufacture and processing of HBCD, and the processing and use of products containing HBCD. HBCD in the form of dust or attached to particulates has been measured in indoor domestic and commercial environments, therefore there may be risks to consumers. Preliminary exposure calculations for the US population suggest that the methodology used in available assessments underestimates consumer exposure to HBCD from dust for US consumers. Of particular interest for evaluation are toddlers whose exposure to HBCD from dust in non-residential microenvironments contributes to their total HBCD exposure (Abdallah and Harrad, 2011). HBCD may also make its way into the outdoor environment by transportation through the air and/or washed down the drains (or storm drains) to enter waterways.

These exposure scenarios have been considered in risk assessments conducted by other countries and the toxicity and risk of HBCD to aquatic organisms and human health have been assessed and summarized in several publications (EC, 2008; Environment CA and Health CA, 2011; EPA, 2008a, 2014b; NICNAS, 2012; OECD, 2007). However, it is unknown how these conclusions apply to current HBCD manufacture, processing, use and exposure in the US. Therefore, EPA plans to evaluate information in the non-US published risk assessments to determine whether data from other countries are relevant and applicable to US exposures, and where appropriate, supplementing these risk assessments with current and US specific information.

[1] Generally followed guidance outlined for the High Production Volume Challenge Program at: http://www.epa.gov/chemrtk/pubs/general/datadfin.htm and http://www.epa.gov/champ/pubs/hpv/Methodology%20for%20HBP%20under%20ChAMP_March%202009.pdf and EPA Risk Assessment Guidance at: http://www.epa.gov/raf/

The results of problem formulation as illustrated in the conceptual model and described under the assessment questions indicate that:

- There is the potential for occupational exposure to HBCD during HBCD manufacture and processing and polystyrene foam manufacture and processing.
- There is potential for general population exposure to HBCD from releases to the environment (air, water, soil and fish consumption).
- There is potential for environmental exposure in water, sediment and soil to HBCD from releases to the environment.
- There is potential for consumer exposure to HBCD from the use of consumer products in indoor environments.

In summary, as a result of problem formulation, EPA/OPPT plans to evaluate current risk assessments and conduct additional risk analysis on potential worker, general population, consumer and environmental exposures under the TSCA Existing Chemicals Program using existing data and methods. EPA/OPPT plans to review and evaluate available exposure (See Section 2.4 and Appendix C) and hazard benchmarks (Section 2.5, Appendix D and Appendix E) and to evaluate the potential non-cancer risk to humans using a margin of exposure approach and potential risks to environment using a hazard quotient approach.

1 INTRODUCTION

As a part of EPA's comprehensive approach to enhance the Agency's management of existing chemicals, in March 2012 EPA/OPPT identified a work plan of chemicals for further assessment under the Toxic Substances Control Act (TSCA)[2]. After gathering input from stakeholders, EPA/OPPT 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, the Cyclic Aliphatic Bromides Cluster, specifically hexabromocyclododecane (HBCD), was identified for assessment based on its high production volume and PBT characteristics (persistent, bioaccumulative and toxic).

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 HBCD. The information presented in the risk assessment may be of assistance to

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

other federal, state, and local agencies as well as to members of the general public who are interested in the risks of HBCD.

The initial step 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 and initial assessment for HBCD. During problem formulation, EPA/OPPT identified available exposure and hazard data, and characterized potential exposures, receptors and effects. EPA/OPPT developed a conceptual model (Figure 2-1) and analysis plan (Section 2.6.2) as a result of problem formulation.

1.1 Scope of the Assessment

The members of the cyclic aliphatic bromides cluster are the brominated flame retardants (BFR): Hexabromocyclododecane (**HBCD**; CASRN 25637-99-4)
1,2,5,6,9,10-Hexabromocyclododecane (**1,2,5,6,9,10-HBCD**; CASRN 3194-55-6)
1,2,5,6-Tetrabromocyclooctane (CASRN 3194-57-8)[4]

EPA prioritized the different BFR chemicals and grouped them into different clusters based on structure. The cyclic aliphatic bromide cluster included chemicals that contain a ring of 6 to 12 saturated carbon atoms with different bromine atoms replacing some of the H atoms on the ring or attached in sidechains.

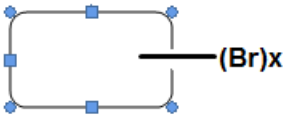


Figure 1-1: Generic Structure of Cyclic Aliphatic Bromides

Chemicals considered for this cluster were: 1,2-Dibromo-4-(1,2-dibromoethyl) cyclohexane [CASRN: 3322-93-8], 1,2,3,4,5,6-hexabromocyclohexane [CASRN: 1837-91-8], 1,2,3,4,5-Pentabromo-6-chlorocyclohexane [CASRN: 87-84-3] and 1,2,5,6-tetrabromocyclooctane [CASRN: 3194-57-8]. One other chemical, Accession number 27248, with generic name polybromocycloalkane would be a member of this Work Plan of chemicals; however, no

[4] No domestic uses were identified for 1,2,5,6-Tetrabromocyclooctane (CASRN 3194-57-8). This flame retardant is not functional in current EPS and XPS manufacturing processes. Its thermal stability does not meet operating temperature requirements for the manufacture of XPS foam (EPA, 2014b).

production volume has been reported since 1977. Therefore, these chemicals were rejected, along with the individual 1,2,5,6,9,10-HBCD diastereomers, because they were either not on the TSCA Inventory or were not manufactured at sufficient production volume to be reported in the IUR/CDR data collection.

Two HBCD commercial chemicals meet this cluster criteria and are the subject of this assessment. These are the only two chemicals being considered for problem formulation in this work plan which differs from the action plan (EPA, 2010a) inclusion criteria.

- Hexabromocyclododecane [CASRN 25637-99-4] is produced as a mixture of 16 possible isomers of 1,2,5,6,9,10-hexabromocyclododecane from the bromination of 1,5,9-cyclododecatriene. HBCD is the only member of this cluster that is on the TSCA Inventory that has a significant production volume (as reported in the IUR and CDR).

- 1,2,5,6,9,10-hexabromocyclododecane [CASRN 3194-55-6] is a mixture of three main diastereomers of the 16 possible 1,2,5,6,9,10-hexabromocyclododecane isomers. Each individual isomer in this HBCD cluster member contains a ring of 12 saturated carbon atoms with 6 bromine atoms replacing 6 hydrogen atoms. Each isomer has a molecular formula of C12H18Br6. The three most common individual diastereomers are designated as alpha-, beta-, and gamma-HBCD and each has an individual CAS Registry Number (as do all 16 isomers)[5].

For the purposes of this assessment, the use of "HBCD" refers to either CASRN (25637-99-4 and 3194-55-6), or both. In addition, the conclusions drawn for this assessment will be applicable to both CASRNs.

Section 2.6.1 presents the conceptual model developed by EPA/OPPT for HBCD. Using available tools and approaches, the Agency identified the relevant TSCA use of HBCD for this assessment is its use as flame retardants in EPS and XPS products found in commercial and residential environments. Its use in HIPS is not being assessed because the level of HBCD in HIPS in the US is unknown, it is not used in typical consumer products (e.g. computer or TV chassis), its use in other consumer products (e.g. electrical appliances) is enclosed limiting potential exposure and a low risk to consumers was indicated in available risk assessments. Consumer exposure to HBCD in textile finishings is not being assessed because it was considered low risk by the CPSC in upholstered furnishings (CPSC, 2001), it was not reported to be used in consumer fabrics or textiles in the 2012 CDR (EPA, 2012a) and the extent of institutional (e.g. prisons), military or aviation use is unknown (EPA, 2012e).

EPA determined that the major source of exposure to HBCD for human health and the environment was via HBCD dust and/or HBCD in dust generated during the manufacture and processing of HBCD, and the processing and use of products containing HBCD. HBCD in the form of dust or attached to particulates has been measured in indoor domestic and commercial

[5] This is significant because much of the data are reported for the individual alpha, beta, and gamma isomers rather than for the two commercial products.

environments, therefore there may be risks to consumers. Preliminary exposure calculations for the US population suggest that the methodology used in available assessments underestimates consumer exposure to HBCD from dust for US consumers. Of particular interest for evaluation are toddlers whose exposure to HBCD from dust in non-residential microenvironments contributes to their total HBCD exposure (Abdallah and Harrad, 2011). HBCD may also make its way into the outdoor environment by transportation through the air and/or washed down the drains (or storm drains) to enter waterways.

These exposure scenarios have been considered in risk assessments conducted by other countries and the toxicity and risk of HBCD to aquatic organisms and human health have been assessed and summarized in several publications (EC, 2008; Environment CA and Health CA, 2011; EPA, 2008a, 2014b; NICNAS, 2012; OECD, 2007). However, it is unknown how these conclusions apply to current HBCD manufacture, processing, use and exposure in the US. Therefore, EPA plans to evaluate information in the non-US published risk assessments to determine whether data from other countries are relevant and applicable to those in the US, and where appropriate, supplement these risk assessments with current and US specific information.

1.2 Regulatory and Assessment History

The regulatory and assessment history of HBCD in the US and internationally are summarized in Table_Apx A-1.

United States - National

HBCD was sponsored in the HPV Challenge Program by BFRIP (BFRIP, 2001). Subsequently, EPA/OPPT prepared a risk based prioritization document in 2008 (EPA, 2008a) which concluded that there was a high concern for potential risk to aquatic organisms, a medium concern for potential risk to the general population from environmental releases and a high concern for potential risk to workers, consumers and children. In 2010, EPA/OPPT prepared an action plan for HBCD (EPA, 2010a). Subsequently, HBCD has been nominated for listing on the Toxic Releases Inventory (TRI; in review 2014) and is subject to rulemaking for use in textiles (EPA, 2012e). In addition, OPPT/DfE (OPPT Design for the Environment) published a flame retardant alternatives assessment for HBCD in 2014 (EPA, 2014).

HBCD is currently on the EPA Integrated Risk Information System (IRIS) program agenda. The anticipated date for a completed assessment has not yet been determined (EPA, 2015c). HBCD is not regulated in drinking water under the National Primary Drinking Water Regulations (EPA, 2015b) and is not on the Contaminant Candidate List (CCL) (EPA, 2015a). Published risk assessments indicate low risk to the general population from drinking water exposure (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012). HBCD is under consideration for inclusion in the NHANES human bio-monitoring program.

In 2006, the Consumer Product Safety Commission (CPSC) assessed the risk of exposure to HBCD in residential upholstered furniture (CPSC, 2001) and concluded that HBCD did not present a hazard to consumers, as defined by the Federal Hazardous Substances Act (FHSA).

The Occupational Safety and Health Administration (OSHA) has not established occupational exposure limits for HBCD.

United States – States

In California, HBCD is listed as an initial informational candidate under California's Safer Consumer Products regulations (DTSC, 2010), on the state's Proposition 65 list (OEHHA, 2007) and is designated a priority chemical for biomonitoring; however, California has not yet started biomonitoring HBCD (SGP, 2014). In Maine, Minnesota and Washington, HBCD is considered a chemical of high concern (DEP, 2013; MDH, 2013; WSDE, 2013). Oregon considers HBCD a priority persistent pollutant (DEQ, 2010a, 2011) and publishes use, exposure pathways and release data for HBCD under this program (DEQ, 2010b).

International

HBCD is of international concern because of its PBT properties. The toxicity of HBCD to aquatic organisms and human health have been assessed and summarized in several publications (EC, 2008; Environment CA and Health CA, 2011; EPA, 2008a, 2014b; NICNAS, 2012; OECD, 2007). HBCD was added to ECHA's list of Substances of Very High Concern (SVHCs) on October 28, 2008 (ECHA, 2008). Risk assessments have been published by Australia (NICNAS, 2012), Canada (Environment CA and Health CA, 2011) and the European Union (EC, 2008). The conclusions from these assessments are as follows:

Occupational, General Population and Consumer Exposure
In the Health Canada assessment, the margin of exposure for neurobehavioral effects in infants and children was determined using the LOAEL (0.9 mg/kg-day) from a 90-day study in mice (Eriksson et al., 2006) (Environment CA and Health CA, 2011). This study was not used by the European Commission or the Australian Government (EC, 2008; NICNAS, 2012). For reproductive effects, all three assessments used the NOAEL (10 mg/kg-day) from the two-generation study in rats (Ema et al., 2008). In addition, the European Commission used the NOAEL (22.9 mg/kg-day) from the 28-day study in rats (van der Ven et al., 2006). All three risk assessments concluded that the risk to general population and consumers was of low concern. The occupational risk conclusions vary in different countries due to variations in exposure (e.g. HBCD is not manufactured in Australia) and the risk varies with the activity associated with the extent of exposure to HBCD; low to high, depending on the activity relevant to each country.

Environmental Exposure
HBCD is persistent and bioaccumulative and is considered a risk to the environment in all three published risk assessments (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012). In May 2013, HBCD was added to the United Nation's Stockholm Convention list of Persistent

Organic Pollutants (Stockholm Convention, 2013). The chemical is scheduled to be eliminated by November 2014 with specific exemptions for production and uses in expanded or extruded polystyrene building insulation. As required by the convention, parties that use these exemptions must register with the secretariat and the exemptions will expire in November 2019.

Currently, under the Commission for Environmental Cooperation (CEC), Canada, Mexico and the US are evaluating the presence and migration of flame retardants, including HBCD, from consumer products (CEC, 2015). The information gathered from this effort will inform exposure assessors and risk managers and the executive summary of the final report(s) will be available to the public.

2 PROBLEM FORMULATION

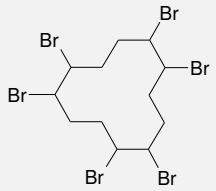
Problem formulation aims to determine the major factors to be considered in an assessment, including exposure pathways, receptors and health endpoints (EPA, 1998a, 2014c). Accordingly, this problem formulation summarizes the exposure pathways, receptors and health endpoints EPA/OPPT considered to determine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

The outcome of this evaluation is summarized in a conceptual model (Figure 2-1) that illustrates the exposure pathways, receptors and effects that were considered for potential risk assessment. An analysis plan is developed if the results of problem formulation indicate the need for further analysis.

2.1 Physical and Chemical Properties

The physical-chemical properties of HBCD are shown in Table 2-1. Commercial preparations of HBCD may contain some impurities, such as tetrabromocyclododecene or other isomeric HBCDs (UNEP, 2010) which are not separately included in this problem formulation.

Table 2-1: Select Physical-Chemical Properties *

Properties [a]	 **1,2,5,6,9,10-Hexabromocyclododecane HBCD**
Melting Point	175 – 195 °C
Boiling Point	> 200 °C [decomposes] [b]
Vapor Pressure	6.27 E-5 Pa at 21°C
Water Solubility	66 µg/L at 20°C [c]
Octanol Water Partition Coefficient (Log K_{ow})	5.625 at 25 °C

*PCHEM Properties reported in the HPV Robust Summary (BFRIP, 2001) are measured values from a composite of commercial products from 3 different manufacturers.
[a]HPV Data Summary and Test Plan for Hexabromocyclododecane (HBCD) CASRN 3194-55-6
[b]EC HBCD RAR (EC, 2008)
[c]Sum of solubilities for 3 major isomers [alpha, beta, and gamma] in commercial product (ECHA, 2008)

2.2 Production Volume and Uses

This section discusses the production volume and uses of the cyclic aliphatic bromides cluster chemicals and is organized as follows:

- The 2012 Chemical Data Reporting (CDR) production, import, and export volumes for these chemicals are listed in Appendix B.
- Additional details on production volume for HBCD can be found in Section 2.2.1.
- Use information can be found in Section 2.2.2.
- Future market trends are discussed in Section 2.2.3.

2.2.1 Production Volume

EPA/OPPT's 2012 public Chemical Data Reporting (CDR) database (EPA, 2012a), formerly the Inventory Update Reporting (IUR) database includes national-level production volume data; however, the 2012 public CDR database provides limited information on the domestic production volumes of HBCD. For both CAS numbers, site-specific production volumes and national level production volumes were withheld as TSCA Confidential Business Information (CBI) for the 2011 reporting year (EPA, 2012a). Therefore, EPA/OPPT proposes to assess the production volume of HBCD based on the best publicly available production volume data which is the historical IUR and CDR data presented in Appendix B . EPA/OPPT assumes that current

production volumes are equal to the most recently reported production volumes (the 2002 and 2006 data for CASRNs 25637-99-4 and 3194-55-6, respectively).

For the 2011 reporting year, the data indicate that two sites currently import at least one of the chemicals and that three sites domestically manufacture the chemicals. However, according to the US International Trade Commission, the US imported 92,270 pounds of HBCD (CASRN 25637-99-4) in 2012 (USITC, 2013). This volume does not include HBCD imported as part of an article. Three sites reported export volumes as CBI, and two sites reported no exports (EPA, 2012a).

Five sites are identified by the 2012 CDR database as manufacturers or importers of HBCD: BASF Corporation, Albemarle Corporation, The Dow Chemical Company, and two CBI sites (EPA, 2012a). Albemarle manufactures HBCD flame retardants under the Saytex®HP-900 trade name (Albemarle Corporation, 2000). Both Dow and BASF indicate in the CDR data that they are importers; however, trade names of the BASF or Dow Chemical products that use or contain HBCD could not be found in a literature search. For more detailed information on manufacturers of HBCD who reported for the 2012 CDR collection period, see Appendix B.

2.2.2 Uses

2.2.2.1 Use in Expanded Polystyrene Foam (EPS) and Extruded Polystyrene Foam (XPS)

HBCD is used as a flame retardant in polystyrene foam, textiles, and high impact polystyrene. The chemical has been in production since the 1960s although there is limited data about the historical use of HBCD in products.

The main use of HBCD in the US, the EU, Japan, and Switzerland is as a flame retardant in expanded polystyrene foam (EPS) and extruded polystyrene foam (XPS) (UNEP, 2010; Weil and Levchik, 2009). Use in EPS and XPS accounts for 95 percent of all HBCD applications and began in the 1980s (EPA, 2014b; UNEP, 2010). EPS and XPS are used in the US for thermal insulation boards and laminates for sheathing products used in the building and construction industry. In addition, EPS is used to provide protection from moisture, prevent freezing, provide a stable fill material, and create high-strength composites in construction applications. XPS foam board is used mainly for roofing applications and architectural molding. HBCD is used in both types of foams, because it is highly effective at low-use levels, and therefore maintains the insulation properties of the EPS and XPS foam (Morose, 2006). EPS boards contain approximately 0.5 percent HBCD by weight in the final product while XPS boards contain 0.5 to 1 percent HBCD by weight (Extruded Polystyrene Foam Association, 2011; Morose, 2006).

The National Institute of Heath's (NIH) Household Products Database lists HBCD as an ingredient in several extruded and foam insulation products, all of which are manufactured by Owens Corning for use in the US. Currently, Owens Corning lists HBCD in two of its products:

Foamular® Extruded Polystyrene Insulation and Foamular® Extruded Polystyrene Insulation - Zero Ozone Depletion Formula, at levels between 0.5 and 1.0 percent (Owens Corning, 2005).

The Australian Department of Health and Aging reports that EPS resins are also used in industrial packaging including packaging durable goods and beanbag fill (NICNAS, 2012). Historic data indicate that EPS was used in packaging in North America (Kinshore, 2007), however EPA/OPPT was unable to confirm if this is a current use of HBCD in the US. It should be noted that uses of polystyrene foam in consumer products, such as packaging, generally do not require the use of a flame retardant (EPA, 2014b).

2.2.2.2 Use in Textiles

In the US, HBCD was historically used as a flame retardant in the back coating of textiles. However, supported by information gathered from research, industry, and consumer product organizations, EPA/OPPT believes that HBCD is no longer used in consumer textile applications outside of the auto industry. EPA/OPPT received information from a group of textile formulators that the end uses of HBCD-containing textiles are for military, institutional, and aviation applications such as durable carpet tiles for hospitals or prisons (EPA, 2012e; Friddle, 2011). Use in this application is quite small; in 2005 only 1 percent of total production volume of HBCD was used in textiles in the US (EPA, 2012e). HBCD is typically found in textile back coatings at levels of 10-25 percent (Harscher, 2011).

In Europe, only 2 percent of HBCD was used in textile applications in 2007 (ECHA, 2009).

2.2.2.2.1 Use in Automotive Textiles

Within the US auto industry, EPA/OPPT found that a small amount of HBCD is used in floor mats, headliners, and possibly other interior fabrics in automobiles made or imported to the US (EPA, 2012e).

HBCD is currently regulated under Annex XIV of European Union's Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), which sets a "sunset date" for the use of the chemical of August 21, 2015. In response to the REACH regulation, the auto industry has formed a consortium to help US manufacturers understand the new requirements; develop tools, processes and best practices; and coordinate compliance efforts. The consortium consists of five North American sponsoring companies, Chrysler, Ford, General Motors, Honda, and Toyota (AIAG, 2011). It is likely that as companies discontinue the use of HBCD in European cars to comply with the REACH regulation, they will discontinue its use in North American automobiles as well.

2.2.2.2.2 Historic Use in Textiles

HBCD was historically used as a flame retardant in the US in the back-coating of textiles, upholstered furniture, draperies, wall coverings, and interior textiles such as roller blinds (ECHA, 2009; Morose, 2006). The majority of HBCD used in textiles was for upholstered furniture, because textiles treated with the chemical meet the stringent fire safety laws of the United Kingdom (UK) and California (Morose, 2006).

In the 2006 IUR data, one manufacturer/importer of HBCD (CASRN 3194-55-6) reported the use of the chemical substance under the NAICS code for textile and fabric finishing mills (EPA, 2006a). For this use, less than 1 percent of the total production volume of the chemical substance was in consumer and commercial products. The reporting does not distinguish between commercial and consumer use (EPA, 2006a).

EPA/OPPT conducted research to determine whether HBCD was used in textile applications for end products sold to consumers in the US. In 2010, an HBCD expert with the Consumer Product Safety Commission (CPSC) expressed to EPA/OPPT his understanding that HBCD is used only in non-consumer textiles such as firefighters' suits (EPA, 2012e). In 2011, EPA/OPPT requested information from current and former manufacturers of HBCD. The responses indicated that only one manufacturer sells HBCD for textile uses. The company did not know whether the end use of any of those textiles is a consumer article (EPA, 2012e). Additionally, a representative of the furniture manufacturing company Herman Miller told EPA/OPPT that HBCD is not in its products (EPA, 2012e). HBCD was not reported to be used in fabrics or textiles in the 2012 CDR (EPA, 2012a).

2.2.2.3 Use in High Impact Polystyrene (HIPS)

In both the US and Europe, HBCD is used as a flame retardant in high impact polystyrene (HIPS) for electrical and electronic appliances such as audio-visual equipment, refrigerator lining, and some wire and cable applications (ECHA, 2009; Morose, 2006). Use in television sets is the predominant application of HIPS (Weil and Levchik, 2009). HBCD is found in HIPS products in levels of 1-7% by weight (EC, 2008). Similar data for the US are not available.

2.2.2.4 Other Identified Uses

The Australian Department of Health and Aging also reports that minimal amounts of HBCD are imported into the country already incorporated into various articles such as inkjet printers, projectors, scanners, ventilation units for offices, compact fluorescent lights, and LCD digital audiovisual systems (NICNAS, 2012). There are no data to indicate that HBCD is used in the US for these uses.

2.2.2.5 Summary of All Uses

2.2.2.5.1 Summary of CDR Information

Appendix B summarizes the HBCD use data as reported in the 2012 CDR. This Appendix also presents information on potential end uses of the chemical beyond what is reported in the CDR. The information is based on additional sources as described in the preceding sections of the report.

2.2.2.5.2 Summary of EU Data

Table_Apx B-4 provides a summary of HBCD uses and potential end products as presented in the EU risk assessment report (EC, 2008). Although the EU market and industry for HBCD are considered to be similar to those in the US, differences do exist in building technologies, climate, and consumption patterns, limiting the comparison of the two markets.

2.2.3 Future Market Trends

EPA/OPPT expects future use of HBCD to decrease worldwide as the result of forthcoming international regulations. HBCD is listed under Annex XIV of European Union's REACH, which sets a "sunset date" for August 21, 2015. After this date, only persons with approved authorization applications may continue to use the chemical (BSEF, 2012). In addition, in May of 2013, the Conference of the Parties (COP) to the Stockholm Convention on Persistent Organic Pollutants (Convention) decided to list HBCD on the Convention's "elimination" annex, with specific exemptions for production and use for expanded polystyrene and extruded polystyrene in buildings for parties listed in the register of specific exemptions for the substance. The specific exemptions can last up to 5 years and, subject to approval by the COP, can be renewed for a period of up to 5 years. However, the US is not a party to the Stockholm Convention and therefore this action is not applicable to the US.

Given that HBCD is going to be phased out for some uses in the majority of the world, including the EU, Canada, Australia, and most of Asia, it is likely that global processors and users of HBCD will work towards phasing out the chemical rather than endure the cost of maintaining a separate supply chain for the US. It is expected that the Stockholm Convention may incentivize US processors, manufacturers, and importers to consider alternatives to HBCD for some applications, which may impact future demand growth for the chemical.

2.3 Fate and Transport

The environmental fate of HBCD has been summarized in several publications (EC, 2008; Environment CA and Health CA, 2011; EPA, 2008a, 2014b; NICNAS, 2012; OECD, 2007). A general overview of persistence and bioaccumulation is presented below. Additional details can be found in Appendix D.

HBCD is persistent in environmental media. It is expected to be stable to hydrolysis and direct photolysis. Measured aerobic biodegradation half-lives either range up to months, or are greater than months. Anaerobic biodegradation may be more rapid but in anaerobic conditions degradation is also slow with half-lives ranging to months or greater. HBCD is expected to sorb to particulates and sediments and have limited mobility in soil. It is expected to volatilize to some extent from soils and water surfaces. In the atmosphere, HBCD is expected to occur primarily as particulates and may undergo long range transport. It will be removed from the atmosphere by wet or dry deposition, and has an estimated vapor phase half-life of 2.1 days for reaction with hydroxyl radicals. HBCD is highly bioaccumulative with measured fish bioconcentration factor (BCF) values of greater than 18,000.

2.4 Exposures

2.4.1 Releases to the Environment

HBCD is manufactured or imported as a powder or pellets (EPA, 2012a) and incorporated into a polymer matrix, including polystyrene foam, as an additive that is incorporated into the matrix (EC, 2008). The life cycle of HBCD includes the manufacture and processing of HBCD followed by the commercial and consumer use, service life, and disposal of products that contain HBCD (EC, 2008; Stockholm Convention, 2010). HBCD is released to the environment throughout the life cycle (EC, 2008; EPA, 2014; Stockholm Convention, 2010).

TRI data are not yet available for HBCD, but releases from industrial sites to waste water treatment plants (WWTP), surface water, air and landfill are expected (EC, 2008; Environment Canada, 2011; NICNAS, 2012). HBCD is expected to remain largely immobile in landfills (EPA, 2014) and therefore industrial releases to water and air are of greater interest to EPA/OPPT than industrial releases to landfills. Sawing of EPS or XPS during commercial and consumer use results in release of HBCD (EC, 2008). Emissions of HBCD from EPS and XPS and wear of these products result in release of HBCD during their service life (EC, 2008). The total of releases of HBCD from construction sites to air or surface water from professional use of EPS or XPS is large in comparison with the total releases to each of these media from the manufacture of HBCD or processing of HBCD (to make EPS and XPS) (EC, 2008). However, releases from construction sites are dispersed and therefore are likely to be lower than industrial releases on a per-site basis. Disposal of EPS and XPS may result in releases to the environment as a result of demolition of buildings or material that is left on or in the soil (EPA, 2014); EPA/OPPT believes these releases are likely to be lower than industrial releases on a per-site basis.

Manufacturing and processing steps to be assessed are summarized in Appendix C.

2.4.2 Presence in the Environment

2.4.2.1 Surface Water

Studies of surface water in the US are limited to a study of suspended sediment from the Detroit River, a highly industrialized area. The maximum measured concentration in suspended sediment was 3.7 µg/kg dw (Marvin et al., 2006) with similar values measured in China and Sweden (Arnot et al., 2009; He, S. et al., 2013). HBCD was identified in lakes, tributaries and streams in China and the UK with measured concentrations in the ng/L levels (BRE, 2009; Harrad et al., 2009; MOE, 2000, 2005). Measurements of marine water were not found, and these values would be expected to be low. Geographically and temporally distributed monitoring data of this cluster in US surface waters were not found.

2.4.2.2 Wastewater

HBCD in wastewater influent (dissolved phase) at sewage treatment plants in South Africa and the UK were measured at concentrations of ng/L to <1 µg/L levels (Chokwe et al., 2012; De Boer et al., 2002). Measurements of the suspended phase of influent from sewage treatment plants in the UK and Netherlands were as high as 3800 µg/kg dw (De Boer et al 2002, Morris et al., 2004). Measurements of suspended phase in effluent were as high as 18 µg/kg dw (Morris et al., 2004). Measured concentrations of HBCD in wastewater in the US are not available.

2.4.2.3 Sludge

Measurements of HBCD levels in sludge have been made throughout Europe (Covaci et al., 2006; De Boer et al., 2002; Gorga et al., 2013; Guerra et al., 2010; Morris et al., 2004) and Asia (Feng et al., 2012; Hwang et al., 2012) with values ranging from non-detect (detection limit = 4 ng/g) at a WWTPs in Spain (Gorga et al., 2013)(Guerra et al., 2010) to as high as 29 mg/kg dw in industrial sludge from Korea (Hwang et al., 2012). A study in the US of processed sludge from activated sludge-type secondary treatment facility treating domestic & industrial waste (including automotive interior manufacturer) found comparatively high levels of HBCD, on the order of g/kg (La Guardia et al., 2010). Samples analyzed from the EPA 2001 National Sewage Sludge Survey showed approximately 20 ug/kg HBCD (Venkatesan and Halden, 2014).

2.4.2.4 Soil

Soil sampling is limited to measurements from Sweden (Arnot et al., 2009), Germany and Belgium (Arnot et al., 2009; Covaci et al., 2006), and throughout Asia (Eguchi et al., 2013; Li et al., 2012b; Wang et al., 2013) with the highest values (µg/kg dw) found in the soil near a HBCD manufacturing plant in the Laizhou Bay area. Studies with measured levels of HBCD in soils in the US were not available.

2.4.2.5 Sediment

Sediment measurements have been made in numerous countries throughout the world including Asia, South America, North America, Europe and South Africa (Al-Odaini et al., 2013; Arnot et al., 2009; Baron et al., 2013; Canton et al., 2008; Covaci et al., 2006; De Boer et al., 2002; de Boer et al., 2004; Feng et al., 2012; Guerra et al., 2012; Harrad et al., 2009; He, M.-J. et al., 2013; Klosterhaus et al., 2012; La Guardia et al., 2012; La Guardia et al., 2013; Li et al., 2013; Li et al., 2012b; Managaki et al., 2012; MOE, 2000, 2005; Morris et al., 2004; Xu et al., 2013; Zhang et al., 2013) with the highest value (>300 mg/kg dw) found at the Yadkin River at the outfall downstream from a textile facility in North Carolina, US (La Guardia et al., 2012).

2.4.2.6 Biota

HBCD has been reported in several fresh water and marine species throughout North America. In the US, carp from the Hyco River in Virginia were reported with mean HBCD levels of 4640 µg/kg lipid weight (Chen et al., 2011). HBCD was also measured in the blubber or liver of various marine mammals: Bottlenose dolphin (Johnson-Restrepo et al., 2008), Bull shark (Johnson-Restrepo et al., 2008), Atlantic Sharpnose shark (Johnson-Restrepo et al., 2008), White Sided dolphin (Peck et al., 2008), and California sea lions (Stapleton et al., 2006) with the highest mean concentration of 130 µg/kg lipid weight reported in the White Sided dolphin (Peck et al., 2008). Similarly, HBCD has been detected in the blubber or liver of marine species (Budakowski and Tomy, 2003; Muir et al., 2006; Tomy et al., 2009) and in whole or the muscle of fresh water fish in Canada (Law et al., 2006a; Tomy et al., 2008).

2.4.3 Occupational Exposure

EPA/OPPT considers inhalation and dermal exposure to be important exposure pathways for workers. Sometimes, the inhalation of air-suspended particulate matter that is subsequently trapped in mucous and moved from the respiratory system to the gastrointestinal tract (EPA, 2011b) is a contributor to aggregate exposures. This will be referred to here as incidental ingestion of inhaled particulates.

HBCD is manufactured as a powder at two US sites and is imported as pellets at two other sites. The processing of HBCD for the manufacture of EPS and XPS and the subsequent commercial use of these products by workers is described in EC (2008) and EPA (2014b). Industrial and commercial workers are potentially exposed to HBCD (EC, 2008; Kuo et al., 2014; NICNAS, 2012; Zhang et al., 2012). Exposure monitoring data for workers in the US is not available in the scientific literature. The number of potentially exposed industrial workers in the US is estimated to be less than 2100 (EPA, 2012a).

The greatest potential for occupational exposure is expected at industrial sites. Inhalation exposure concentrations of HBCD dust in the form of inhalable particles for workers handling standard grade HBCD powder at sites for the manufacture or processing (for the manufacture of XPS or EPS) of HBCD are in the range of 0.1 to 2.5 mg/m^3 (EC, 2008). For dermal exposures,

the exposure range is 84 to 840 mg/day of HBCD dust (EC, 2008). Workers who cut EPS or XPS boards (e.g., at construction sites) are potentially exposed to HBCD via inhalation at much lower concentrations of HBCD in air in the form of respirable particles (Kuo et al., 2014; Zhang et al., 2012).

2.4.4 General Population Exposure

2.4.4.1 Ambient Air

The concentrations of HBCD are generally higher indoors than outdoors. However, spatial variation is likely with proximity to point sources. Concentrations are generally reported in picograms/m^3. Samples have been collected in a wide variety of locations including remote locations in the arctic far removed from sources indicating long-range transport. Some studies characterized vapor and particulate phase of HBCD with HBCD most often reported in the particulate phase (Abdallah et al., 2008b; Alaee et al., 2003; Li et al., 2012a; Takigami et al., 2009a; Tue et al., 2013).

2.4.4.2 Drinking Water

Measured concentrations of HBCD in drinking water are limited to one study in the UK (BRE, 2009) where sampling from main water inlet and borehole water indicated concentration of 5-16 µg/L and samples of process water from the Netherlands were an order of magnitude lower. Monitoring studies identifying HBCD in drinking water in the US are not readily available.

2.4.4.3 Fish Consumption

Measured concentrations of HBCD in fish are reported throughout the world, typically in the µg/kg range and are expected to vary spatially and temporally (Law et al., 2014). Fewer studies are available in the US and Canada (Arnot et al., 2009; Covaci et al., 2006; Ismail et al., 2009; Klosterhaus et al., 2012).

2.4.4.4 Biomonitoring

While fewer studies have characterized HBCD levels in humans compared to wildlife, several studies have shown detection in human breast milk, blood, adipose tissue and hair in the US and other countries. HBCD has been detected in breast milk at ng/gram lipid levels. (Arnot et al., 2009; Carignan et al., 2012; Covaci et al., 2006; Croes et al., 2012; Devanathan et al., 2012; Malarvannan et al., 2013; Marvin et al., 2011; Pratt et al., 2013; Shi et al., 2013). Two studies have detected HBCD in adipose tissue (Arnot et al., 2009; Johnson-Restrepo et al., 2008). HBCD has also been detected in human blood at ng/g lipid levels (Arnot et al., 2009; Covaci et al., 2006; de Winter-Sorkina et al., 2006; Kiciński et al., 2012; Kim et al., 2013; WWF, 2004).

2.4.5 Consumer Exposures

Consumer exposure to HBCD may include inhalation exposure, dermal exposure through direct skin contact with HBCD on the surface of objects or articles, incidental ingestion of inhaled particulates (see 2.4.3), and incidental ingestion of indoor settled dust via hand-to-mouth behaviors.

Based on HBCD's relatively low vapor pressure and relatively high octanol-air partition coefficient, it is likely to preferentially partition to smaller suspended particles in the air and larger settled particles in dust (Blanchard et al., 2014; Law et al., 2014). HBCD has been detected in the dust of residences, commercial buildings, automobiles, and airplanes both in the US and other countries. The available assessments have addressed data relevant to US exposure scenarios up to and including 2011.

Concentrations vary widely across different microenvironments and within microenvironments and are generally reported in the nanograms/gram or micrograms/gram range (Abdallah et al., 2008a; Abdallah and Harrad, 2010; Ali et al., 2012; Allen et al., 2013a; Allen et al., 2013b; Bjorklund et al., 2012; Covaci et al., 2006; D'Hollander et al., 2010; de Wit et al., 2012; Dodson et al., 2012; Harrad et al., 2010; Johnson et al., 2013; Kalachova et al., 2012; Kopp et al., 2012; Kukučka P*, 2013; Ni and Zeng, 2013; Sahlström et al., 2012; Shoeib et al., 2012; Stapleton et al., 2008a; Stapleton et al., 2009; Stapleton et al., 2014; Takigami et al., 2008, 2009a; Thuresson et al., 2012; Tue et al., 2013; van den Eede et al., 2012; Wang et al., 2013). HBCD was detected at nanogram levels in handwipe samples in a recent study (Stapleton et al., 2014). HBCD has also been also detected in indoor air. Concentrations are generally reported in picograms/m^3 (Abdallah et al., 2008b; Abdallah and Harrad, 2010; de Wit et al., 2012; Ni and Zeng, 2013; Tue et al., 2013).

2.5 Hazard Endpoints

2.5.1 Ecological Hazard

The ecological hazard of HBCD has been summarized in several publications (EC, 2008; Environment CA and Health CA, 2011; EPA, 2008a, 2014b; NICNAS, 2012; OECD, 2007). A general overview is presented below. Additional details and tabulated data summaries can be found in Appendix D.

HBCD has been tested for acute and chronic aquatic toxicity, soil organisms, sediment organisms, avian species, and terrestrial plants. EPA/OPPT concludes that HBCD is hazardous to the environment. This conclusion is based on the potential for bioaccumulation (fish bioconcentration factor [BCF]=8,974–18,100) and biomagnification (fish biomagnification factor [BMF]=4.3–9.1), observed acute toxicity values as low as 0.009 mg HBCD/L (72-hour EC_{50}) in the marine algae, *Skeletonema costatum,* that indicates high aquatic toxicity to plants, a chronic aquatic toxicity value of 0.0042 mg HBCD/L (maximum acceptable toxicant concentration, MATC) in *Daphnia magna* that indicates high chronic aquatic invertebrate toxicity, and reduced

chick survival in Japanese quails (*Coturnix coturnix japonica*) at 15 ppm in diet (2.1 mg HBCD/kg-body weight/day) that indicates high terrestrial toxicity (Drottar and Krueger, 1998, 2000; Law et al., 2006b; MOEJ, 2009; Walsh et al., 1987).

2.5.2 Human Health Hazard

The human health hazard of HBCD has been summarized in several publications (EC, 2008; Environment CA and Health CA, 2011; EPA, 2008a, 2014b; NICNAS, 2012; OECD, 2007). A general overview is presented below. Additional details and tabulated data summaries can be found in Appendix E.

For humans, there is a potential for oral, inhalation and dermal exposure. Available toxicokinetics data in rodents indicate that HBCD is moderately absorbed via the gastrointestinal tract, metabolized, and distributed to a number of tissues, with preferential distribution and accumulation of unchanged HBCD in fatty tissue. Elimination of HBCD is predominantly via feces (as unchanged parent compound), but is also eliminated in the urine (as secondary metabolites). The acute hazard concern is low via the oral, dermal and inhalation routes. The chronic hazard concern is based on reproductive effects which are described in detail in Appendix E. There is also some evidence of neurodevelopmental toxicity suggestive of hearing impairment, however, it is difficult to determine if the effect is due to developmental exposure to HBCD, a result of repeated-dose exposure, or a combination of the two. Available data suggest that HBCD is not genotoxic. No adequate carcinogenicity studies are available (EPA, 2014b). Existing assessments have also concluded, based on genotoxicity information and one limited lifetime study, that HBCD is not carcinogenic (NICNAS, 2012; TemaNord, 2008) or that further study of carcinogenicity is not warranted (EC, 2008; OECD, 2007). However, the only available dietary study evaluating the carcinogenic potential of HBCD in mice is not considered adequate to draw conclusions regarding carcinogenicity (EC, 2008; Environment CA and Health CA, 2011; EPA, 2014b; OECD, 2007). Given this data gap, EPA's HBCD assessment will not include carcinogenicity assessment.

2.6 Results of Problem Formulation

The results of problem formulation are a conceptual model, key assessment questions and an analysis plan for human health and the environment (EPA, 1998a, 2014b).

2.6.1 Conceptual Model

During problem formulation, a conceptual model (see Figure 2-1) was developed to identify important sources, pathways, and receptors of exposure (See Sections 2.3 and 2.4). Potential exposures to HBCD (derived from the manufacture, processing and use of HBCD-containing polystyrene products) in homes, offices, the environment, and occupational settings were linked to hazard endpoints in human and non-human receptors.

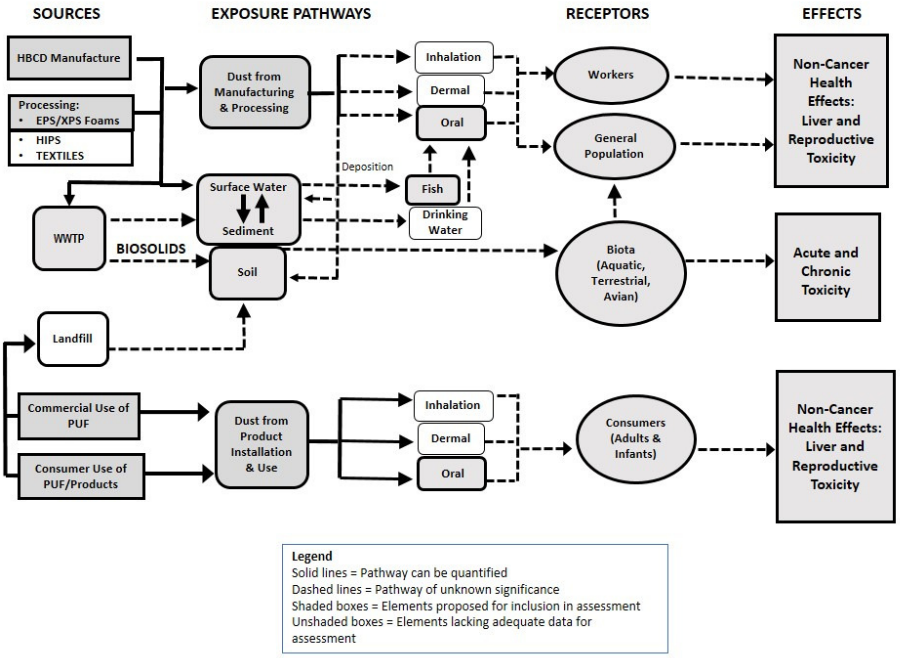


Figure 2-1: Conceptual Model for HBCD

In the conceptual model, the schematic depicts the pathways (denoted by arrows) of potential exposure to HBCD and HBCD dust generated during the manufacture and processing of HBCD and use of HBCD containing products. The solid lines denote the exposure pathways considered likely and with available exposure and hazard data to assess them. The dashed lines designate pathways which are of unknown significance i.e. uncertain, have limited data or which are not quantifiable. The shaded boxes indicate elements proposed for assessment while the unshaded boxes indicate elements lacking adequate data for assessment. These scenarios are elaborated in Table 2-2.

Table 2-2: Summary of Use/Exposure Scenarios Considered for Assessment

#	USE/EXPOSURE SCENARIO CONSIDERED	POTENTIAL ROUTE OF EXPOSURE	PROPOSED FOR ASSESSMENT	RATIONALE/LIMITATIONS/ UNCERTAINTIES
1	Worker exposure to HBCD during manufacturing and processing	ORAL – Unintended oral exposure via the incidental ingestion of inhaled particles of HBCD and HBCD in dust	YES	Risk identified for HBCD handling in occupational settings in non-US assessments

#	USE/EXPOSURE SCENARIO CONSIDERED	POTENTIAL ROUTE OF EXPOSURE	PROPOSED FOR ASSESSMENT	RATIONALE/LIMITATIONS/ UNCERTAINTIES
		DERMAL	NO	Experimental data for reliable route extrapolation from oral to inhalation & dermal routes are not available
2	General population exposure from HBCD resulting from releases to the environment	ORAL – Ingestion of HBCD particles	YES	No TRI data
		ORAL – Fish Consumption	YES	Low risk in available non-US assessments; confirm low risk using US data
		ORAL – Drinking Water	NO	Low risk in available non-US assessments; No US drinking water monitoring data
		ORAL – Food other than fish from ambient water	NO	Low risk in available non-US assessments; Not regulated under TSCA
		INHALATION	NO	Low risk in available non-US assessments
3	Ecological Receptors	WATER	YES	Available US monitoring data and estimated/modeled releases from industrial sites
		SEDIMENT	YES	Available US monitoring data and estimated/modeled releases from industrial sites
		SOIL	YES	Available US monitoring data and estimated/modeled releases from industrial sites
4a	Consumer exposure to HBCD from the use of consumer products in indoor environments	ORAL – Incidental ingestion of inhaled particles of HBCD in dust Hand-to-mouth exposure of HBCD from dust	YES	Data available for oral exposures only
4b	Consumer exposure to HBCD from the use of consumer products in indoor environments	INHALATION DERMAL	NO	Experimental data for reliable route extrapolation from oral to dermal route is not available. Inhalation of neat HBCD potentially released from products is expected to contribute less to overall exposure than the ingestion pathway due to low volatility.
4c	Consumer exposure to HBCD from use of EPS/ XPS commercial products.	ORAL INHALATION DERMAL	NO	Exposure considered insignificant and not assessed in EURAR; Risk to workers low in NICNAS; The HBCD content of these boards 1-5%; EPS/XPS boards may generate dust during cutting during construction, renovations or DIY projects. Consumer dust exposure captured in “1.0” above; Experimental data for reliable route extrapolation from oral to dermal route is not available. Inhalation of neat HBCD potentially released from products is not expected due to low volatility.

#	USE/EXPOSURE SCENARIO CONSIDERED	POTENTIAL ROUTE OF EXPOSURE	PROPOSED FOR ASSESSMENT	RATIONALE/LIMITATIONS/ UNCERTAINTIES
4d	Consumer exposure to HBCD in specific articles made with high impact polystyrene (HIPS)	ORAL INHALATION DERMAL	NO	Low risk in available non-US assessments; Level of HBCD in HIPS in the US is unknown; Not used in typical consumer products (computer or TV chassis); Use in other consumer products (e.g. electrical appliances) is enclosed limiting potential exposure
4e	Consumer exposure to HBCD in textile finishings	DERMAL	NO	Low risk in available non-US assessments; Low risk in CPSC study with furnishings; In the 2012 CDR, HBCD was not reported to be used in consumer fabrics or textiles; The extent of HBCD institutional (e.g. prisons), military or aviation use is unknown.

EPA developed four key questions from the conceptual model.

1. Are there risks to workers exposed to HBCD during manufacturing and processing of HBCD for the manufacture of EPS and XPS?

HBCD has been assessed globally (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012). For human health, the toxicological point of departure (POD; NOAEL for the two-generation toxicity study) used in the published risk assessments (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012) to calculate the margin of exposure (MOE) is based on a study that EPA would consider adequate for the oral route of exposure. No chronic hazard data are available for the dermal and inhalation routes of exposure. To address these exposure scenarios and minimize uncertainty in the risk conclusions, EPA uses physiologically-based pharmacokinetic (PBPK) modeling for route-to-route extrapolation; however, these data are not robust for HBCD. Therefore, EPA/OPPT proposes to evaluate the methodology used in the published risk assessments, confirm the study used for the POD, and in conjunction with EPA's assessment of the exposure of workers in the US (Section 2.6.2), determine if there are risks to workers.

2. Are there risks to the general population from HBCD released to the environment during the lifecycle of HBCD?

Releases of HBCD to air, including releases to air during manufacture and processing of EPS and XPS, are expected to partition to particulate matter and deposit in the environment (water and soil) and is expected to be bioaccumulated up the food chain. Therefore, for the general population, exposures to HBCD are expected to occur indirectly through water or fish consumption.

Drinking Water: No monitoring data for HBCD in drinking water are available. However, published risk assessments indicate low risk to the general population from drinking water exposure.

Fish Consumption:

- For the general population, available risk assessments (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012) concluded that risk to general population from consumption of HBCD in fish is low. In addition, the Canadian assessment included sensitive subpopulations such as indigenous populations (Nunavut) and nursing infants and concluded that risks to these populations is low.
- However, recent publications (Abdallah and Harrad, 2011; Aylward and Hays, 2011; Carignan et al., 2012; Gheorghe et al., 2013; Kalachova et al., 2012) containing additional information warrant evaluation.

A biomonitoring-based risk assessment (Aylward and Hays, 2011) (i.e., based on HBCD concentrations found in breast milk and serum) indicated that the margins of exposure (MOE) were greatly in excess of target values, suggesting that the risk to the general population is low.

3. Are there risks to ecological receptors from HBCD found in the environment?

Available risk assessments (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012) concluded that HBCD poses a risk to the environment. EPA/OPPT plans to evaluate the potential risk to the environment based on US release estimates and exposure.

4. Are there risks to consumers from HBCD found in household dust?

Dust: Available risk assessments (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012) concluded that risk to consumers from exposure to HBCD in household dust is low. These assessments included hand-to-mouth transfer of dust by children. Preliminary evaluation of recent data for the US population suggest that the available assessments underestimate consumer exposure to HBCD from dust for US consumers. In addition, for toddlers, exposure to HBCD from dust in other microenvironments, such as vehicles and childcare environments, may contribute to their total HBCD exposure (Harrad and Abdallah, 2011). Therefore, EPA/OPPT plans to evaluate the methodology used in the published risk assessments, confirm the study used for the hazard assessment and in conjunction with the current and aggregate exposure information relevant to the US population, assess potential risks to US consumers.

2.6.2 Analysis Plan

Based on problem formulation EPA/OPPT plans to conduct the following additional analyses.

2.6.2.1 Workers

EPA/OPPT plans to evaluate the applicability of data for worker exposure to HBCD through manufacturing and processing for the manufacture of EPS and XPS reported in EC (2008) and NICNAS (2012) to US occupational exposure scenarios. If the available data are not applicable, develop estimates of occupational exposures based on modeling and assumptions (e.g. approaches used in the new chemicals program).

2.6.2.2 Risks to General Population and Environmental Biota (aquatic, terrestrial and avian)

Robust monitoring datasets for US locations do not exist. EPA/OPPT plans to use estimates of releases to the environment during HBCD manufacture and processing for the manufacture of EPS and XPS from manufacturing, processing and use to estimate surface water, sediment and soil concentrations. EPA/OPPT does not plan to consider degradation losses but may consider partitioning.

EPA/OPPT plans to estimate releases to the environment from industrial sites based on CDR (EPA, 2012a) data on production volume and number of sites and emission factors (i.e. 'loss factors')[6] reported in various HBCD risk assessment reports (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012). EPA/OPPT will assume emission factors for releases from manufacturing and processing, in processes in other countries, are applicable to the US.

The release factor of a chemical is dependent on the design and operation of a chemical process. EPA/OPPT assumes the basic process design and operation of the processes for the manufacture or processing of HBCD in the US to be similar to those of the corresponding processes in other countries. The descriptions of the processes for the manufacture of EPS resin beads, the manufacture of foamed plastics including EPS and XPS, and plastics compounding in general that are reported in the literature (Burkhardt et al., 2011; EPA, 2014b; Maul et al., 2007; Suh, 2000) are similar to descriptions reported in EC (2008) and NICNAS (2012) of the corresponding processes. EPA/OPPT's compilation of the non-site specific emission factors reported in EC (2008), NICNAS (2012) and Environment CA and Health CA (2011) is given in Table_Apx C-2 in Appendix C. EPA/OPPT's preliminary estimate of the values of input variables for the assessment of releases is reported in Table_Apx C-3; EPA/OPPT plans to assess a range of release values from the ranges of input variables given in this table.

Additionally, EPA/OPPT may consider other available information to assess releases and concentrations to other media (i.e. air). For a discussion of the approach for how air releases could be modeled to estimate concentrations in nearby media see EPA/OPPT's TBBPA problem formulation document (http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html). However, there will be important differences in the assessments because site-specific modeling parameters were used with TBBPA and those are not likely to be available for HBCD industrial sites.

Mathematical modeling approaches may be necessary to yield exposure estimates. EPA/OPPT will consider the use of sensitivity analyses to determine key elements of uncertainty. EPA/OPPT plans to estimate MOE for fish consumption (including sensitive populations) using US exposure information not captured in previous assessments and modeled fish ingestion (EPA, 2007) from release estimates. EPA/OPPT is considering values for adult general population consumption typically used by EPA Office of Water (e.g., 22 g/day for adults in the

[6] Ratio of amount of chemical released to amount manufactured or processed

general population and 142.5g/day for subsistence fishers in the absence of local or similar fish ingestion data). Based on NHANES data from 2003 to 2010 (EPA, 2014a), this value represents the 90th percentile consumption rate of freshwater and estuarine fish for the US adult population 21 years of age and older.

EPA/OPPT will identify hazard endpoints and benchmarks from published assessments (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012) and data sources (See Appendix D and Appendix E). EPA/OPPT will calculate non-cancer risks using MOE or HQ approaches.

2.6.2.3 Consumers

Mathematical modeling approaches may be necessary to yield exposure estimates. EPA/OPPT will consider the use of sensitivity analyses to determine key elements of uncertainty. EPA/OPPT plans to use available or modeled (to be determined) data relevant to US exposure scenarios to estimate consumer exposure using available or modeled data relevant to US exposure scenarios with particular emphasis on sensitive populations (e.g. toddlers exposed in microenvironments).

Consumer exposures to HBCD will be evaluated based on incidental ingestion of dust (as described above), and incidental ingestion of indoor settled dust via hand-to-mouth behaviors. Oral exposure by incidental ingestion of house dust and hand-to-mouth transfer can be quantified based on US values of monitored house dust. Several recent studies of house dust are available which are expected to be representative of US households. The EPA Exposure Factors Handbook (EPA, 2011b) can be utilized to determine typical quantities of dust ingested and time-activity patterns.

EPA/OPPT will identify hazard endpoints and benchmarks from published assessments (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012) and data sources (See Appendix E). EPA/OPPT will calculate non-cancer risks using MOE.

Aggregate oral exposures will be assessed considering hand-to-mouth dust ingestion, incidental ingestion of dust and high-end fish consumption.

Conclusion

EPA/OPPT plans to evaluate potential risk to workers, the general population, consumers and environmental biota under the TSCA Existing Chemicals Program using existing data and methods. EPA/OPPT plans to review and evaluate available exposure and hazard benchmarks and determine margins of exposure to evaluate the potential risk from human and environmental exposure to HBCD. EPA/OPPT plans to estimate releases to the environment from industrial sites based on CDR (EPA, 2012a) data on production volume and number of sites and emission factors (i.e. 'loss factors')[7] reported in various HBCD risk assessment reports (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012).

[7] Ratio of amount of chemical released to amount manufactured or processed

2.6.3 Sources and Pathways Excluded From Further Assessment

Several scenarios were identified where exposure to HBCD is expected to be low or unknown, and where further analysis is not recommended by EPA/OPPT under TSCA:

- Exposure from HBCD in landfills is not being assessed due to uncertainties in release from these sites.

- General population exposure from HBCD in drinking water is not being assessed because drinking water monitoring data for the US are not available and conclusions from available risk assessments indicate a low concern from this exposure pathway (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012).

- Consumer exposure to HBCD in HIPS is not being assessed because the level of HBCD in HIPS in the US is unknown, it is not used in typical consumer products (e.g. computer or TV chassis), its use in other consumer products (e.g. electrical appliances) is enclosed limiting potential exposure and a low risk to consumers was indicated in available risk assessments.

- Consumer exposure to HBCD in textile finishings is not being assessed because it was considered low risk by the CPSC in upholstered furnishings (CPSC, 2001), it was not reported to be used in consumer fabrics or textiles in the 2012 CDR (EPA, 2012a) and the extent of institutional (e.g. prisons), military or aviation use is unknown.

- There are no adequate toxicological data based on inhalation or dermal exposures or a PBPK model readily available for route-to-route extrapolation. Therefore EPA/OPPT will not assess inhalation or dermal contact in this assessment. However, EPA is considering the quantification of incidental ingestion of particulates that would result from exposure to HBCD dust in occupational settings. A similar approach will be used to address consumer exposure to HBCD in dust.

2.6.4 Uncertainties and Data Gaps

2.6.4.1 Exposure Assessment

2.6.4.1.1 Releases to the Environment

The major uncertainties in EPA's proposed approach are the following:

Production and Processing Volumes and Number of Sites:
HBCD production and processing volumes are uncertain because CDR information on current production, export and import volumes is CBI. EPA will assume the HBCD production volume to be in a range of values that is derived from the most recent publically reported CDR information

and will assume the processing volume to be equal to the production volume. Refer to Table_Apx C-3 for EPA's preliminary values for production and processing volumes.

The number of sites for most processing steps is uncertain. EPA will estimate the number of sites based on CDR data which is data on ranges of number of sites. Furthermore, the processing and product descriptions reported in CDR are general and preclude an accurate determination of specific processing steps. Refer to Table_Apx C-1 for EPA's preliminary assessment of the number of sites. The share of the HBCD production volume that is processed to manufacture XPS using HBCD powder or HBCD masterbatch is unknown.

2.6.4.1.2 Occupational Exposure

Exposure monitoring data for workers in the US are not available in the scientific literature. The greatest potential for occupational exposure is expected at industrial sites. Maximum exposure occurs while workers load or unload HBCD powder or pellets (EC, 2008), which is a worker activity that EPA expects in the US. Data are available for inhalation and dermal exposures to workers (EC, 2008). Workers who cut EPS or XPS boards (e.g., at construction sites) are potentially exposed to HBCD via inhalation at much lower concentrations of HBCD in air in the form of respirable particles.

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

2.6.4.1.3 General Population and Consumer Exposure

Some of the available measured environmental concentrations were outside the US and it is not clear how representative they are of exposure scenarios within the US. Significant uncertainties may exist in a quantitative evaluation. There are limited US surface water, sediment, and soil measurements.

Available monitoring data may not be representative of concentrations in the environment across all areas of the US. There are very limited data of HBCD in fish from the US and it is uncertain if concentrations in fish in Canada and abroad would be similar to the US. Fish ingestion exposures will need to be modeled based on releases to the environment from manufacturing/processing/use. Exposure factors exist for fish consumption, however there would be uncertainty in determining the concentration of HBCD in edible fish. If specific receiving waters are not identified, there will be uncertainty in the amount of dilution that may occur. EPA/OPPT will clearly document the uncertainty and limitations associated with the fish consumption analyses.

Modeled releases to water from industrial facilities may result in the over- or under-estimation of concentrations in the aquatic environment. Modeling default values will need to be modified

(e.g., fish consumption) to account for high-end consumption. EPA/OPPT will consider the use of sensitivity analyses to determine key elements of uncertainty.

The concentration of HBCD in indoor air or dust in offices or workplaces may be greater than in homes. There are uncertainties using existing methodologies to estimate exposure for the different sub-environments. Incidental ingestion of dust by adults is expected to be low whereas ingestion of dust through incidental ingestion or hand to mouth behavior is expected to be higher for small children due to their activity patterns and increased proximity to indoor areas where dust may gather. Concentrations of HBCD in dust are likely to vary by microenvironment and will need to be a consideration in exposure estimations.
It is not possible to develop source-to-dose exposure models with currently available information. Sources such as dust and presence in fish must be considered integrative metrics for the purposes of exposure assessment. Source-to-dose models are absent or limited for most of the identified exposure scenarios, therefore linking the exposure to specific products or the use patterns of any one product will be challenging.

2.6.4.2 Ecological Endpoints

Overall, adequate aquatic toxicity data are available to characterize the hazard to the environment for HBCD.

2.6.4.3 Human Health Endpoints

Toxicokinetics (by the oral route), acute, repeated-dose, developmental, and reproductive toxicity data are available to characterize the potential human health hazard of HBCD. Although no standard neurotoxicity or developmental neurotoxicity studies on HBCD are available, information on neurotoxicity was obtained from Functional Observational Battery, locomotor activity evaluations, neurobehavioral testing, surface righting reflex, negative geotaxis reflex, mid-air righting reflex, and brainstem auditory evoked potentials (BAEPs) in several repeated-dose and reproductive toxicity studies. Several assays testing for genotoxicity, and irritation/sensitization are also available. The only available dietary study evaluating the carcinogenic potential of HBCD in mice is not considered adequate to draw conclusions regarding carcinogenicity (EC, 2008; Environment CA and Health CA, 2011; EPA, 2014b; OECD, 2007). EPA agrees with these conclusions and therefore in its HBCD assessment will not consider carcinogenicity to be an endpoint of concern.

Neither a complete mechanistic PBPK model for HBCD, nor a PBPK model for humans is available. This precludes the use of a model for cross-route or cross-species extrapolation. There is no PBPK model readily available for route-to-route extrapolation. Exclusion of dermal and inhalation exposure routes will result in the underestimation of risks. The lack of a lifetime exposure study and/or adequate assessment of carcinogenicity increases uncertainty in EPA's assessment of long-term exposures to HBCD. Therefore, inhalation, dermal and lifetime exposure assessment data gaps add uncertainty to EPA's risk assessment of HBCD.

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APPENDICES

Appendix A Regulatory and Assessment History

Table_Apx A-1: Regulatory and Assessment History of HBCD[8]

COUNTRY/ORGANIZATION	ASSESSMENT
UNITED STATES	**Environmental Protection Agency** • Office of Environmental Information - Proposed HBCD for listing to the Toxic Release Inventory (TRI) Program (2014). For current list of chemicals see: http://www2.epa.gov/toxics-release-inventory-tri-program/tri-listed-chemicals • Office of Research and Development – Draft Toxicological Review Scoping Document to support an IRIS assessment (http://www.ecy.wa.gov/programs/wq/swqs/IRISAgendaChemicals.pdf) • Office of Pollution Prevention and Toxics (OPPT) – Flame retardant alternatives to hexabromocyclododecane (2014) (http://www.epa.gov/dfe/pubs/projects/hbcd/hbcd-full-report-508.pdf) • OPPT - Proposed SNUR (Mar 2012) to designate manufacture or processing of HBCD for use as a flame retardant in consumer textiles as a significant new use • OPPT Action Plan for HBCD (2010) (all congeners; http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/RIN2070-AZ10_HBCD%20action%20plan_Final_2010-08-09.pdf) • OPPT Risk Based Prioritization (RBP) including Hazard Characterization (2008) (http://www.epa.gov/chemrtk/hpvis/rbp/HBCD.3194556.Web.RBP.31308.pdf) for CASRNs 3194-55-6 and 25637-99-4 • OPPT – CASRN 3194-55-6 (2001) High Production Volume Challenge Program test plan and robust summaries submission (http://www.epa.gov/chemrtk/pubs/summaries/cyclodod/c13459cv.pdf)
	Occupational Safety and Health Administration (OSHA) • No occupational exposure limits (OSHA PEL, NIOSH REL, ACGIH TLV) are established (www.osha.gov)
	Consumer Product Safety Commission (CPSC) • CPSC staff exposure and risk assessment of flame retardant chemicals in residential upholstered furniture (2001) (http://www.cpsc.gov/en/) • CPSC staff preliminary risk assessment of flame retardant (FR) chemicals in upholstered furniture foam (2006) (http://www.cpsc.gov/en/) • Quantitative assessment of potential health effects from the use of fire retardant (FR) chemicals in mattresses (2006) (http://www.cpsc.gov/en/)
	State – California • HBCD is listed as an informational initial candidate chemical under California's Safer Consumer Products regulations. (DTSC, 2010) (http://www.dtsc.ca.gov/SCP/ChemList.cfm) • HBCD is listed on the state's Proposition 65 list because it is known to cause cancer or birth defects or other reproductive harm (OEHHA, 2007, 2014). (http://oehha.ca.gov/) (http://oehha.ca.gov/prop65/prop65_list/files/P65single050214.pdf)

[8] The risk assessment conclusions summarized in the table are selected conclusions from the reports that address the pertinent US exposure scenarios and should not be construed as EPA's conclusions. EPA refers the reader to the full reports for detailed explanations of the context of the conclusions reached in all risk assessments.

COUNTRY/ORGANIZATION	ASSESSMENT
	• California lists HBCD as a designated and priority chemical for biomonitoring. However, California has not yet started biomonitoring HBCD (SGP, 2014). (http://www.biomonitoring.ca.gov/chemicals/chemicals-biomonitored-california)
	State – Maine • Maine classifies HBCD as a chemical of high concern (DEP, 2013). (http://www.maine.gov/dep/safechem/highconcern/)
	State – Minnesota • Minnesota classifies HBCD as a chemical of high concern (MDH, 2013). (http://www.health.state.mn.us/divs/eh/hazardous/topics/toxfreekids/chclist/mdhchc2013.pdf)
	State - Oregon • The Oregon Department of Environmental Quality lists HBCD as a priority persistent pollutant (DEQ, 2010a, 2011). (http://www.deq.state.or.us/wq/SB737/docs/LegRpAtt20100601.pdf) (http://www.deq.state.or.us/wq/SB737/) • Oregon posts use, exposure pathways and release data for HBCD under this program (DEQ, 2010b). (http://www.deq.state.or.us/wq/SB737/docs/LegRpAtt420100601.pdf)
	State – Washington • Washington classifies HBCD as a chemical of high concern to children (WSDE, 2013). (http://www.ecy.wa.gov/programs/swfa/cspa/chcc.html)
CANADA	• HBCD meets Canada's regulatory criteria for persistence and bioaccumulation potential. (http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=7882C148-1#a4) • On November 1, 2012, Canada added HBCD to Schedule 1 of CEPA 1999 (Virtual Elimination List). Proposed risk reduction measures would prohibit the manufacture, import, use, sale, and offer for sale of HBCD and products containing HBCD. (http://www.ec.gc.ca/lcpe-cepa/eng/regulations/detailReg.cfm?intReg=82)
	• *Health Canada (Health CA)* and *Environment Canada (ENV CA)* have published a screening-level assessment. (http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=7882C148-1#a4)
EUROPEAN UNION	• HBCD is listed as a substance of very high concern (SVHC) and it is also listed under Annex XIV (Authorisation list) of European Union's REACH. After August 21, 2015, only persons with approved authorization applications may continue to use the chemical. (http://echa.europa.eu/candidate-list-table) (http://echa.europa.eu/documents/10162/13640/prioritisation_hbccd_en.pdf) • The European Chemicals Agency (ECHA) is currently considering two applications to authorize the use of HBCD: (i) formulation of flame retarded expanded polystyrene (EPS) to solid unexpanded pellets using HBCD as the flame retardant additive (for onward use in building applications); and (i) manufacture of flame retarded expanded polystyrene (EPS) articles for use in building applications. (http://echa.europa.eu/documents/10162/18584504/afa_opinion_hbcdd_use_2_en.pdf) • HBCD is recommended to be reviewed for the EU Directive's list of banned substances under the restriction of hazardous substances (RoHS) in electrical and electronic equipment. (http://ec.europa.eu/environment/waste/weee/pdf/hazardous_substances_report.pdf) • The WEEE (Waste Electrical and Electronic Equipment) directive in the European Union requires the separation of plastics containing brominated flame retardants prior to recycling. (http://ec.europa.eu/environment/waste/weee/index_en.htm)
	• The European Commission published a *European Union Risk Assessment Report (EC, 2008)* on HBCD. (http://ec.europa.eu/health/ph_risk/committees/04_scher/docs/scher_o_093.pdf)
AUSTRALIA	• HBCD is listed as a Priority Existing Chemical. (http://www.nicnas.gov.au/chemical-information/pec-assessments)

COUNTRY/ORGANIZATION	ASSESSMENT
	• Australia (National Industrial Chemicals Notification and Assessment Scheme) has prepared a risk assessment for HBCD. (http://www.nicnas.gov.au/Publications/CAR/PEC/PEC34/HBCD_Report_June_2012_PDF.pdf)
JAPAN	• HBCD is subject to mandatory reporting requirements in Japan under the Chemical Substances Control Law (CSCL), specifically Japan requires type III monitoring for all substances that may interfere with the survival and/or growth of flora and fauna. (http://www.meti.go.jp/policy/chemical_management/english/cscl/files/about/150408Progres.pdf)
STOCKHOLM CONVENTION ON PERSISTENT ORGANIC POLLUTANTS (POPs)	• In May 2013, HBCD was added to the United Nation's Stockholm Convention list of Persistent Organic Pollutants. The chemical is scheduled to be eliminated by November 2014 with specific exemptions for production and uses in expanded or extruded polystyrene building insulation. As required by the convention, parties that use these exemptions must register with the secretariat and the exemptions will expire in November 2019. (http://chm.pops.int/default.aspx)
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD)	• Published SIDS Initial Assessment Profile (SIAP) and SIAR in 2007 for CASRNs 3194-55-6 and 25637-99-4. (http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?key=39a31bc9-3719-4c55-a7d4-a8bbdd9afe04&idx=0) (http://webnet.oecd.org/HPV/UI/handler.axd?id=ea58ac11-e090-4b24-b281-200ae351686c)

Appendix B Uses Supplement Tables

Table_Apx B-1: 2012 CDR Production Data (Data Reported for 2011)

CASRN	Manufacturing Site	Domestic Manufacturing	Imported	Volume Exported (lbs)	Volume Used on the Site (lbs)[1]	2010 Past Production Volume (import+ manufacture)	2011 National Production Volume (lbs/yr)
25637-99-4	CBI	CBI	ND	CBI	0	CBI	Withheld
	CBI	CBI	ND	0	0	CBI	
	BASF Corporation 100 Campus Drive Florham Park, NJ 07932	ND	CBI	CBI	CBI	CBI	
3194-55-6	Albemarle Corporation 1550 Hwy. 371 W. Magnolia, AR 71753	CBI	ND	CBI	CBI	CBI	Withheld
	The Dow Chemical Company 2020 Dow Center Midland, MI 48674	ND	CBI	0	N/A	CBI	

[1]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.
"Withheld" in the CDR public database indicates that the national production volume of a chemical was unable to be aggregated in order to protect CBI claims.

Table_Apx B-2: Historic IUR and CDR Production Volumes

CASRN	Year							
	1986	1990	1994	1998	2002	2006	2010	2011
25637-99-4	10K - 500K	No Reports	No Reports	10K - 500K	10K - 500K	No Reports	CBI	Withheld
3194-55-6	>1M - 10M	>1M - 10M	>10M - 50M	>10M - 50M	>10M - 50M	10 to < 50M	CBI	Withheld

[1]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
"Withheld" in the CDR public database indicates that the national production volume of a chemical was unable to be aggregated in order to protect the CBI claims.

Table_Apx B-3: Summary of 2011 CDR Production Volume and Use Information

CAS Number	Industrial Sector Reported in CDR	Description of Industrial Use	Commercial or Consumer Product Category	Potential End Product	2011 PV	Approximate % of 2011 National PV
25637-99-4	Plastics Material and Resin Manufacturing	Flame retardant in electrical and electronic equipment	Plastic and Rubber Products not Covered Elsewhere (Commercial and Consumer use)	• Electric housings for VCR • Electrical and electronic equipment (e.g., distribution boxes for electrical lines) • Video cassette housings	CBI	CBI
	Construction	Flame retardant in insulation boards	Building/Construction Materials Not Covered Elsewhere (Commercial and Consumer use)	• Construction, insulation boards (packaging material) • Insulation boards (against cold or warm) of transport vehicles (e.g., lorries and caravans) • Insulation boards in building constructions, e.g. houses' walls, cellars and indoor ceilings and "inverted roofs" (outdoor) • Insulation boards against frost heaves of road and railway embankments	CBI	CBI
			Building/Construction Materials Not Covered Elsewhere (Commercial use)		CBI	100

CAS Number	Industrial Sector Reported in CDR	Description of Industrial Use	Commercial or Consumer Product Category	Potential End Product	2011 PV	Approximate % of 2011 National PV
3194-55-6	Utilities	Flame retardant in insulation boards	Building/Construction Materials Not Covered Elsewhere (Consumer use)	• Construction, insulation boards (packaging material) • Insulation boards in building constructions, e.g., houses' walls, cellars and indoor ceilings and "inverted roofs" (outdoor)	CBI	100
			Building/Construction Materials Not Covered Elsewhere (Commercial use)	• Construction, insulation boards,(packaging material) • Insulation boards (against cold or warm) of transport vehicles (e.g., lorries and caravans) • Insulation boards in building constructions e.g. houses' walls, cellars and indoor ceilings and "inverted roofs" (outdoor) • Insulation boards against frost heaves of road and railway embankments	CBI	50

Note:

1) Plastic and rubber products with consumer/commercial categories in the CDR data include:

- Food packaging
- Toys, playground, and sporting equipment

2) Building and construction materials with consumer/commercial categories in the CDR data include:

- Building/construction materials - wood and engineered wood products

CBI = Confidential Business Information

PV = Production Volume

Table_Apx B-4: Uses of HBCD as Listed in the 2008 EU Risk Assessment

Material[1]	Use/ Function[1]	Percent of HBCD Production Volume[2]	End Products[1]	Ongoing Use in the United States (US)?
EPS	Insulation	45%	Construction, insulation boards (packaging material)	Yes; based on use in construction insulation boards in 2012 CDR data[2]
			Packaging material (minor use and not in food packaging)	Unknown; it is unclear if this is an ongoing use in the US, and uses of polystyrene foam in consumer products generally do not require the use of a flame retardant[3]
			Insulation boards (against cold or warm) of transport vehicles (e.g., lorries and caravans)	Possibly; based on use in insulation boards in 2012 CDR data[2]
			Insulation boards in building constructions e.g. houses' walls, cellars and indoor ceilings and "inverted roofs" (outdoor)	Yes; based on use in construction insulation boards in 2012 CDR data[2]
			Insulation boards against frost heaves of road and railway embankments	Possibly; based on use in insulation boards in 2012 CDR data[2]
XPS	Insulation	51%	Construction, insulation boards	Yes; based on use in construction insulation boards in 2012 CDR data[2]
			Insulation boards (against cold or warm) of transport vehicles (e.g. lorries and caravans)	Possibly; based on use in insulation boards in 2012 CDR data[2]
			Insulation boards in building constructions e.g. houses' walls, cellars and indoor ceilings and "inverted roofs" (outdoor)	Yes; based on use in construction insulation boards in 2012 CDR data[2]
			Insulation boards against frost heaves of road and railway embankments	Possibly; based on use in insulation boards in 2012 CDR data[2]
HIPS	Electrical and electronic parts	2%	Electric housings for VCR	Possibly, based on use in electronic plastics in 2012 CDR[2]
			Electrical and electronic equipment, e.g., distribution boxes for electrical lines	Possibly, based on use in electronic plastics in 2012 CDR[2]
			Video cassette housings	Possibly, based on use in electronic plastics in 2012 CDR[2]

Material[1]	Use/ Function[1]	Percent of HBCD Production Volume[2]	End Products[1]	Ongoing Use in the United States (US)?
Polymer dispersion on cotton or cotton/ synthetic blends	Textile coating agent	2%	Upholstery fabric	Historic Use in the US[4]
			Bed mattress ticking	Historic Use in the US[4]
			Flat and pile upholstered furniture (residential and commercial furniture)	Historic Use in the US[4]
			Upholstery seating in transportation	Possibly, based industry response to SNUR[2]
			Draperies, and wall coverings	Historic Use in the US[4]
			Interior textiles e.g. roller blinds	Historic Use in the US[4]
			Automobile interior textiles	Possibly, based industry response to SNUR[2]

Note: The uses in this table describe recorded HBCD applications for both the US and other countries. Given that HBCD will be phased out internationally under REACH and the Stockholm Convention, it is unclear to what extent HBCD is currently used in these applications outside of the US.

Sources:

1) EC, 2008
2) EPA, 2012a
3) EPA, 2014
4) EPA, 2012e

Appendix C Exposure Supplement Tables

Table_Apx C-1: 2012 CDR Data (Data Reported for 2011) for Release Assessment

Table Line Number	Manufacture / Import		Industrial Processing / Use					Commercial / Consumer Use
	Site Identity	Max Concentration and Physical Form	Processing Use	Processing Sector	Function	% PV	Number of Sites	Use Product Category
1	CBI	90%+; Dry Powder or Other Solid	Processing-incorporation into formulation, mixture, or reaction product	Plastics Material and Resin Manufacturing	Flame retardants	50	< 10	Building / Construction Materials Not Covered Elsewhere
2			Processing-incorporation into article	Construction	Flame retardants	50	< 10	
3	BASF, Florham Park, NJ	1 to < 30%; Pellets / Large Crystals	Processing-incorporation into article	Construction	Other	CBI	10 to 24	Building / Construction Materials not covered elsewhere
4			Processing-incorporation into article	Plastics Material and Resin Manufacturing	Other	CBI	25 to 99	Plastic and Rubber Products not covered elsewhere
5	Albemarle Corporation, Magnolia, AR	90%+; Dry Powder	Processing-incorporation into article	Utilities	Flame retardants	NKRA	10 to 24	Building / Construction Materials not covered elsewhere
6			Processing-incorporation into formulation, mixture, or reaction product	Utilities	Flame retardants	NKRA	10 to 24	
7	The Dow Chemical Company, Midland, MI	60 to < 90%; Pellets / Large Crystals	Not Reported					

CBI = Confidential Business Information
NKRA = Not Known or Reasonably Ascertainable
PV = Production Volume

Table_Apx C-2: Compilation of Release Factors and Other Release-Related Information in Various Risk Assessments

Operation (Manufacture or Processing Step)	Reference	Release Media	Loss Factor (Emission Factor)		Number of Release Days	
			Value	Description	Value	Description
Manufacture of EPS resin beads that contain HBCD (also referred to as "formulation of EPS compound" (EC, 2008) or "compounding raw HBCD into resins" (NICNAS, 2012))	EC (2008)	water	7.6E-06	This is the emission factor for a generic site and was determined based on the 90th percentile of measurements of concentration in the effluent from the on-site sewer treatment plants of 9 of the total of 13 sites.	300	This is the value is for the generic site and was determined in accordance with the general risk assessment guidance of the EU. Site-specific values are in the range of 61 to 350 with the exception of one value that is equal to 1.
		air	7.3E-06	This is the emission factor for a generic site and is equal to the maximum emission factor calculated from site-specific data that pertain to three processing steps including formulation of EPS and XPS compounds.		
	NICNAS (2012)	water	6.8E-03	These values are reasonable worst case values that are the sums of emission factors for handling and compounding solid flame retardants with particle sizes <40 µm that are also of relatively high volatility as reported in OECD (2004b).	150	This is a site-specific value.
		air	2.5E-04			
Manufacture of EPS that contains HBCD (also referred to as "industrial use of EPS compound" (EC, 2008) or "conversion or processing of polymeric resin into EPS foam products" (NICNAS, 2012))	EC (2008)	water	3.0E-05	These are the emission factors for the generic site and are reported in OECD (2004b) as the emission factors for organic flame-retardants of relatively low volatility in partially open plastics conversion processes.	300	This is the value for the generic site and was determined in accordance with the general risk assessment guidance of the EU.
		air	3.0E-05			
	NICNAS (2012)	water	1.6E-03	These emission factors are weighted averages of emission factors for organic flame of relatively high volatility in closed plastics conversion processes that are reported in OECD (2004b). The emission factors that were averaged include values for high process temperature and low plastics production volume.	200	This is an assumed value.
		air	1.6E-03			
Compounding of Polystyrene Resin to Produce XPS Masterbatch containing HBCD (also referred to as "formulation of XPS compound for the manufacture of	EC (2008)	water	7.4E-06	This is the emission factor for a generic site and is equal to the maximum of emission factors calculated from site-specific data for three sites.	300	This is the value for the generic site and was determined in accordance with the general risk assessment guidance of the EU.
		air	7.3E-06	This is the emission factor for a generic site and is equal to the maximum emission factor calculated from site-specific data that pertain to three processing steps including formulation of EPS and XPS compounds.		

Operation (Manufacture or Processing Step)	Reference	Release Media	Loss Factor (Emission Factor)		Number of Release Days	
			Value	Description	Value	Description
flame retarded XPS" (EC, 2008)	Environment CA and Health CA (2011)	water	6.6E-03	This is the emission factor for a generic site and is the sum of emission factors for handling and compounding organic solid flame retardants with particle sizes <40 µm that are of relatively medium volatility as reported in OECD (2004b).	60 or 200	These values are for generic sites, are functions of the processing rate, and were determined in accordance with the general risk assessment guidance of the EU.
Manufacture of XPS using XPS Masterbatch containing HBCD	EC (2008)	water	2.6E-05	These are the emission factors for the generic site and are equal to the maxima of the emission factors that were derived from site-specific data but were not explicitly reported. EPA calculated these factors, each of which is equal to the ratio of total annual releases from 13 sites for which site-specific data was not reported and the total annual processing rate for these sites.	1	This value was assumed as a reasonable worst case for the number of release days from a generic site. Site-specific values are in the range of 1 to 15.
		air	5.8E-05		300	The number of release days for the generic site is not reported. Site-specific values are in the range of 15 to 300.

Table_Apx C-3: Preliminary Values of Input Variables for Calculation of the Range of Release Rates from Manufacturing Sites or the Processing Sites of Each Processing Step

Operation (Manufacture or Processing Step)	Processing Rates as Fractions of the HBCD Manufacturing Rate[1]	Manufacturing or Processing Rate (kg/yr)[2]		Number of Sites[3]		Number of Release Days[4]	The Minimum and Maximum Values of the Compiled[5] and Calculated[6] Loss Factors for Each Medium of Release (kg of HBCD released per kg of HBCD manufactured or processed)			
							water		air	
		lower limit of range	upper limit of range	minimum	maximum		min	max	min	max
manufacture of HBCD	Not Applicable	4.540.E+06	2.290.E+07	3		250	1.2E-07	4.0E-04	3.3E-07	6.8E-04
manufacture of EPS resin beads	0.45	2.043.E+06	1.031.E+07	1	4	250	7.6E-06	6.8E-03	7.3E-06	2.5E-04
manufacture of EPS	0.45	2.043.E+06	1.031.E+07	5	15	250	3.0E-05	1.6E-03	3.0E-05	1.6E-03
manufacture of XPS using HBCD powder	0.51	2.316.E+06	1.168.E+07	6	18	1 (water) 250 (air)	1.0E-05	1.0E-05	7.3E-06	
compounding of polystyrene resin to produce XPS masterbatch containing HBCD	0.51	2.316.E+06	1.168.E+07	10	29	250	7.4E-06	6.6E-03	7.3E-06	
manufacture of XPS using XPS masterbatch containing HBCD	0.51	2.316.E+06	1.168.E+07	10	24	1 (water) 250 (air)	2.6E-05		5.8E-05	

Note:

1) The share of production volume that is processed to manufacture of EPS or XPS is reported in Table_Apx B-4. The share of production volume that is processed to manufacture of XPS using HBCD powder or HBCD masterbatch is unknown and therefore EPA will conservatively assume this share is equal to the total share that is processed to manufacture XPS.

2) EPA estimated the lower-end of the current range of production volumes by summing the lower-ends of the ranges of production volumes for CAS number 25637-99-4 reported in 2002 and CAS number 3194-55-6 reported in 2006 that are given in Table_Apx B-2. EPA estimated the upper-end of the current range of production volume by summing the upper-ends of these two ranges.
3) The number of sites was estimated from data reported in EPA (2014b) and Table_Apx C-1.
4) EPA estimated the number of release days to be equal to 250 assuming each facility has an operation schedule of five days per week and 50 weeks per year, allowing for two-week annual downtime for maintenance. The values of the number of release days given Table_Apx C-2 are of similar magnitude. The exceptions are the values for releases to water from the manufacture of XPS using HBCD powder and XPS using XPS masterbatch; EPA assessed each of these parameters to be 1 day per year in consideration of the data presented in Table_Apx C-2.
5) The compilation of non-site specific release factors is given in Table_Apx C-2.
6) EPA calculated release factors for HBCD manufacturing and the manufacture of XPS using HBCD powder from data reported in EC (2008) because non-site specific release factors are not reported for these two operations.

Appendix D Environmental Hazard Study Summaries

D-1 Persistence in Environmental Media

D-1-1 Air and Water

HBCD does not absorb light in the UV/Visible frequencies so is not expected to undergo direct photolysis in air or water (Zhou et al., 2014). Kajiwara et al (Kajiwara and Takigami, 2013) studied photolysis of HBCD on textiles (4% by wt.) and reported "no substantial loss of any of the HBCD diastereomers during the entire exposure period (371 days)" confirming that photolytic degradation did not occur.Indirect photolysis with methane as a co-solvent has been observed to result in debromination (Zhou et al., 2012) and indirect photolysis with Fe(III) and H2O2 also can occur (Zhou et al., 2014).

Although HBCD is expected to exist primarily in the particulate phase in the atmosphere, a small percentage is expected to exist in the vapor phase based on its vapor pressure (Bidleman, 1988; CMA, 1997; Covaci et al., 2006). HBCD in the vapor phase can be degraded by reaction with hydroxyl radicals in the atmosphere with an estimated rate constant of 5.01×10^{-12} cm^3/molecules-sec at 25 °C corresponding to an atmospheric half-life of 2.1 days (EPA, 1993, 2011a). HBCD associated with particulates is expected to be removed from the atmosphere through wet or dry deposition. Removal rates are unknown and the widespread detection of HBCD in air samples and biota from remote locations far from release locations indicate that long-range atmospheric transport occurs (Covaci et al., 2006; EPA, 2010a; Ueno et al., 2006).

D-1-2 Soil, Sediment and Sludge

Based on an estimated K_{oc} value of 7.6×10^4 HBCD is expected to be fairly immobile in soil and to bind strongly to soil, sediment, and suspended organic matter. It may undergo abiotic and microbial degradation while associated with solids. The limited data available show that biodegradation is slow and that anaerobic processes may be faster than aerobic.

A soil simulation test was conducted according to OECD TG 307 for commercial HBCD (BFRIP, 2001; EC, 2008). Activated sludge was inoculated with soil and HBCD at a nominal concentration of 34-89 µg/kg dry weight for 120 days. The disappearance half-life was 63 days in aerobic soil and >120 days in abiotic aerobic controls. In the anaerobic soil, the half-life was 7 days compared to 82 days in abiotic anaerobic controls.

A closed bottle screening-level test for ready biodegradability (OECD TG 301D) was performed using an initial HBCD concentration of 7.7 mg/L and an activated domestic sludge inoculum (BFRIP, 2001; EC, 2008). No biodegradation was observed (0% of the theoretical oxygen demand) over the test period of 28 days. Gerecke et al (Gerecke et al., 2006) studied

degradation of BFRs, including HBCD, under anaerobic conditions in digested sewage sludge. They reported a half-live for a technical HBCD mixture of 0.66 days. They found no statistically significant enantioselective degradation of alpha-, beta-, or gamma-HBCD. The reported reduction in concentration the HBCD mixture decreased in sterile controls at a rate 50 times slower in incubations under non-sterile conditions.

A water-sediment OECD TG 308 study for commercial HBCD with a nominal concentration of 34-89 µg/kg dry weight found that aerobic half-lives were 11-32 days in aerobic sediments and 30-190 days in abiotic aerobic controls (BFRIP, 2001; EC, 2008). In the anaerobic sediments, disappearance half-lives were 1.1-1.5 days compared to 9.9-10 days in abiotic anaerobic controls.

Davis et al (2006) studied degradation of ^{14}C radiolabeled HBCD with sludge, sediment, and soil simulation tests with initial concentrations of HBCD of 3.6-4.2 mg/L in the sludge systems and 3.0-4.7 mg/kg dry weight in the sediment and soil systems. As shown in Table_Apx D-1 below, they observed decrease in total initial radioactivity in the viable systems and abiotic controls.

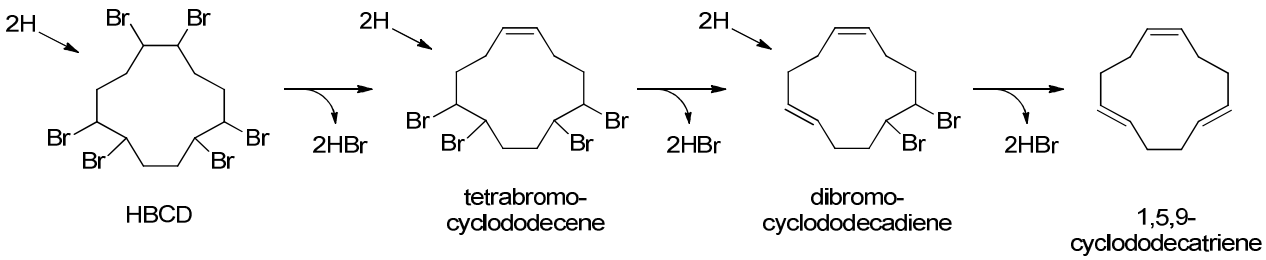
Table_Apx D-1: Percent Decrease in Total Initial Radioactivity in Viable Systems and Abiotic Controls During Sludge, Sediment, and Soil Simulation Tests Using ^{14}C-labeled HBCD

Compartment	Viable System	Abiotic Control	Time Period
Anaerobic digester sludge	87%	84%	60 days
Aerobic activated sludge	21%	15%	65 days
Anaerobic freshwater sediment	61%	33%	112-113 days
Aerobic freshwater sediment	44%	15%	112 days
Aerobic soil	10%	6%	112 days

Source: (BFRIP, 2001; Davis et al., 2006; EC, 2008)

HBCD degradation observed in these tests was attributed to abiotic reductive dehalogenation. Degradation proceeded through a stepwise process to form TETRABROMOCYCLODODECENE, DIBROMOCYCLODODECADIENE, AND 1,5,9-CYCLODODECATRIENE **(See**

Figure_Apx 2.6.4-1). Further degradation of **1,5,9-CYCLODODECATRIENE** was not observed. General trends observed were increased HBCD degradation under anaerobic conditions compared to aerobic conditions and slower degradation of α-HBCD compared to the β- and γ-stereoisomers.



Source: Davis et al., 2006; ECB, 2008

Figure_Apx 2.6.4-1: Stepwise Reductive Dehalogenation of HBCD

D-1-3 Water and Wastewater

HBCD is not expected to undergo hydrolysis in environmental waters because of its low solubility and lack of hydrolyzable functional groups. Based on the studies described above it is not expected to be readily degradable in WWTPs and is expected to be persistent in surface and groundwater. It may undergo indirect photolysis or abiotic degradation catalyzed by iron or organic matter and can be biodegraded slowly under aerobic and anaerobic conditions. Degradation rates in the environment are expected to be slower than those in lab studies. This is consistent with environmental observations. For example the detection of HBCD at concentrations ranging from 112 to 70,085 µg/kg dry weight in sediment at locations near a production site in Aycliffe, UK collected two years after the facility was closed down demonstrates the persistence of this substance in the environment (EC, 2008).

D-1-4 Bioaccumulation

High bioconcentration of HBCD in aquatic organisms has been observed in fish. Veith et al. (Veith et al., 1979) measured a BCF of 18,100 for HBCD in fathead minnows. In a flow-through bioconcentration test, BCF values of 8974 and 13,085 were determined for HBCD in rainbow trout (EC, 2008). These BCF values indicate that HBCD has a very high potential to bioconcentrate in aquatic organisms. The widespread detection of this substance in aquatic organisms also suggests that HBCD bioconcentrates in the environment (Covaci et al., 2006; EC, 2008). Biomagnification of HBCD in the aquatic food web has also been reported based on measurements in invertebrates, fish, birds, and marine mammals, with the highest levels of HBCD measured in seals and porpoises (Covaci et al., 2006; EC, 2008; EPA, 2010a). Higher concentrations of HBCD were measured in eggs from wild peregrine falcons feeding on birds from terrestrial food webs in southwestern Sweden than in the eggs of captive falcons feeding on domestic chickens, indicating that HBCD bioaccumulation in terrestrial food chains may also be important (EPA, 2010a; Lindberg et al., 2004). Bioaccumulation may be isomer specific with γ-HBCD is the dominant stereoisomer present in commercial HBCD formulations (>75%)

(Becher, 2005). Similar proportionality is observed with HBCD stereoisomers detected in environmental media (Covaci et al., 2006). However, in living organisms, α-HBCD is the predominant stereoisomer, accounting for 70-90% of all HBCD detected (Covaci et al., 2006). The reason for the difference in HBCD composition found in the environment compared to that found in living organisms is unknown. Possible explanations include different rates of bioconcentration for the α- and γ- stereoisomers or different rates of metabolism within organisms (Covaci et al., 2006; EC, 2008).

D-2 Toxicity to Aquatic Organisms

The toxicity to aquatic organisms has been summarized in several publications (EC, 2008; Environment CA and Health CA, 2011; EPA, 2008a, 2014b; NICNAS, 2012; OECD, 2007). Guideline studies in freshwater fish, daphnia, and green algae mostly reported no lethal or sublethal effects at concentrations approaching saturation (Calmbacher, 1978; EPA, 2014b; Graves and Swigert, 1997a, 1997b; Roberts and Swigert, 1997; Siebel-Sauer and Bias, 1990).

D-2-1 Aquatic Plant Toxicity

The toxicity to aquatic plants is summarized below and presented in Table_Apx D-2. The study denoted with an asterisk is proposed for use by EPA/OPPT for risk assessment. Those studies not considered adequate for risk assessment by EPA/OPPT are shaded in the table.

Green algae (*Selanastrum capricornutum*) were exposed to nominal test concentrations of HBCD ranging from 1.5 to 6.8 µg HBCD/L (Roberts and Swigert, 1997). The mean measured concentration of HBCDs (3.7 µg HBCD/L) at the maximum nominal test concentration of 6.8 µg HBCD/L (with solvent) was similar to the independently measured water solubility limit (8.6 µg/L). No effects were observed at any test concentration. Another freshwater aquatic plant study reported that green algae (*S. subspicatus*) had no effects at nominal test concentrations ranging from 7.8 to 500 mg HBCD/L (Siebel-Sauer and Bias, 1990). However, the actual concentrations of HBCD in test solution are unknown. No effects were observed at the highest tested concentration.

Adverse effects observed following exposure were found in studies with the estuarine/marine algae species *Skeletonema costatum* (Desjardins et al., 2004, 2005; Walsh et al., 1987). Walsh et al. (1987) reported measured 72-hour EC_{50} values in *S. costatum* ranging from 0.009 to 0.012 mg HBCD/L based on reduced growth rate in five different types of saltwater media. The study also tested two species, *Chlorella sp.* and *Thalassiosira pseudonana*, that were found to be less sensitive. Desjardins et al. (2005) further substantiated observed toxicity in *S. costatum* when a single saturated solution of 0.0545 mg HBCD/L (without a solvent) resulted in 51% growth inhibition after 72 hours of exposure. Desjardins et al. (2004) also reported 19, 21, and 7.3% inhibition of cell density, biomass, and growth rate, respectively, following exposure of *S. costatum* to 0.041 mg HBCD/L (with a solvent), the only concentration tested, for 72 hours.

Table_Apx D-2: Toxicity of HBCD to Aquatic Plants

Test Species	Fresh/ Salt Water	Duration	End-point	Conc. (mg/L)	Test Analysis	Effect	References
Green algae (*Selanastrum capricornutum*)	Fresh	96-hour	EC_{50}	>0.0037	Static, Measured	Biomass/Growth rate	Roberts and Swigert, 1997
Green algae (*S. subspicatus*)	Fresh	96-hour	EC_{50}	>500	Static, Nominal		Siebel-Sauer and Bias, 1987
Algae (*S. costatum*)	Marine	72-hour	EC_{50}	>0.041	Static, Measured		Desjardins et al., 2004
Algae (*S. costatum*)	Marine	72-hour	EC_{50}	>0.01	Static, Measured	Growth inhibition	Desjardins et al., 2005
Algae (*S. costatum*)	Marine	72-hour	EC_{50}	0.052	Static, Measured		
*Algae (*S. costatum*)	Marine	72-hour	EC_{50}	0.009-0.012	Static, Measured	Growth rate	Walsh et al., 1987
Algae (*Thalassiosira pseudonana*)	Marine	72-hour	EC_{50}	0.05-0.37	Static, Measured		
Algae (*Chlorella* Sp.)	Marine	72-hour	EC_{50}	>1.5	Static, Measured		

* The study denoted with an asterisk is proposed for use by EPA/OPPT for risk assessment.
Shaded studies will not be used to evaluate the risk of HCBD because inadequate test methods or incomplete information were provided for the study.

D-2-2 Aquatic Invertebrate Toxicity

The toxicity to aquatic invertebrates is summarized below and presented in Table_Apx D-3. The study denoted with an asterisk is proposed for use by EPA/OPPT for risk assessment. Those studies not considered adequate for risk assessment by EPA/OPPT are shaded in the table.

Water fleas, (*Daphnia magna; 10 animals per replicate*) were exposed to nominal concentrations of 0.0015, 0.0022, 0.0032, 0.0046 and 0.0068 mg/L HBCD under flow through conditions for 48 hours (Graves and Swigert, 1997a). On day 0, mean measured exposure concentrations were 0.0021, 0.0018, 0.0018, 0.0026 and 0.0031mg/L and on day two, the mean measured exposure concentrations were 0.0024, 0.0017, 0.0023, 0.0015, and 0.0034 mg/L. The reported 48-hr EC_{50} was >0.0032 mg/L.

Jatzek (Jatzek, 1990) reported a lowest-observed-effect-concentration (LOEC) of 10 mg HBCD/L and an EC_{50} of 146.34 mg HBCD/L for daphnia immobility based on nominal test concentrations that greatly exceeded measured water solubility values for HBCD (0.0488, 0.0147, and 0.0021 µg/L for α-, β-, and γ-HBCD); however, because the appearance of the test solutions was not reported, it is possible that reduction in daphnid swimming was related to the presence of insoluble material at higher concentrations.

For chronic toxicity, hazard was determined based on reduced size (length) of surviving young daphnids, resulting in a measured MATC of 0.0042 mg HBCD/L (Drottar and Krueger, 1998).

This study used a flow-through test system and reported additional effects, including decreased reproductive rate and decreased mean weight of surviving young at 0.011 mg HBCD/L. Mortality of adult daphnids in HBCD treatment groups was not significantly different from control mortality.

Sublethal effects to invertebrates following chronic exposure were found in supporting studies that assessed endpoints beyond those evaluated in guideline studies. In invertebrates, degenerative changes in the gills of clams (*Macoma balthica*), manifested by the increased frequency of nuclear and nucleolar abnormalities and the occurrence of dead cells, were observed at nominal concentrations of 0.1 mg HBCD/L (50-day LOEC) (Smolarz and Berger, 2009).

Table_Apx D-3: Toxicity of HBCD to Aquatic Invertebrates

Test Species	Fresh/ Salt Water	Duration	End-point	Conc. (mg/L)	Test Analysis	Effect	References
Aquatic Invertebrates – Acute Toxicity							
*Water flea (*Daphnia magna*)	Fresh	48-hour	EC_{50}	>0.0032	Flow-through, Measured	Immobilization	Graves and Swigert, 1997a
Water flea (*D. magna Straus*)	Fresh	48-hour	EC_{50}	146.34 Exceed WS	Static, Nominal	Immobilization	Jatzek, 1990
Aquatic Invertebrates – Chronic Toxicity							
Clam *(Macoma balthica)*	Marine	50-day	LOEC	0.1	Static, Nominal	degenerative changes in the gills manifested by the increased frequency of nuclear and nucleolar abnormalities and the occurrence of dead cells	Smolarz and Berger, 2009
*Water flea (*Daphnia magna*)	Fresh	21-day	LOEC	0.0056 mg/L	Flow-through, Measured	reduced length of surviving young	Drottar and Krueger, 1998
			NOEC	0.0031 mg/L			

* The study denoted with an asterisk is proposed for use by EPA/OPPT for risk assessment.
Shaded studies will not be used to evaluate the risk of HCBD because inadequate test methods or incomplete information were provided for the study.

Toxicity studies for sediment organisms are summarized in Table_Apx D-4. The study denoted with an asterisk is proposed for use by EPA/OPPT for risk assessment. Those studies not considered adequate for risk assessment by EPA/OPPT are shaded in the table.

In two prolonged sediment toxicity tests (Thomas et al., 2003a, 2003b) with *Hyalella azteca* exposed to spiked sediment in the presence of 2 or 5% TOC, no effects were seen at the highest concentration tested (1000 mg HBCD/kg dry weight sediment). Results of a non-GLP range-finding test were submitted in conjunction with the definitive tests that showed reduced survival of *H. azteca* at 500 mg HBCD/kg dry weight sediment in the presence of 2 or 5% TOC.

In another study, *Lumbriculus variegatus* were tested at nominal test concentrations of 0.05, 0.5, 5, 50, and 500 mg HBCD/kg dry weight sediment. Corresponding measured concentrations were ND, 0.2, 3.1, 28.7, 303.2 mg HBCD/kg dry weight. No HBCD was detected in the overlaying water or in the pore water. Study details were excerpted from a secondary source (Oetken et al., 2001).

Table_Apx D-4: Toxicity of HBCD to Sediment Organisms

Test Species	Fresh/ Salt Water	Duration	End-point	Conc.	Test Analysis	Effect	References
*Amphipod *(Hyalella azteca)*	Fresh	28-day	LOEC	500 mg/kg dwt sediment	Flow-through, Measured	reduced survivability	Thomas et al., 2003a, b
			NOEC	100 mg/kg dwt sediment			
Amphipod *(H. azteca)*	Fresh	28-day	NOEC	1,000 mg/kg dwt sediment	Flow-through, Measured	Unspecified	Thomas et al., 2003b
*Amphipod *(H. azteca)*	Fresh	28-day	NOEC	1,000 mg/kg dwt sediment	Flow-through, Measured	Unspecified	Thomas et al., 2003a
Chironomid (*Chironomus riparius*)	Fresh	28-day	No Dose	Not dose-responsive	N/A	Not dose-responsive	Thomas et al., 2003a
Lumbriculus variegatus	Fresh	28-day	LOEC	28.7 mg/kg dwt sediment	Static, Measured	reduction in worm number	Oetken et al., 2001
			NOEC	3.1 mg/kg dwt sediment			

* The study denoted with an asterisk is proposed for use by EPA/OPPT for risk assessment; N/A = not applicable

Shaded studies will not be used to evaluate the risk of HCBD because inadequate test methods or incomplete information were provided for the study.

D-2-3 Fish Toxicity

The toxicity to fish is summarized below and presented in Table_Apx D-5. The study denoted with an asterisk is proposed for use by EPA/OPPT for risk assessment. Those studies not considered adequate for risk assessment by EPA/OPPT are shaded in the table.

Acute Effects

Rainbow trout (*Oncorhynchus mykiss*) were exposed to mean measured concentration of HBCDs of 0.00075, 0.0015, 0.0023, 00.23 and 0025 mg/L (with solvent) under flow through conditions for 96 hours. No effects were observed at any test concentration (Graves and Swigert, 1997b).

Bluegill sunfish (*Lepomis macrochirus*) were exposed to nominal concentrations ranged from 10 to 100 mg/L under static conditions for 96 hours. These test concentrations exceeded the test substance water solubility. A white flocculate was formed on the surface of the water in all test solutions. No effects were seen at the highest test concentration of 100 mg/L (Calmbacher, 1978)(Calmbacher, 1978).

Acute effects observed following acute exposure were found in a 96-hour test with zebrafish embryos (Deng et al., 2009). In a 96-hour toxicity study with zebrafish embryos, increased malformation rate was observed at a nominal concentration of 0.1 mg HBCD/L and decreased survival and increased heart rate were observed at a nominal concentration of 0.05 mg HBCD/L (lowest concentration tested); an EC_{50} or LC_{50} value was not reported (Deng et al., 2009).

Chronic Effects

A chronic study in rainbow trout conducted following EPA recommended guidelines, found no effects at concentrations approaching saturation (Drottar et al., 2001). No effects were observed in European flounder (*Platichthys flesus*) following 78 days of diet or sediment exposure to maximum concentrations of 3000 µg HBCD/g lipid in food and 8000 µg HBCD/g total organic carbon (TOC), respectively (Kuiper et al., 2007).

Sublethal effects to fish following chronic exposure were found in supporting studies that assessed endpoints beyond those evaluated in guideline studies. Effects observed in fish include increased formation of reactive oxygen species (ROS) resulting in oxidative damage to lipids, proteins, and DNA, decreased antioxidant capacities in fish tissue (e.g., brains, hepatocytes, or erythrocytes), and increasing levels of ethyoxyresorufin-O-deethylase (EROD, detoxification enzyme) and pentoxyresorufin-O-deethylase (PROD, detoxification enzyme) levels in hepatocytes of fish exposed to the nominal concentration of ≥0.1 mg HBCD/L (corresponds to ~0.2 mg HBCD/g whole fish [wet weight]) for 42 days (Zhang et al., 2008). Indications of endocrine disruption were reported following dietary exposure to HBCD that impacted the thyroid system of juvenile rainbow trout (*Oncorhynchus mykiss*). Each of the diastereoisomers of HBCD (administered separately via diet at concentrations of 5 ng/g of α-, β-, or γ-HBCD) disrupted thyroid homeostasis, as indicated by lower free circulating triiodothyronine (T3) and thyroxine (T4) levels (Palace et al., 2010; Palace et al., 2008).

Table_Apx D-5: Toxicity of HBCD to Fish

Test Species	Fresh/ Salt Water	Duration	End-point	Conc. (mg/L)	Test Analysis	Effect	References
Fish – Acute Toxicity							
Bluegill sunfish (*Lepomis macrochirus*)	Fresh	96-hour	LC_{50}	>100	Static, Nominal	Mortality	Calmbacher, 1978
*Rainbow trout (*Oncorhynchus mykiss*)	Fresh	96-hour	LC_{50}	>0.0025	Flow-through, Measured	Mortality	Graves and Swigert, 1997b
Zebra fish embryos (*Danio rario*)	Fresh	96-hour	LC_{50}	0.05	Static, Nominal	decreased survival, reduced heart rate	Deng et al., 2009
Fish – Chronic Toxicity							
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	88-day	NOEC	0.0037	Flow-through, Measured	No effects	Drottar et al., 2001
Rainbow trout (*Oncorhynchus mykiss*)		28-day			Intraperi-toneal injection using 50 and<500 mg/kg-bw	Significant catalase activity at 50 and<500 mg/kg-bw; EROD activity; LSI increase; No effects on blood plasma, vitellogenin levels or DNA adducts formation.	(Ronisz et al., 2004)
Chinese rare minnow (*Gobiocypris rarus*)	Fresh	42-day	LOEC	0.1	Static, Nominal	DNA damage in erythrocytes; induction of EROD and PROD in hepatocytes; ROS formation in brain tissue	Zhang et al., 2008
			MATC	0.032			
European flounder (*Platichthys flesus*)	Fresh	78-day	NOEC	8,000 µg/g TOC	Sediment exposed	No effects on behavior, survival, growth rate, relative liver and gonad weights	Kuiper et al., 2007
				3000 µg/g lipid in muscle	Diet exposed		
*Rainbow trout (*O. mykiss*)	Fresh	32-day	LOEC	5 ng/g of α-, β-, or γ-HBCD	Diet exposed	thyroid effects	Palace et al., 2010

* The study denoted with an asterisk is proposed for use by EPA/OPPT for risk assessment.
Shaded studies will not be used to evaluate the risk of HCBD because inadequate test methods or incomplete information were provided for the study.

D-3 Toxicity to Terrestrial Organisms

D-3-1 Terrestrial Plant Toxicity

Available toxicity studies for terrestrial plants are summarized in Table_Apx D-6.

Studies using monocot and dicot plant species exhibited no toxicity up to the maximum test concentration of 5,000 mg HBCD/kg soil (Porch et al., 2002).

Table_Apx D-6: Toxicity of HBCD to Terrestrial Plants

Test Species	Duration	End-point	Conc.	Test Analysis	Effect	References
Corn (*Zea mays*)	21-day	NOEC	>5,000 mg HBCD/kg soil	Nominal	No treatment-related effects on emergence, survival or growth	Porch et al., 2002
Cucumber (*Cucumis sativa*)						
Onion (*Allium cepa*)						
Ryegrass (*Lolium perenne*)						

D-3-2 Soil Invertebrate Toxicity

The available toxicity study in soil organisms summarized below and presented in Table_Apx D-7 is adequate for risk assessment*.

Aufderheide et al., (Aufderheide et al., 2003) reported an EC_{10} and no-observed-effect-concentration (NOEC) values of 21.6 and 128 mg HBCD/kg dry soil, respectively, based on reproductive effects in earthworms following 56 days of exposure. High variability in the data at the lower test concentrations (as indicated in ECB, 2008) resulted in wide confidence limits for the EC_{10}, differences from the control that were not significant, and a NOEC that was greater than the EC_{10}. Two worms from the lowest test concentrations were lost during the study and treated as dead (as reported in ECB, 2008), which may have contributed to the high variability by reducing the sample size at the lowest test concentration; however, study details, data tables, and statistical methodology were not available.

Table_Apx D-7: Toxicity of HBCD to Terrestrial Invertebrates

Test Species	Duration	End-point	Conc.	Test Analysis	Effect	References
*Earthworm *(Eisenia fetida)*	56-day	EC_{10}	21.6 mg HBCD/kg dry soil	Nominal, Static, Soil	reproduction	Aufderheide et al., 2003
		NOEC	128 mg HBCD/kg dry soil			

D-3-3 Avian Toxicity

Available toxicity studies to avian species are summarized in Table_Apx D-8.

Japanese quail eggs exposed for 6 weeks to an isomeric mixture of HBCD in the diet experienced a reduction in hatchability at all tested concentrations (12–1000 ppm) (MOEJ, 2009). Additional effects included a significant reduction in egg shell thickness starting at 125 ppm, decreases in egg weights and egg production rates starting at 500 ppm, increases in cracked eggs starting at 500 ppm, and adult mortality at 1000 ppm. A subsequent test, conducted at lower dietary concentrations, determined a lowest-observed-adverse-effect-level (LOAEL) and no-observed-adverse-effect-level (NOAEL) values of 15 and 5 ppm, respectively, based on significant reduction of survival of chicks hatched from eggs of HBCD-fed quails (MOEJ, 2009). In another study, a number of effects were reported in American Kestrels exposed *in ovo* to 164.13 ng HBCD/g wet weight (Kobiliris, 2010).

Table_Apx D-8: Toxicity of HBCD to Avian Species

Test Species	Duration	End-point	Conc.	Test Analysis	Effect	References
Japanese quail (*Coturnix coturnix japonica*)	6-week	LOAEL	125 ppb	Diet exposed	reduction in hatchability	MOEJ, 2009
			15 ppm (2.1 mg/kg body wt/day		reduced chick survival	
			5 ppm			
American kestrel *(Falco sparverius)*		LOAEL	164.3 ng/g wet weight of egg	In ovo exposed	reduced corticosterone response in male nestling kestrels, reduced flying activities in juvenile males, delayed response time to predator avoidance in juvenile females	Kobiliris, 2010

Appendix E Human Health Hazard Study Summaries

E-1 Toxicokinetics

For humans, there is a potential for oral, inhalation and dermal exposure. Available toxicokinetics data in rodents indicate that HBCD is moderately absorbed via the gastrointestinal tract, metabolized, and distributed to a number of nonfat tissues including blood, muscle, and the liver, where it accumulates unchanged (Arita et al., 1983; Brandsma et al., 2009; Hakk et al., 2012; Reistad et al., 2006; Sanders et al., 2013; Szabo et al., 2010; Szabo et al., 2011b; van der Ven et al., 2009; van der Ven et al., 2006; Yu and Atallah, 1980). Elimination of HBCD is predominantly via feces (as the parent compound), but it is also eliminated in urine (as secondary metabolites) (Arita et al., 1983; Yu and Atallah, 1980; Szabo et al., 2010). In humans, HBCD has been detected in breast milk, adipose tissue, blood, and both maternal and umbilical serum (Abdallah and Harrad, 2011; Antignac et al., 2008; Covaci et al., 2006; Fangstrom et al., 2008; Fangstrom et al., 2005; Johnson-Restrepo et al., 2008; Kakimoto et al., 2008; Meijer et al., 2008; Rawn et al., 2014; Thomsen et al., 2007; Weiss et al., 2006)

E-2 Acute Toxicity Studies

Several acute toxicity studies in rats and rabbits by the oral, dermal, and inhalation routes with HBCD are available (BASF, 1990; Gulf South Research Institute, 1988; IRDC, 1977, 1978a, 1978b; Lewis and Palanker, 1978; Momma et al., 1993). The acute toxicity of HBCD is low *via* the oral route in rats and low *via* the dermal route in rabbits (Lewis and Palanker, 1978), with LD_{50} values >680 mg/kg-bw. Acute inhalation exposure to HBCD resulted in some minor symptoms (such as eye squint, slight dyspnea, salivation, lacrimation, and nasal discharge), but no LC_{50} has been identified.

The acute toxicity of HBCD is summarized in Table_Apx E-1 (oral) and Table_Apx E-2 (inhalation).

Table_Apx E-1: Acute Oral Toxicity of HBCD

Species/strain/ test	Exposure	Result	Notes	Reference
Rat/Charles River/LD_{50}	Single gavage (corn oil)	LD_{50} >10,000 mg/kg	No mortality; transient hypoactivity and diarrhea; corneal opacity and ptosis in 3/5 males, which did not resolve by end of 14-day observation.	IRDC, 1977
Rat/Charles River CD/ LD_{50} test of HBCD residue	Single gavage (corn oil)	LD_{50} = 1258 mg/kg (male); 680 mg/kg (female)	Tested Firemaster 100; increased activity, eye squint, dyspnea, lacrimation, and nasal discharge.	IRDC, 1978a

Species/strain/ test	Exposure	Result	Notes	Reference
			Weight loss in all animals; recovery noted by conclusion of study.	
Mouse/NR/LD_{50}	Single gavage (30% aqueous tragacanth)	LD_{50} >6,400 mg/kg; data not shown	7-day observation period; increasing apathy, trembling and late mortalities; peritonitis at necropsy.	BASF, 1990
Rat/Sprague-Dawley/limit test of HBCD bottoms	Single gavage (corn oil)	LD_{50} >5,000 mg/kg; clinical signs	This study tested HBCD bottoms described as black solids, lacrimation, and facial swelling resolved by post-exposure day 4; no gross lesions were observed.	Pharmakon Research International Inc., 1990
Rat/NR/LD_{50} test	Single gavage (corn oil)	LD_{50} >10,000 mg/kg	No significant changes observed.	Gulf South Research Institute, 1988

Abbreviations: NR, not reported

Table_Apx E-2: Acute Inhalation Toxicity of HBCD

Species/strain/test	Exposure	Result	Notes	Reference
Rat/Charles River/LD_{50}	4-hr exposure to Firemaster 100 dust: 202.14 mg/L	No mortality; slight dyspnea at the end of exposure only	All rats gained weight over the observation period, but no control data were reported.	IRDC, 1977
Rat/Wistar/limit test	1-hr exposure to 200 mg/L GLS-S6-41A (highest possible concentration)	No mortality; no clinical signs	All rats gained weight over the observation period, but no control data were reported.	Lewis and Palanker, 1978
Rat/Charles River/LC_{50} test of Firemaster 100 residue (liquid)	4-hr exposure to Firemaster 100 residue: 22.9 mg/L	One death (female, Day 3 post-exposure); dyspnea, salivation, lacrimation, and nasal discharge during exposure, resolved by Day 3; significant body weight loss through Day 3, but beginning to recover by Day 14 post exposure; signs of nasal and lung irritation at gross necropsy of rat that died.		IRDC, 1978b
Rat/NR/LC_{50} test	1 hr. whole-body inhalation exposure to GLS-S6-41A	LC_{50} >200 mg/L	No significant effects observed.	Gulf South Research Institute, 1988

Abbreviations: NR, not reported

E-3 Repeated-Dose Toxicity Studies

Short-term and subchronic toxicity studies on HBCD are available and summarized Table_Apx E-3. In these studies, HBCD demonstrated effects on the thyroid and liver (Chengelis, 2002;

Chengelis, 1997, 2001; van der Ven et al., 2006). However, most of these effects were not significant after a recovery period of 14 days and 28 days, respectively (Chengelis, 2002; Chengelis, 1997, 2001). Older short-term and chronic toxicity studies using an HBCD product that is no longer manufactured concluded that observed liver findings were adaptive rather than adverse (Zeller and Kirsch, 1969, 1970). Developmental behavioral defects were observed in 3-month old mice after a single oral exposure on postnatal day (PND) 10 (Eriksson et al., 2006).

This following summary is extracted from the hazard characterization found in the supporting documents for Initial Risk-Based Prioritization of High Production Volume Chemicals (EPA, 2008a):

The potential toxicity from repeated oral exposure to HBCD was assessed in a variety of studies in laboratory animals. Liver effects were observed in several studies but based on the inconsistency of effects between studies and sexes, and lack of dose-response, it is not clear if the observed effects are treatment-related. Effects on the thyroid (one or both sexes) were observed at moderate to high doses in some repeated-dose studies but not others, but could be due to the fact that the thyroid system was not thoroughly studied in the early studies. More recent studies showed increased thyroid weights in females only. One study indicates decreased serum T4 and increased serum TSH in both sexes, whereas another study only shows effects in females. Taken together, however, the data are suggestive of possible treatment-related thyroid effects in adult animals. Several recent *in vivo* and *in vitro* studies have been conducted to try and elucidate the possible mechanisms for both the observed liver and thyroid effects, but with no clear conclusions. Functional observation battery and motor activity evaluations in adult animals showed no evidence of neurotoxicity.

Table_Apx E-3: Repeated-Dose Toxicity of HBCD

Species/strain	Exposure	Result	Notes	Reference
Sprague-Dawley rats	28-days	Liver weight increase from the lowest dose (940 mg/kg-day) in both sexes. Thyroid hyperplasia from the lowest dose (940 mg/kg-day) in both sexes.	The authors attributed the increased liver weight to hyperactivity as a result of increased thyroid activity and concluded the increased liver weights were not pathologic. NOAEL = 940 mg/kg-day.	Zeller and Kirsch, 1969
Sprague-Dawley rats	90-days	Liver weight increases from the lowest dose (120 mg/kg-day) in both sexes. No histopathological effects in thyroid were reported.	Demonstrates a low order of toxicity and may reflect a reversible adaptive change. Data supports that the liver and thyroid glands are targets.	Zeller and Kirsch, 1970

Species/strain	Exposure	Result	Notes	Reference
Sprague-Dawley rats	28-days	Liver weight increase in females from the lowest dose (125 mg/kg-day) and in males from the mid dose (350 mg/kg-day). No histological effects observed in the thyroid in either sex.	The effects on the liver especially in female rats indicate a LOAEL of 125 mg/kg-day.	Chengelis, 1997
Sprague-Dawley rats	90 days	Liver weight increase from the lowest dose (100 mg/kg-day) in both sexes.	Thyroid weight was increased from the mid-dose in females (300 mg/kg-day), but not in males. Serum T4 was decreased and TSH increased in all dose groups of both sexes. LOAEL of 100 mg/kg-day based on increases in liver weights and changes in thyroid serum concentrations.	Chengelis, 2001
Wistar rats	28 days	Liver weight increases in females at 23 mg/kg-day	Most sensitive endpoint was a 10% increase in thyroid weight in females at 3 mg/kg-day.	Van der Ven et al., 2006

E-4 Reproductive and Developmental Toxicity Studies

The available toxicity data for HBCD also includes evidence of reproductive, developmental, and neurological toxicity in rats and mice which are summarized in Table_Apx E-4 and Table_Apx E-5. An exposure-response array for reproductive and developmental toxicity is presented in Figure_Apx 2.6.4-2 and for neurological effects is presented in Figure_Apx 2.6.4-3.

Information on the developmental and reproductive toxicity of HBCD comes from a single-generation reproductive toxicity study (van der Ven et al., 2009), a study incorporating gestational and post-natal exposure (Saegusa et al., 2009), a two-generation reproduction toxicity study (Ema et al., 2008), a gestational exposure study (Murai et al., 1985), and a neurotoxicity study of adult mice neonatally exposed to HBCD (Eriksson et al., 2006).

Table_Apx E-4: Reproductive and Developmental Toxicity of HBCD*

Species/strain	Exposure	Result	Notes	Reference
Wistar rats	One full spermatogenic or two full estrous cycles (males: 70 d prior to mating; females: 14 d prior to mating) and continued during pregnancy and lactation for a total of 11 wks post weaning	No exposure related changes in reproductive parameters, including mating success, time to gestation, gestation duration, number of implantation sites, litter size, and sex ratio.	NOAEL ~ 100 mg/kg-day (highest dose tested)	Van der Ven et al., 2009
Crl:CD(SD) rats	10 wks prior to mating and through gestation, lactation, and for two generations (multi-generation reproductive toxicity study)	A significant decrease in the number of primoridal follicles in the ovary; decreased size of the thyroid follicles in both sexes and an increase in pup mortality during lactation	LOAEL ~ 101 mg/kg-day NOAEL ~ 10 mg/kg-day	Ema et al., 2008
Wistar rats	GD 0-20	No significant changes in the number of implants, resorptions, live or dead fetuses or external, visceral or skeletal anomalies	NOAEL ~ 750 mg/kg-day (highest dose tested)	Murai et al., 1985
Crj:CD(SD)IGS rats	GD 10–PND 20 (weaning)	No exposure-related changes in reproductive parameters; however, increased thyroid weight and decreased serum T_3 in male offspring at ~146 mg/kg-day	NOAEL ~ 1505 mg/kg-day (highest dose tested)	Saegusa et al., 2009
Wistar rats	See Van der Ven et al., 2009	Effect on Brainstem Auditory Evoked Potentials (BAEPs) observed in the low frequency range and only in male off-spring (see text)	Neurobehavioral assessment of the rats in the Van der Ven et al., 2009 study.	Lilienthal et al., 2009

*Only studies considered adequate for risk assessment are presented in the table.

Signs of developmental toxic effects in Wistar rats included immune system effects, indications of liver toxicity, and decreases in bone mineral density at very low doses, i.e., <1.3 mg/kg-day (van der Ven et al., 2009); however, the authors noted that the vehicle used (corn oil) may have affected observations at higher doses, including: increased mortality during lactation, decreased liver weight in males, decreased adrenal weight in females, decreased plasma cholesterol in females, and other immunological markers of toxicity. Saegusa et al. (2009) observed an increased relative thyroid weight and decreased triiodothyronine (T3) levels in F1 male Sprague-Dawley rats at postnatal week (PNW) 11 following dietary exposure to 1,000 ppm (approximately 146.3 mg/kg-day) HBCD. Saegusa et al. (2009) also reported a significant reduction in the number of CNPase-positive oligodendrocytes at 10,000 ppm (approximately 1,504.8 mg/kg-day). Developmental toxicity was not observed in F1 Wistar rats following dietary exposure to HBCD during gestation (Murai et al., 1985).

Ema et al. (2008) reported a reduced viability index on Day 4 and Day 21 of lactation among second generation (F2) offspring at 15,000 ppm (approximately 1,363 mg/kg-day). Ema et al. (2008) observed additional developmental effects at doses as low as 1,500 ppm (approximately 115 and 138 mg/kg-day for F1 males and females, respectively), including: an increase in dihydrotestosterone (DHT) in F1 males and an increased incidence of animals with decreased thyroid follicle size in both sexes and generations. These authors reported no effects on sexual development indicated by anogenital distance, vaginal opening, or preputial separation among F1 or F2 generations.

Reproductive toxic effects have also been observed in Ema et al. (2008). A decrease in the number of primordial follicles in first generation (F1) female Crl:CD(SD) rats at 1,500 ppm (approximately 138 mg/kg-day) and a significant increase in the number of litters lost in the F1 generation at 15,000 ppm (approximately 1,363 mg/kg-day) were reported. No other treatment-related adverse effects were reported in any generation for indicators of reproductive health, including: estrous cyclicity, sperm count and morphology, copulation index, fertility index, gestation index, delivery index, gestation length, number of pups delivered, number of litters, or sex ratios.

Neither van der Ven et al. (2009) nor Saegusa et al. (2009) observed reproductive effects at the doses tested (up to 100 mg/kg-day in Wistar rats and approximately 1,504.8 mg/kg-day in Sprague-Dawley rats, respectively).

No standard neurotoxicity or developmental neurotoxicity studies on HBCD are available. Information on neurotoxicity was obtained from Functional Observational Battery, locomotor activity evaluations, neurobehavioral testing, surface righting reflex, negative geotaxis reflex, mid-air righting reflex, and brainstem auditory evoked potentials (BAEPs) in several repeated-dose and reproductive toxicity studies.

For example, in a subacute toxicity study, HBCD was administered orally by gavage in corn oil to Sprague-Dawley Crl:CD BR rats for 28 days at doses of 0, 125, 350, or 1,000 mg/kg-day (6

rats/sex/dose in 125 and 350 mg/kg-day groups and 12 rats/sex/dose in the control and 1,000 mg/kg-day groups) (Chengelis, 1997). At the end of 28 days, 6 rats/sex/dose were necropsied, while the remaining rats in the control and 1,000 mg/kg-day groups were untreated for a 14-day recovery period prior to necropsy. Functional Observational Battery and motor activity evaluations were carried out prior to study initiation, during the last week of HBCD administration (Week 3), and during the recovery period (Week 5). No changes in the Functional Observational Battery and motor activity tests were reported.

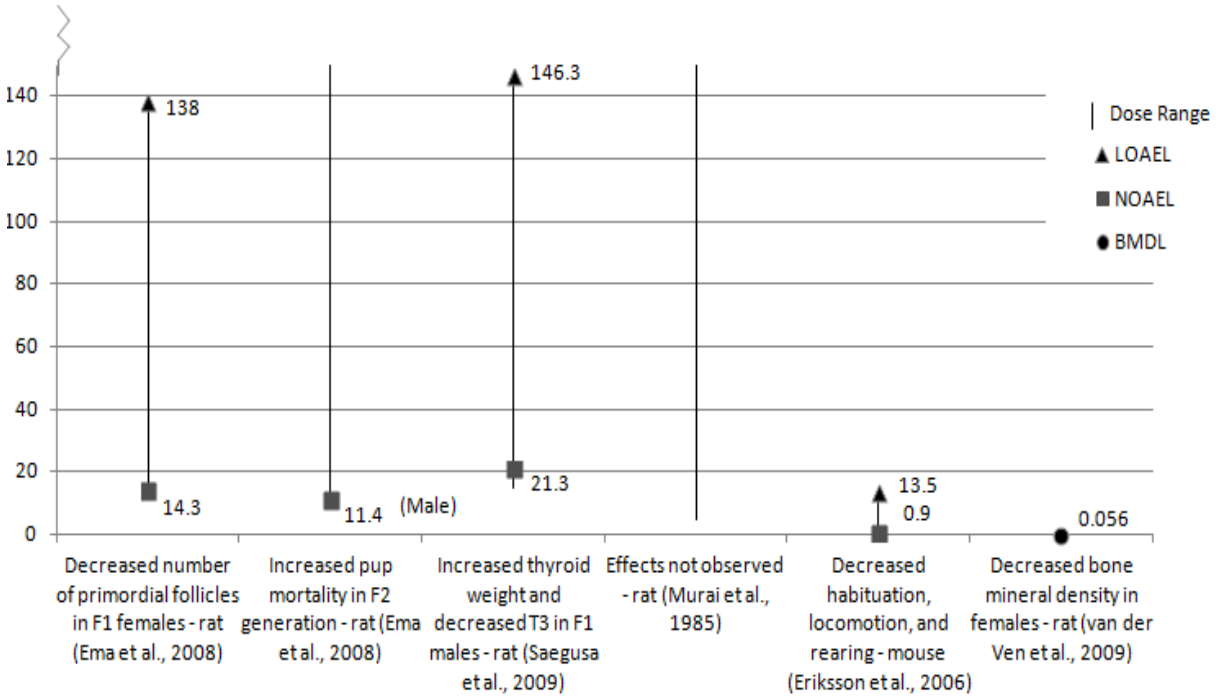
In another subchronic toxicity study, (Chengelis, 2002; Chengelis, 2001) administered HBCD by oral gavage in corn oil daily to Crl:CD(SD)IGS BR rats (15/sex/dose) at dose levels of 0, 100, 300, or 1,000 mg/kg-day for 90 days. At the end of 90 days, 10 rats/sex/dose were necropsied, while the remaining rats were untreated for a 28-day recovery period prior to necropsy. Functional Observational Battery and locomotor activity evaluations were carried out on 5 animals/sex/dose prior to study initiation, during the last week of HBCD administration (Week 13), and during the recovery period. There were no treatment-related effects on Functional Observational Battery and locomotor activity observed.

In a one-generation study that included additional immunological, endocrine and neurodevelopmental endpoints, van der Ven (2009) exposed Wistar rats (10/sex/dose) to a composite mixture of technical-grade HBCD in the diet at concentrations resulting in doses of 0.1, 0.3, 1.0, 3.0, 10, 30, or 100 mg/kg-day. This study followed OECD Guidelines 415 and 407 (OECD, 1983, 1995). Just prior to the end of the study, at approximately 8 weeks of age, the remaining F1 pups were assigned to separate groups for necropsy (5/sex/dose), immunological testing (4 males/dose), or neurobehavioral testing (6/sex/dose plus additional males and females from selected dose groups). Lilienthal et al. (Lilienthal et al., 2009) reported the results of the neurobehavioral assessment from the one-generation study conducted by van der Ven et al. (2009). Lilienthal et al. (2009) examined 110 day-old F1 rats for haloperidol-induced catalepsy to determine possible effects of HBCD on the dopaminergic system. One month after the catalepsy measurements, brainstem auditory evoked potentials (BAEPs) to broadband click and frequency-specific tone stimuli were recorded in males and females to examine potential effects on auditory functions. The study authors concluded that the observed dose-dependent decreases in latencies may be due to HBCD-related effects on dopaminergic activity or to HBCD-related induction of metabolizing liver enzymes resulting in enhanced metabolism of haloperidol. HBCD-related effects on BAEP were observed in the low frequency range and only in male offspring. The study authors hypothesized that HBCD exerts a cochlear effect on males based on the results of the BAEPs. The authors noted that an alternative explanation could be HBCD-induced changes in retinoids, which may be involved in development of the inner ear. Too little information is available in this study to determine the significance of its findings.

Finally, in a two-generation reproductive toxicity study, Ema et al. (2008) administered HBCD to Crl:CD(SD) rats conducted according to OECD Guideline 416 (OECD, 2001), US EPA Guidelines (EPA, 1991, 1996), and good laboratory practices (GLP). Groups of male and female rats

(24/sex/dose) were fed HBCD (as a mixture of α-HBCD, β -HBCD, and γ-HBCD with proportions of 8.5, 7.9, and 83.7%, respectively) in the diet at concentrations of 0, 150, 1,500, or 15,000 ppm from 10 weeks prior to mating through mating, gestation, and lactation. Reproductive and developmental milestones were monitored, including: surface righting reflex, negative geotaxis reflex, mid-air righting reflex, and anogenital distance. F2 females exposed to 15,000 ppm HBCD completed the mid-air righting reflex (76.9%) than control F2 females (100%). These findings were not consistent over generations or sexes and were not considered treatment related. No other effects of HBCD exposure on the development of reflexes were observed in either F1 or F2 progeny.

An additional study on the neurotoxicity of HBCD is available. Eriksson et al. (2006) observed effects on spontaneous motor behavior, learning, and memory in adult NMRI mice following exposure to HBCD on postnatal day (PND) 10. At 0.9 mg/kg, the authors reported significantly reduced mean locomotor activity. However, this study was not conducted according to current guidelines (EPA, 1998b) and GLP, therefore EPA reserves judgment on the significance of these findings. The authors used too few dose groups and the behavioral alterations were induced at doses that did not produce clinical signs or affect weight gain. Additionally, effects due to litter size were not considered. However, this study did demonstrate good repeatability for control values and for relevant active substances tested several times.



Figure_Apx 2.6.4-2: Exposure-Response Array for Developmental and Reproductive Toxicity Studies of HBCD

Table_Apx E-5: Summary of Effects in Parental and F1 Rats After Dietary, Gestational, Lactational and Postnatal Exposure to HBCD

	HBCD (ppm in diet)							
	Males[c]				Females[c]			
Generation	**0**	**100**	**1,000**	**10,000**	**0**	**100**	**1,000**	**10,000**
F0								
Thyroid								
Relative weight (mg/100 g BW)	ND	ND	ND	ND	5.73	6.75	6.30	7.47*
Histopathology: diffuse follicular cell hypertrophy (±/+/++/+++)[a]	ND	ND	ND	ND	3/10 (0/3/0/0)[b]	5/10 (2/3/0/0)	6/10 (1/3/2/0)	9/10# (0/3/4/2)§§
F1								
Relative organ weights, PND 20								
Liver (g/100 g BW)	3.68	3.82	3.98	4.66*	3.77	3.83	4.01	4.83*
Relative organ weights, PNW 11								
Liver (g/100 g BW)	3.45	3.81**	3.58	3.53	3.35	3.59	3.44	3.30
Thyroid (mg/100 g BW)	4.85	5.66	5.78*	6.20**	8.20	6.84	7.35	7.72
Epididymides (mg/100 g BW)	0.23	0.21*	0.22	0.21	NA	NA	NA	NA
Thyroid-related hormones								
PND 20								
T_3 (ng/ml)	1.09	1.13	1.06	0.93**	ND	ND	ND	ND
T_4 (µg/dl)	4.39	4.20	4.78	4.20	ND	ND	ND	ND
TSH (ng/ml)	5.40	6.66	6.07	7.00*	ND	ND	ND	ND
PNW 11								
T_3 (ng/ml)	0.96	0.93	0.88*	0.89**	ND	ND	ND	ND
T_4 (µg/dl)	4.77	4.84	5.21	5.20	ND	ND	ND	ND
TSH (ng/ml)	4.74	5.81	5.36	4.96	ND	ND	ND	ND
Histopathology								
PND 20								
Liver: Vacuolar degeneration, liver cells, diffuse (+/++)[a]	0/10	0/10	0/10	6/10* (6/0)	0/10	0/10	0/10	6/10* (0/6)§§
PNW 11								
Adrenal: Vacuolar degeneration, diffuse, cortical cells (+/++)[a]	0/10	0/10	0/10	4/10* (2/2)§	ND	ND	ND	ND

Abbreviations: BW, body weight; PND, postnatal day; ppm, parts per million; PNW, postnatal week; ND, no data; NA, not applicable; [a]Grade of change: (±) minimal; (+) slight; (++) moderate; (+++) severe; [b]Number of animals with each grade; [c]n=10 rats/sex/group; * Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (p<0.05)

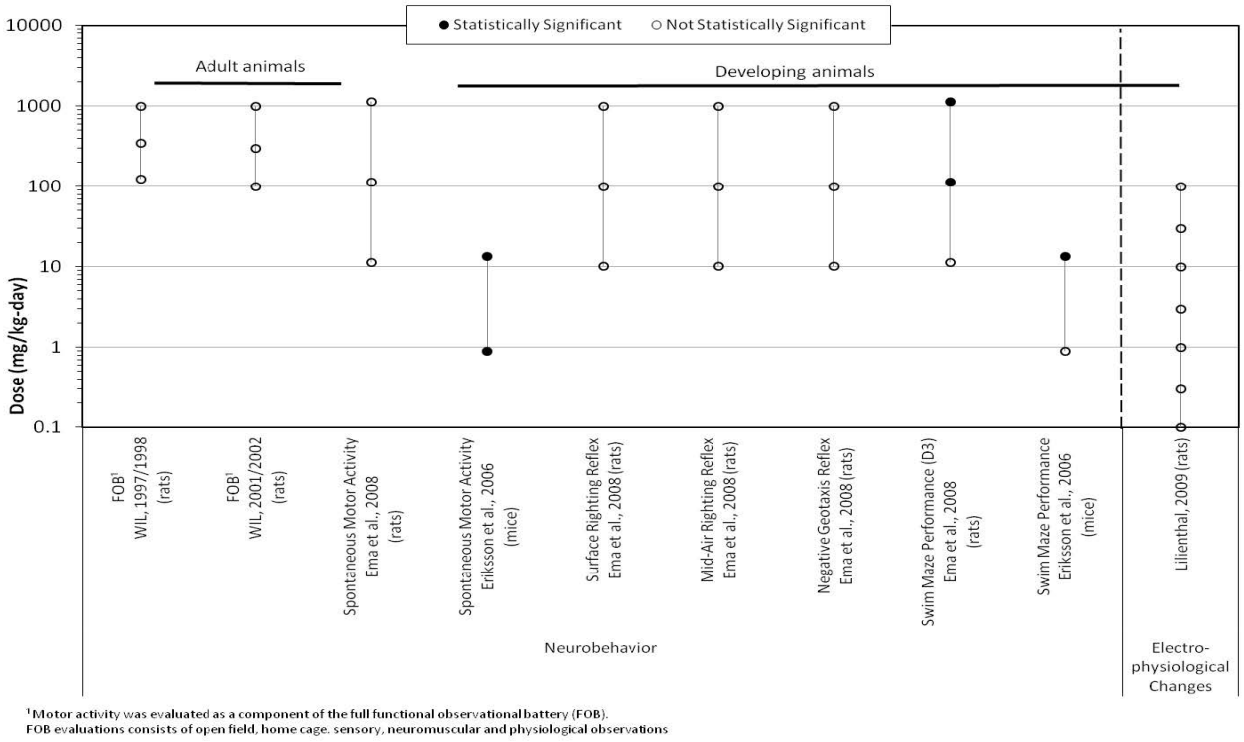
** Significantly different from the controls by Dunnett's test or Dunnett-type rank-sum test (p<0.01)

Significantly different from the controls by Fisher's exact probability test (p<0.05)

§ Significantly different from the controls by Mann-Whitney's U-test (p<0.05)

§§ Significantly different from the controls by Mann-Whitney's U-test (p<0.01)

Source: (Saegusa et al., 2009)



Figure_Apx 2.6.4-3: Exposure-Response Array for Neurological Effects of HBCD

Source: (EPA, 2014d)

E-5 Skin Irritation and Sensitization Studies

The available literature indicates that HBCD is not a dermal irritant in guinea pigs at concentrations up to 0.5 mL, but one study found HBCD to be a mild skin allergen (Momma et al., 1993). Acute eye irritation studies in rabbits showed HBCD to be a mild transient ocular irritant (Gulf South Research Institute, 1988).

E-6 Genotoxicity and Cancer Studies

A limited number of studies investigated the genotoxicity of HBCD. These studies, summarized in Table_Apx E-6, indicate that HBCD is not likely to be genotoxic.

The majority of these studies were standard Ames tests for detecting mutagenic potential in *Salmonella typhimurium* (*S. typhimurium*). Most Ames tests conducted with HBCD yielded negative results (Huntington Research Center, 1978; IBT, 1990; Litton Bionetics Inc, 1990; Pharmakoligisches Institute, 1978; SRI, 1990; Zeiger et al., 1987). Two Ames tests showed positive, dose-dependent results for strain TA1535; one for TA1535 only using a liquid residue of HBCD in DMSO (IBT, 1990); and one for strains TA1535 and TA100 using an unidentified

mixture characterized only as HBCD bottoms in acetone (Ethyl Corporation, 1985a). Both of these strains detect reversions by base pair substitution. However, the Ames tests in the strains that were positive in these two studies (TA1535 and TA100) were negative in the other studies cited above.

In mammalian systems, a reverse mutation assay with Chinese hamster ovary (CHO) Sp5 and SPD8 cell lines exposed to HBCD yielded positive results (Helleday et al., 1990). A test of unscheduled DNA synthesis with rat hepatocytes exposed to HBCD bottoms was also positive with a dose-response relationship (Ethyl Corporation, 1985b). The reverse mutation assay in CHO cells (Helleday et al., 1999) and the unscheduled DNA synthesis assay in F344 hepatocytes (Ethyl Corporation, 1985b) were not repeated by any other group.

Several assays performed to determine the genotoxicity of HBCD were negative even when testing at cytotoxic concentrations, including: one in yeast (Litton Bionetics Inc., 1990), one detecting chromosomal aberrations in human peripheral lymphocytes *in vitro* (Microbiological Associates Inc, 1996), and one *in vivo* mouse micronucleus test following intraperitoneal injection of HBCD (BASF, 2000). Several previous assessments have concluded that based on the lack of mutagenicity *in vitro* and *in vivo*, HBCD does not have genotoxic potential *in vitro* or *in vivo* (EC, 2008; Environment CA and Health CA, 2011; NICNAS, 2012; OECD, 2007). EPA agrees with this conclusion.

Existing assessments have also concluded, based on genotoxicity information and one limited lifetime study, that HBCD is not carcinogenic (NICNAS, 2012; TemaNord, 2008) or that further study of carcinogenicity is not warranted (EC, 2008; OECD, 2007). However, the only available dietary study evaluating the carcinogenic potential of HBCD in mice is not considered adequate to draw conclusions regarding carcinogenicity (EC, 2008; Environment CA and Health CA, 2011; EPA, 2014b; OECD, 2007). Given this data gap, EPA's HBCD assessment will not include carcinogenicity assessment.

Table_Apx E-6: Genotoxicity of HBCD

Test/species/strain/ route	Test doses (per plate)[a]	Results[b]		Notes	Reference
		–S9	+S9		
Eukaryotic systems, *in vitro*					
S. typhimurium TA98, TA100, TA1537	3,000 µg in DMSO	–	–	Doses ≥1,000 µg were partially insoluble.	Pharmako-logisches Institute, 1978
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	250 µg (Firemaster, FM-100, Lot 53, white powder) in DMSO	–	–	Doses ≥250 µg were insoluble.	IBT, 1990
	1,000 µg (FM-100, Lot 3322, liquid residue) in DMSO	–	+ (TA1535 only)	Positive in TA1535 at highest dose only; lower doses showed positive trend with dose.	
S. typhimurium TA98, TA100, TA1535	10,000 µg in DMSO	–	–	Insoluble at 10,000 µg.	Huntingdon Research Center, 1978
S. typhimurium TA98, TA100, TA1535, TA1537	10,000 µg in DMSO	–	–		Zieger et al., 1987
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	5,000 µg in DMSO	–	–		SRI, 1990
S. typhimurium TA98, TA100, TA1535, TA1537	50 µg (HBCD bottoms) in acetone	+ (TA1535 and 100 only)	+ (TA100 only)	No cytotoxicity observed. Dose-response only in TA1535 (–S9) ≥100 µg/plate. TA100 positive at highest dose only (5,000 ug/plate). All doses had a black precipitate thought to be carbon.	Ethyl Corporation, 1985a
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	50 µg	–	–		Litton Bionetics, 1990
Prokaryotic non-mammalian systems, *in vitro*					
Saccharomyces cerevisiae D4	50 µg	–	–		Litton Bionetics, 1990
Mammalian systems, *in vitro*					
Chromosomal aberration test In human peripheral blood lymphocytes	750 µg/mL (-S9) and 250 µg/mL (+S9) in DMSO	– (T)	– (T)	Doses 750 – 2,500 were partially insoluble, and fully insoluble >2,500 µg/mL. Repeated test for two harvest time points: 20 hr (-S9) or 4 hr (+S9) incubations, and 20 or 44 hr incubations (-S9 and +S9).	Microbiological Associates, 1996

Test/species/strain/ route	Test doses (per plate)[a]	Results[b]		Notes	Reference
		–S9	+S9		
Unscheduled DNA Synthesis rat/F344 male/primary hepatocytes	5 – 1,000 µg/well in acetone (HBCD bottoms)	+	NA	Five highest doses (from 5 µg/well) showed an increased response with dose over solvent control, but only four highest were statistically significant (χ^2). Highest dose (1,000 µg/well) was cytotoxic.	Ethyl Corporation, 1985b
Reversion assay CHO/V79/Sp5 and SPD8 Intragenic recombination at *hprt* locus in Sp5 (non-homologous recombination) and SPD8 (homologous recombination) duplication cell lines	3–20 µg/mL in DMSO	+	NA	A statistically significant increase in reversion frequency was observed in both assays in the highest dose group as determined by linear regression analysis.	Helleday et al., 1999
Mammalian systems, *in vivo*					
Micronucleus test mouse/NMRI/intraperitoneal injection	2,000 mg/kg in DMSO	– (T)	NA		BASF, 2000

[a]Lowest effective dose for positive results; highest dose tested for negative results.

[b]+ = positive, ± = equivocal or weakly positive, – = negative, T = cytotoxicity, NA = not applicable, ND = no data.