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CRITICAL REVIEW

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Hexabromocyclododecane: Current Understanding of Chemistry, Environmental Fate and Toxicology and Implications for Global Management

Christopher H. Marvin,[†,*] Gregg T. Tomy,[‡,§,*] James M. Armitage,[∥,⊥] Jon A. Arnot,[∥] Lynn McCarty,[#] Adrian Covaci,[▽] and Vince Palace[‡,§]

[†]Water Science and Technology Directorate, Environment Canada, Burlington, Ontario L7R 4A6 Canada

[‡]Fisheries & Oceans Canada, Winnipeg, Manitoba R3T 2N6 Canada

[§]Faculty of Environment and Geography, University of Manitoba, Winnipeg, Manitoba, R3T 2N2 Canada

[∥]University of Toronto Scarborough, Ontario, M1C 1A4, Canada

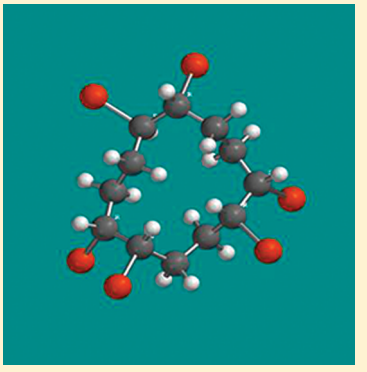
[⊥]Department of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark

[#]LS McCarty Scientific Research and Consulting, Ontario, Canada

[▽]Toxicological Centre, University of Antwerp, 2610 Wilrijk, Belgium

Supporting Information

ABSTRACT: Hexabromocyclododecane (HBCD) is a globally produced brominated flame retardant (BFR) used primarily as an additive FR in polystyrene and textile products and has been the subject of intensified research, monitoring and regulatory interest over the past decade. HBCD is currently being evaluated under the Stockholm Convention on Persistent Organic Pollutants. HBCD is hydrophobic (i.e., has low water solubility) and thus partitions to organic phases in the aquatic environment (e.g., lipids, suspended solids). It is ubiquitous in the global environment with monitoring data generally exhibiting the expected relationship between proximity to known sources and levels; however, temporal trends are not consistent. Estimated degradation half-lives, together with data in abiotic compartments and long-range transport potential indicate HBCD may be sufficiently persistent and distributed to be of global concern. The detection of HBCD in biota in the Arctic and in source regions and available bioaccumulation data also support the case for regulatory scrutiny. Toxicity testing has detected reproductive, developmental and behavioral effects in animals where exposures are sufficient. Recent toxicological advances include a better mechanistic understanding of how HBCD can interfere with the hypothalamic-pituitary-thyroid axis, affect normal development, and impact the central nervous system; however, levels in biota in remote locations are below known effects thresholds. For many regulatory criteria, there are substantial uncertainties that reduce confidence in evaluations and thereby confound management decision-making based on currently available information.



1. INTRODUCTION

The compound 1,2,5,6,9,10-hexabromocyclododecane (HBCD, $C_{12}H_{18}Br_6$) has been produced since the 1960s and is today the most used cycloaliphatic additive brominated flame retardant (BFR). HBCD is employed primarily in the building industry where it is incorporated typically at <3% by weight into extruded or expanded polystyrene foam materials. Secondary uses include upholstered furniture, automobile interior textiles, car cushions, and electric and electronic equipment.

Recent global annual production estimates for HBCD are not available, in 2001 the total production volume was 16 700 t behind only tetrabromobisphenol-A (>130 000*t*) and decabromodiphenyl ether (56 100 t); The EU-wide consumption of HBCD in 2007 was 11 000 t (http://echa.europa.eu/doc/consultations/recommendations/tech_reports/tech_rep_hbcdd.pdf)[1].

Technical HBCD (*t*-HBCD), synthesized by bromine addition to 1,5,9-cyclododecatriene, is dominated by three diastereoisomers: α, β, and γ. The relative amounts of these isomers in the *t*-HBCD ultimately depends on the manufacturer, but the γ-isomer accounts for ca. 70% of the total with the α- and β-isomer contributing ca. 10 and 6%, respectively. Although quantitative data are not available, there are trace amounts of other diastereoisomers (δ and ε) present in *t*-HBCD.[2]

In 2009, HBCD underwent screening-level risk assessments by two international regulatory bodies to determine if it meets criteria of a persistent organic pollutant (POP): (i) United

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Table 1. Summary of Persistence (P), Bioaccumulation (B), and Long-Range Transport Potential (LRTP) Screening Level Criteria and Estimated Values for HBCD. Ranges reflect variability in empirical data or model uncertainty. See SI for additional details.[a]

criterion/characteristic	regulatory threshold	HBCD
persistence (*P*)		
half-life in air (days)	>2	0.4−5.2[b]
half-life in water, (days)	>60	no obs. deg (60−130[b])
half-life in sediment, (days)	>180	1.1−128[c]
aerobic, 20 °C		11−128
anaerobic, 20 °C		1.1−115
half-life in soil, (days)	>180	6.9−no obs. deg[c]
aerobic, 20 °C		63−no obs. deg
anaerobic, 20 °C		6.9
detected in remote region	(yes/no)	yes
overall persistence (P_{ov}, days)		120 (12−1200)[b]
bioaccumulation (*B*)		
log K_{OW}	5	5.4 − 5.8
log BCF (L kg^{-1} wet weight)	3.7	3.9−4.3
Log BAF (L kg^{-1} wet weight)	3.7	3.7−6.1
BMF (lipid-normalized)		0.1−11
TMF (lipid-normalized)		0.3−2.2
long-range transport potential (LRTP)		
persistence in air (days)	>2	inconclusive
vapor pressure (P_a)	<1000	yes
detected in remote region	(yes/no)	yes
CTD (km)		600 (200−1500)

[a] K_{OW} = octanol-water partition coefficient; BCF = bioconcentration factor; BAF = bioaccumulation factor; BMF = biomagnification factor; TMF = trophic magnification factor; CTD = characteristic travel distance (distance at which air concentration is 1/e of initial value). [b] Based on model estimates rather than empirical data. [c] Tests conducted at lower, more environmentally relevant test concentrations (i.e., ug/kg dwt vs mg/kg dwt) yielded the lower-bound estimated degradation half-lives. no obs. deg denotes that degradation rate constants was not quantified; See SI Section S2.

Nations Environment Programme (UNEP) Stockholm Convention on POPs (http://chm.pops.int/Convention/POPsReviewCommittee/POPRCMeetings/POPRC6/tabid/713/mctl/ViewDetails/EventModID/871/EventID/86/xmid/2887/language/en-GB/Default.aspx), and (ii) Protocol on POPs of the United Nations Economic Commission for Europe Convention on Long-Range Transboundary Air Pollution (UNECE-POP-LRTAP, http://live.unece.org/env/lrtap/welcome.html). Although the screening level criteria of persistence (P), bioaccumulation (B) and toxicity (T) are not harmonized between the two treaties, HBCD was judged as fulfilling the P, B, and T criteria as defined under Annex D of the United Nations Environment Program (UNEP) Stockholm Convention and Executive Body Decision 1998/2 of the UNECE-POP-LRTAP.

This paper examines the quality and quantity of information for HBCD in the broad categories of persistence, bioaccumulation, toxicity, and long-range transport. These data are reviewed in the context of possible global action and the impact of uncertainty due to data gaps and poor and/or conflicting data, on decision-making confidence in full, rather than screening-level, risk assessment activities. While two reviews of HBCD were completed in the last 10 years, at the time of writing of this review, 263 additional papers have appeared in the peer-reviewed literature since 2006.[3,4] New information on analytical approaches and challenges to measuring enantiomers and enantiomer-specific environmental processes, detection of the meso-forms (δ and ε) in the environment, temporal trends in biota and abiotic environmental compartments, human exposure, recent work on toxicology and the usefulness of (animal) models to help interpret monitoring data are discussed.

2. PHYSICAL−CHEMICAL PROPERTIES

2.1. Chemical Identity. The CAS Registry contains two numbers representing the undefined mixtures of commercial or *t*-HBCD: 25637-99-4 (without numbering for the position of the bromine substitution pattern) and 3194-55-6 for 1,2,5,6,9,10-HBCD.[5] The stereochemistry of HBCD is complex including 16 stereoisomers[3] and HBCD is subject to isomerization during product synthesis and in the environment.[6−9] Most of the reported chemical properties and toxicity tests to date are for *t*-HBCD, a mixture of isomers; however, as discussed in this review the individual isomers are shown to have characteristic properties related to their fate and behavior in the environment and their potential for toxic effects.

2.2. Chemical Properties. Measured and modeled physical-chemical properties considered to be of primary relevance for evaluating the environmental chemistry and toxicology of *t*-HBCD and the three main diastereoisomers (α-, β-, and γ-HBCD) were compiled and critically reviewed. These data include molar mass (M; $g \cdot mol^{-1}$), melting point (T_M; K), water solubility (*S*; $mol \cdot L^{-1}$), vapor pressure (*P*; Pa), Henry's law constant (*H*; $Pa \cdot m^3 \cdot mol^{-1}$), and the dimensionless equilibrium partition coefficients between air and water (K_{AW}), octanol and water (K_{OW}), and octanol and air (K_{OA}). Recommended methods for establishing thermodynamically consistent, and thus more reliable, solubility and partitioning properties were applied to obtain final adjusted values (FAVs).[10] The details of the data compilation, review and calculation of FAVs is documented in the Supporting Information (SI) (Section S-1). Isomer-specific measurements are recommended for P, H, and K_{OA} to further reduce uncertainty in these parameters.

3. PERSISTENCE (P), BIOACCUMULATION (B), AND LONG-RANGE TRANSPORT POTENTIAL (LRTP)

Screening level criteria used by the Stockholm Convention (SC)[11] and UN-ECE Protocol[9] to categorize compounds according to P, B, and LRT potential are presented in Table 1 along with empirical and model-derived estimates (SI Sections S-2 to S-7). Issues and remaining research questions associated with categorization of HBCD are discussed.

3.1. Persistence. Empirical data characterizing persistence of HBCD are available for water, sediments, soil, and wastewater sludge[12−15] and model-derived estimates are available for air and water.[16] Key remaining uncertainties regarding persistence are related to (i) the paucity of empirical data, (ii) reliability of laboratory test methods and interpretation of data, and (iii) the extrapolation of laboratory-based data to the field.

No empirical data are available for characterizing the reactivity HBCD in the atmosphere and estimates rely on model-derived output (AOPWIN v1.92[17]). The range in half-life in air presented in Table 1 (0.4−5.2 days) reflects different assumptions regarding the concentration of OH radicals (minor influence) and estimated uncertainty in the second-order rate constant for OH radical attack (main factor) (SI Section S-2). Empirical data on atmospheric degradation pathways and rate constants would reduce uncertainty in the determination of HBCD persistence.

Results from one laboratory study (OECD 301D closed bottle test) and model-derived estimates are available to characterize biodegradation of HBCD in water (SI Section S.2).[12] Biodegradation was reported to be negligible over the 28-day laboratory test; however, the reported initial water concentration was 7.7 mg L^{-1}, that is, 2−3 orders of magnitude higher than the water solubility limit (SI Section S.1). As % degradation is calculated as the ratio of biochemical oxygen demand and theoretical oxygen demand, it is possible that biodegradation appeared negligible, because only a small fraction of the total HBCD added was freely dissolved (bioavailable). Model-derived estimates for biodegradation of HBCD in water are based on BIOWIN[12] output and the estimation approaches proposed by Arnot et al.[17] and Aronson et al.[18] These results (60−130 days) indicate HBCD exceeds the criterion for persistence in water. However, it is difficult to assess the uncertainty inherent to these model-based approaches.

The majority of empirical data available to characterize the persistence of HBCD are from studies using sediments, wastewater sludge and soil.[13−15] Degradation of the parent compound in both sediments and soils proceeds faster in anoxic conditions and in the presence of microorganisms.[13] Ranges in values for sediments and soils (Table 1) reflect variability in degradation rate constants at different initial HBCD concentrations (μg/kg vs mg/kg), with observed half-lives 1−2 orders of magnitude higher at mg/kg concentrations.[14] One possible explanation is mass transfer limitations into microorganisms bias biodegradation kinetics at elevated substrate concentrations; however, half-lives were still well described by first-order kinetics. Based on the data presented in Table 1, HBCD does not satisfy the persistence criterion in sediments, but may do so for soils. Arguments to disregard rate constant data derived from tests conducted at elevated concentrations have merit, but need substantiation. Additional biodegradation experiments conducted across a gradient of initial concentrations would be useful.

A remaining question relevant to assessment of persistence is isomer-specific susceptibility to degradation. Davis et al.[14] reported no statistically significant differences in degradation half-lives between α-, β-, and γ-HBCD, whereas Gerecke et al.[15] reported a nearly 2-fold lower susceptibility to degradation for α-HBCD. Photolysis has been hypothesized as an important cause for HBCD isomerization in dust.[6] Results revealed a rapid photolytically mediated shift from γ-HBCD to α-HBCD, and slower degradation via elimination of HBr. Calculated half-lives ($t_{1/2}$) showed decay in ΣHBCDs concentration was faster in light-exposed samples ($t_{1/2}$ = 12 weeks), than in light-shielded dust ($t_{1/2}$ = 26 weeks).

Overall, a key uncertainty is the degree laboratory-based degradation data reflect the behavior of HBCD in the environment. For example, HBCD depth profiles in sediment cores suggest slower degradation kinetics than laboratory-derived estimates.[19] However, since degradation of HBCD is known to be enhanced by microbial activity, presence at depth in sediment could reflect absence of viable microbial communities rather than inhibited biodegradation due to other factors (e.g., temperature). These apparent discrepancies are also relevant for risk management (e.g., allowable uses, disposal practices) and therefore further investigation is warranted.

3.2. Overall Persistence (P_{OV}). Overall persistence (P_{OV}) is a complementary metric for assessing environmental persistence[19] that incorporates distribution in the environment in addition to degradation kinetics in each medium. The OECD Tool was used to calculate P_{OV} for HBCD and benchmark chemicals.[11,20] Based on the median parameter set, the P_{OV} of HBCD is approximately 120 d; however, values range from 12 to 1200 days, reflecting the assumed uncertainty in input variables, particularly in the degradation half-lives assumed for water and soil (SI Section S.3). The P_{OV}s included in the benchmarking exercise range from 70 to 4700 (known POPs) and 10 to 1300 days (non-POPs), respectively. The overlap in the ranges of P_{OV} between categories introduces some ambiguity, but the calculated P_{OV}s for HBCD tend to be lower than model output for other POPs. However, the P_{OV} based on the upper bound degradation half-lives for HBCD is approximately 1 order of magnitude higher, reinforcing the need to better characterize HBCD degradation rate constants, particularly in soil.

3.3. Bioaccumulation. The FAVs for log K_{OW} of HBCD isomers range from 5.4 to 5.8, thus exceeding the B POP criterion. In the absence of biotransformation, neutral organic chemicals with log K_{OW} of this magnitude are expected to be bioaccumulative in both aquatic and air-breathing organisms.[21]

The range of empirical bioconcentration factors (BCFs) [22,23] for technical HBCD and bioaccumulation factors (BAFs) for the isomers [20−22] exceed the B criteria (SI Section S-4). For example, estimated BAFs (L kg^{-1}, wet weight) for α-HBCD in Lake Winnipeg (Canada) range from approximately 50 000−125 000.[20] Average field-derived BAFs reported in Harrad et al. for lucustrine fish from England are 5900, 1300, 810, and 2100 for α-, β-, γ-, and ΣHBCDs, respectively.[21] Note that these BAFs are (i) based on lipid-weight concentrations in muscle tissue and (ii) in units of L g^{-1}. The corresponding average wet-weight BAFs in units appropriate for comparison to regulatory criteria (i.e., L kg^{-1} wet weight), estimated based on the assumptions detailed in Harrad et al.,[21] range from approximately 41 000(γ-)−295 000(α-).

Lipid-normalized biomagnification factors (BMFs) show variability, depending on the isomer and organisms considered (SI Section S.4). For example, the reported BMFs for α-, β-, and γ-HBCD for goldeye/mussels inhabiting Lake Winnipeg are 8.2, 1.0, and 0.3, respectively, but 1.9, 5.0, and 2.9 respectively for burbot/mussels.[20] In a Lake Ontario study, BMFs for α- and γ-HBCD are 4.8 and 7.5, 1.0 and 1.5, and 1.1 and 0.8 for trout/alewife, trout/smelt, and trout/sculpin, respectively.[23] BMFs for the same predator/prey relationship are not always consistent among studies. For example, Sørmo et al.[24] reported a lipid-normalized BMF of approximately 11 (total HBCD) for ringed seal/polar cod sampled from Svalbard, whereas data reported in Tomy et al.[25] for the western Arctic yield a BMF of 0.1. Ranges in trophic magnification factors (TMFs) are more constrained, but still vary by isomer and food web and are not always statistically significant. Law et al.[20,26] reported TMFs for α-, β-, γ-, and ΣHBCD in a freshwater aquatic food web (1,4, 1.3, 2.2, and 1.8 respectively), but only the TMF for γ- and ΣHBCD were significant. In contrast, Wu et al. reported that only the TMF for α-HBCD (2.2, $p < 0.05$) was statistically significant in organisms in a freshwater pond in China.[27]

Additional studies to better understand variability in BMFs and TMFs would be valuable. However, one trend consistent across studies is the shift in isomer profile with trophic level that appears to favor accumulation of α-HBCD over the β- and γ-isomers.[4,20,26,28] This phenomenon possibly results from a combination of differences in (i) solubility and partitioning behavior (i.e., bioavailability) (ii) uptake and depuration kinetics (including biotransformation) as well as (iii) preferential in vivo bioisomerization of β- and γ- isomers to α-HBCD.[4,27] An additional complexity is the extent enantiomer-specificity influences these processes.[28] For example, while HBCD chiral signatures were racemic in water and sediment, data revealed enantiomeric enrichment of $(-)\alpha$-HBCD and $(+)\gamma$-HBCD in fish.[20,27] The potential role of solubility, phase distribution, chemical uptake efficiencies, biotransformation, and bioisomerization were assessed as determinants of isomer-specific bioaccumulation potential (SI Sections S.5 and S.6). These novel analyses support the hypothesis that biotransformation and bioisomerization are key processes resulting in food web attenuation of γ-HBCD. Overall, as lipid-normalized BMFs and TMFs >1 indicate that a substance is bioaccumulative,[29] the available empirical data generally support the conclusion that HBCD fulfills the B criteria.

3.4. Long-Range Transport (LRT) Potential. Under international conventions, LRT potential is characterized based on persistence in air, vapor pressure and detection in remote regions. HBCD fulfills two of three screening criteria unequivocally; however, model-based metrics characterizing LRT potential should also be considered. As with P_{OV}, it is useful to compare model output against other compounds (POPs and non-POPs), as was recently done for characteristic travel distance (CTD) and Arctic contamination potential ($eACP_{10}$)[15] (SI Section S.7). Since substantial overlap for both CTD and $eACP_{10}$ between benchmark categories was found, a definitive categorization of HBCD with respect to other compounds is not possible. The assumed uncertainty in HBCD property values contributes to this ambiguity. With respect to LRT potential, this analysis further demonstrates the need to better characterize the fate of HBCD, particularly atmospheric degradation and gas-particle partitioning.[16]

In characterizing chemicals with respect to LRT potential, it is also important to recognize the presence of chemicals in remote environments is a function not only of LRT potential but also emission rate.[30,31] Information on emission strength and mode of entry are required to interpret remote monitoring data.

4. ANALYTICAL CHEMISTRY

A trend toward liquid chromatography-tandem mass spectrometry (LC-MS/MS) for determination of HBCD has been observed in recent years.[32] Sample preparation methods, including extraction, cleanup, and fractionation have been described for determination of HBCDs in dust[33] human milk,[34] biological samples,[35] and sewage sludge.[36] Increased attention has been also given to methods to determine HBCDs in consumer products and rate of transfer into the indoor environment.[37,38] A detailed overview of these methods is given in SI Section S.9).

The LC-MS/MS methods are routinely applied[39] and may include comprehensive suites of other BFRs, such as tetrabromobisphenol A (TBBPA).[35,40] However, LC-MS analyses using electrospray ionization (ESI) are prone to ion suppression resulting in decreased sensitivity. This can be avoided by thorough sample cleanup and by using ^{13}C- and ^{2}H-labeled HBCDs to compensate for variations in response. Alternatively, other ionization techniques, such as atmospheric pressure photoionization (APPI) and atmospheric pressure chemical ionization (APCI), reportedly less influenced by ion suppression, were assessed for analysis of HBCD together with other BFRs.[41,42]

A limited number of intercalibration studies have been performed at a low participation rate. Haug et al.[43] indicated laboratories determined ΣHBCD concentrations in marine samples with satisfactory quality (RSD <35%). However, analyses of samples with low contamination (<2 ng g^{-1} lipid weight) needed improvement. There are currently no reference materials with certified values for HBCDs, but indicative values are available for some matrices. In any case, certification of HBCDs in relevant materials is imperative.

The α-, β-, and γ-HBCD diastereomers are represented by a corresponding pair of enantiomers, which have been isolated using enantioselective HPLC and confirmed by X-ray diffraction.[44] Since enantiomers can have vastly different biological properties/activities and degradation rates, enantioselective analyses are necessary to fully understand the environmental relevance of HBCD. Extraction and clean up methods for determination of HBCD enantiomers are similar to those for the diastereomers, but a chiral LC phase is required for separation. Most methods use a permethylated β-cyclodextrin chiral stationary phase with an elution order of $(-)\alpha$-HBCD, $(-)\beta$-HBCD, $(+)\alpha$-HBCD, $(+)\beta$-HBCD, $(+)\gamma$-HBCD, and $(-)\gamma$-HBCD.[44] An important issue is the apparent nonracemic nature of LC-MS/MS chromatograms of HBCD standards.[39,45] Matrix effects, stationary phase and mobile phase gradient are causal factors.[39,45] Recent work by Guerra et al. demonstrated influence of temperature in the ESI source.[46]

Most importantly, measurement of enantiomeric fractions (EFs) of HBCD, that is, ratios of enantiomers, must be corrected using labeled surrogates.[39] A comparison of corrected vs uncorrected HBCD EFs in fish demonstrated potential for false conclusions regarding enantioselective bioaccumulation of HBCD when using uncorrected EF values for α-HBCD.[39] However, the same study also indicated enantioselective bioaccumulation of the $(-)\gamma$-HBCD enantiomer. The most recent reports indicate calculation of corrected EFs is now common in investigations of enantiospecific occurrence/accumulation of HBCD.[21,34,46]

5. OCCURRENCE, SPATIAL DISTRIBUTION, AND TEMPORAL TRENDS

HBCD has been detected widely in biota and abiotic matrices in the northern hemisphere, exhibiting a strong gradient with proximity to main historical production/use regions (ref 3, SI Section S.8, Table S22). The paucity of reported concentrations in background/remote soils is the most substantial data gap. Isomeric profiles of HBCD in abiotic matrices (sediment,[47] sewage sludge,[36] and air [33]) are generally similar to the technical mixture.

The meso forms of HBCD have been identified in technical mixtures.[2,44] Recently, the δ-HBCD meso form was quantified in 43% of fish samples (1.0−11% ΣHBCDs) from English lakes,[21] which exceeds abundance in a commercial HBCD formulation (0.5% ΣHBCDs). Its absence from water and sediment samples suggests formation via bioisomerization. Its presence in fish also raises the question whether its suspected presence in piscivorous birds[16] arises from dietary intake and/or occurs via bioisomerization.

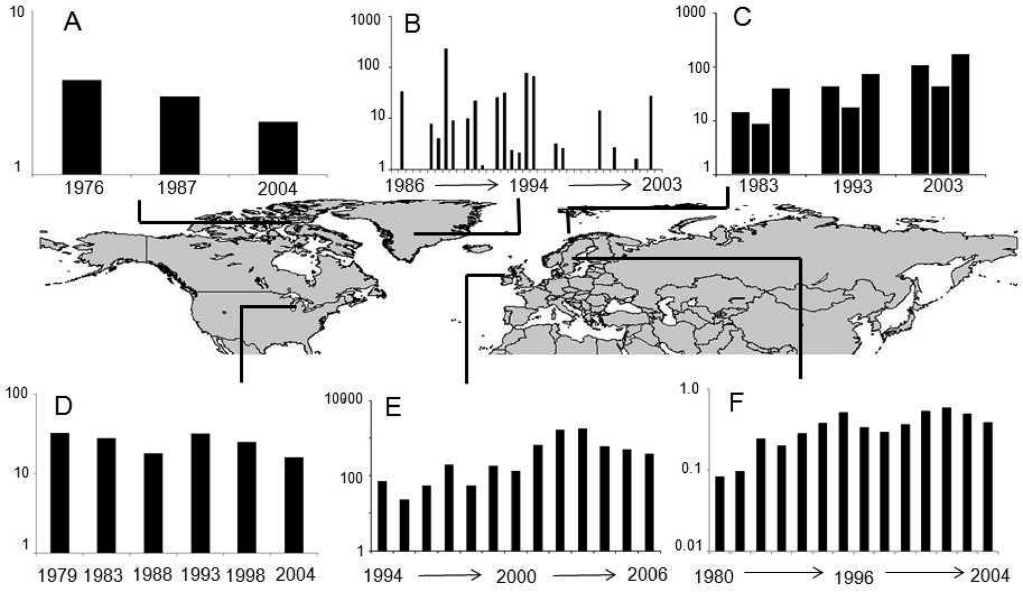

Figure 1. Reported or calculated mean concentrations of HBCD (total, $\mu g\ kg^{-1}$ lipid-normalized) in [A] ivory gull eggs (Canadian Arctic archipelago [103]), [B] peregrine falcon eggs (South Greenland[46]), [C] herring gull, puffin and kittiwake eggs (Norway[104]), [D] whole body lake trout (Lake Ontario[48]), [E] harbor porpoise blubber (United Kingdom[105,106]) and, [F] human milk (Sweden[50]) from different locations in the northern hemisphere over time. Note that each plot has its own scale on the *y*-axis.

Aside from the aforementioned studies, we find no evidence of widespread detections of the meso forms of HBCD in any environmental compartments.

Concentrations of HBCD in biota from different locations in the northern hemisphere over time are shown in Figure 1. Temporal trends do not show a uniform pattern.[16,48] In some studies,[47,49] concentrations may have stabilized or begun to decrease over the past decade, whereas other studies indicate concentrations are increasing in other species, including humans.[50,51] However, human data from urban areas likely indicates local or regional changes in production and/or usage and does not reflect trends in remote areas. Overall, lack of consistent trends in animal tissues convolutes determination of persistence or LRT. Analysis of temporal trend data in biota would be facilitated by (i) information on production/use of HBCD; (ii) temporal trends in exposure media; and (iii) information on stability/metabolism of HBCD isomers.

6. HUMAN EXPOSURE TO HBCDS

Humans are exposed to HBCD via multiple sources including food, dust, air, and consumer products.[4,22,52−54] Exposure may be dermal or oral, and can result from inhalation of vapor and particles.[53] In the work environment, direct dermal exposure and inhalation of fine particles are of particular concern. Industrial workers at plants producing EPS with HBCD had HBCD levels up to 856 ng g^{-1} lw serum in their blood.[55] Serum levels in non-occupationally exposed individuals (<1 ng g^{-1} lw) were typically much lower[54] and indirect exposure via the environment or products becomes in this case of primary concern. HBCD in indoor dust samples ranged from <5 to 130 200 ng g^{-1} (median 230 ng g^{-1} [56]). Abdallah and Harrad[57] found HBCD in household air (median 180 pg m^{-3}), household dust (median 1300 ng g^{-1}), office dust (median 760 ng g^{-1}), and car dust (median 13 000 ng g^{-1}).

Levels of human dietary exposure vary globally and regionally.[58,59] Surveys in Europe and the US reveal levels in the range of <0.01−5 ng g^{-1} w/w.[59] Fatty foods of animal origin such as meat and fish are likely a major source of dietary human exposure and depends on consumption trends.[58,60] Among dietary samples, the highest HBCD concentrations were reported for fish.[51] Accordingly in Norway, where fish is an important part of the diet, intake of fish has been found to closely correlate with serum HBCD levels.[51,61] The presence of HBCD in vegetables and vegetable oils may arise from use of sewage sludge as fertilizer.[62] Stereoisomeric patterns in food samples suggest differences depending on food type.[58,59]

Although diet is a major exposure route in Europe, U.S. and China,[4,58,63] indoor air, and in particular dust, can be important routes of exposure in both adults and toddlers.[64,65] For a toddler of 10 kg who ingests an estimated 200 mg dust day^{-1} with HBCD contamination at the 95th percentile, intake via dust may exceed by 10 times the levels received via diet alone.[64] In the study of Roosens et al.,[59] daily exposure from food and dust was similar in magnitude for adults, and HBCD concentrations in serum only correlated significantly with estimates of exposure via dust. Exposure to dust appears to be an important exposure route because exposure remains more constant over time, compared to periodic intake of contaminated food.[59] As in the case of dietary exposure, there is a large international variation in exposure via pathways like dust and air.[21]

As a result of continuous exposure via diet and via homes, offices and cars,[57] HBCD was found in human adipose tissue[66] and blood.[55,59,67] Exposure occurs in early development as HBCD is transferred across the placenta to the fetus[67] and transferred via breast milk. HBCD has been detected in breast milk from Europe,[34,50,68,69] Asia,[58,70−72] Russia,[73] and the U.S.[63] Hence, exposure to HBCD occurs at critical stages of development, both during pregnancy and postnatally via breast milk. HBCD in breast milk appears to mirror market consumption of HBCD.[70] In breast milk from Japanese women (age 25−29), HBCD was not detected in any sample collected between 1973 and 1983, but increased from 1988 onward. In the period

1988−2006, α-HBCD was detected in all pooled milk samples with levels ranging from 0.4 to 1.9 ng g^{-1} lw. The levels reported from this Japanese study (1−4 ng g^{-1} lw) are higher than reported for women from Norway where HBCD was detected in only 1/10 samples at an average concentration of 0.13 ng g^{-1} lw.[69] Temporal trends show an increase in Swedish milk up to 2002 after which a leveling occurs.[50]

While the extent of oral absorption of HBCD in humans is largely unknown, estimates of uptake via breast milk ranges from 50 to 100%.[74] According to the EU risk assessment,[74] intake of HBCD via breast milk is 1.5 ng kg^{-1} bw day^{-1} for 0−3 month olds and 5.6 ng kg^{-1} bw day^{-1} in 3−12 month old babies. However, Eljarrat et al.[34] calculated the intake to be 175 ng kg^{-1} bw day^{-1} for 1 month olds in northern Spain. This is 12-times higher than the estimated daily intake (EDI) for 0−3 month old infants as determined in the EU risk assessment[74] and 25−1500 times higher than the EDI for European adults.[34,75] A Flemish dietary study suggests that the age group between 1 and 3 years is the highest exposed with an EDI for ΣHBCD of 7 ng kg^{-1} bw day^{-1} day. Newborns and adults are less exposed with EDIs of 3 and 1 ng kg^{-1} bw day^{-1} respectively.[75] In all instances children appear to be more exposed than adults.

Although α-HBCD, followed by γ- and β-HBCD, is the predominant diastereoisomer in all biota, including humans,[74] profiles in human tissues are not consistent.[34,58,59,63] External exposure (time, dose and stereoisomeric pattern), toxicokinetics, biotransformation, and time of sampling may all be important. In the study of Roosens et al.,[59] γ-HBCD isomer dominated in food, whereas α-HBCD dominated in dust and was the sole isomer in serum. Although exposure via dust ingestion correlated with concentrations in serum, no correlation was evident with dietary exposure. While no enantioselective enrichment was detected in either dust or diet, substantial enrichment of (−)α-HBCD was observed in serum. The enrichment of the (−)α-HBCD enantiomer in humans appears to be due to in vivo enantioselective metabolism/excretion rather than ingestion of dust or diet.

7. TOXICITY

Since the last reviews on HBCD toxicology,[4,76−78] there have been significant advances in understanding mechanisms of toxicity. These include a better understanding of effects on thyroid function, brain development and neuron function, and reproduction and development. Recent studies have investigated the importance of oxidative stress and initiation of apoptotic cell death for mediating cellular toxicity (SI Section 10). Figure 2 graphically presents relationships between concentrations of HBCD in tissues or exposure media and disruption of thyroid function, reproductive system, and nerve function and development in classes of vertebrates. SI Table S.23 in Section S.10 provides brief descriptions of the studies cited in Figure 2.

7.1. Thyroid Toxicity. Thyroid effects are a consistent response of exposure to HBCD. Thyroid hyperplasia and lower circulating concentrations of thyroxine (T4) were determined in repeated oral dosing studies with rats.[77] Studies have confirmed HBCDs potential to disrupt the thyroid axis in in vivo and in vitro animal models, including mammals,[79−88] fish [89−91] and birds.[92,93] The specific cellular and molecular mechanisms by which HBCD affects the thyroid axis reveal differences in HBCD accumulation and effects between males and females. Interpretation of data from animal models remains critical as no studies examined potential toxic effects in vivo in humans.

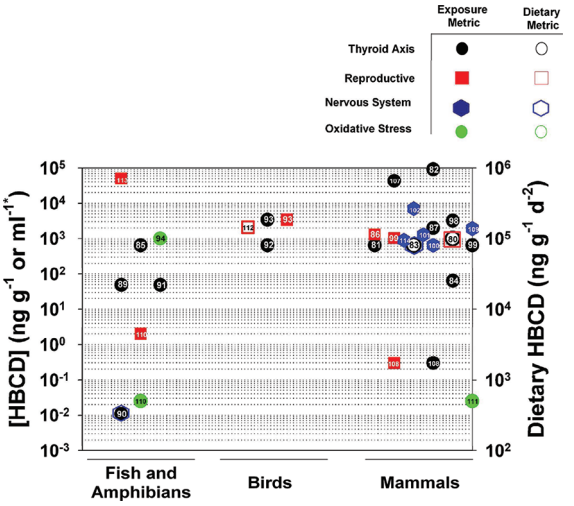

Figure 2. Lowest observed effects levels identified in studies examining effects of HBCD on thyroid end points (black circle), reproduction (red square), nerve function (blue hexagon) and oxidative stress (green circle) in biological systems where in vivo or in vitro HBCD exposure has been quantified (closed symbols), or where dietary HBCD exposure was reported (open symbols plotted against right-hand *y*-axis). Numbers in figure indicate referenced study.[107−114]

Mechanisms for HBCD's effects on thyroid activity have been investigated. It appears likely HBCD affects the thyroid axis by altering expression of biotransformation enzymes. Thyroidal effects of other BFRs, including polybrominated diphenyl ethers, are partially mediated by alterations in CYP1A1 expression; similar mechanisms may occur for HBCD. However, despite at least one report to the contrary,[94] HBCD does not appear to induce CYP1A[82,95] and may inhibit activity of its regulated proteins.[89,96]

There is accumulating evidence that HBCD induces CYP2B and CYP3A through interaction with CAR/PXR receptors and analogues, and that inductions are key to explaining HBCD's thyroid effects. Germer et al.,[82] suggested HBCD effects in rats may be mediated via both the CAR and PXR receptors. However, extrapolation to potential effects in humans should be performed with caution because of the different affinity of the receptors for agonists in these two models.[82]

Other studies examined the ability of HBCD to induce thyroid effects through interaction with PXR and CAR receptors using in vitro exposure systems. Fery et al.,[81] investigated HBCD in inducing CYP3A1 enzymes in rat and human hepatoma cells, and concluded HBCD is a PXR agonist which may account for disrupted thyroid activity in several animal models. Moreover, this induction pattern could explain why females are more affected in terms of thyroid hormone reductions than males.[86] Concentrations required to elicit effects were several orders of magnitude higher than those in humans.

Crump et al.,[92] examined the effect of HBCD on the chicken xenobiotic-sensing orphan receptor (CXR). HBCD did not affect gene expression of CXR in chicken embryo hepatocytes, but the phase I metabolizing enzymes CYP2H1 and CYP3A37 were up-regulated by α-HBCD or *t*-HBCD, suggesting genes of the CXR were activated without activation of the receptor. This result, as well as the study by Germer et al.,[82] shows CYP3 induction is one of the most sensitive end points reported in higher animals.

Elevated rates of phase II conjugation activity have been demonstrated in HBCD-exposed organisms. Using tissues from the same rats as Germer et al.,[82] Van der Ven et al.,[86] reported an increase in hepatic T4-UGT activity accompanied by lower circulating total T4, increased pituitary weight, and increased thyroid weight and epithelial cell heights, indicative of glandular activation. These effects were noted only in females. Canton et al.,[79] showed UGT1A1 was up-regulated in males, but down-regulated in females, which provides a mechanistic hypothesis for greater accumulation and slower elimination of HBCD by females. Elevated glucuronidation rates were demonstrated in fish fed HBCD.[89] Evidence indicates circulating thyroid hormones may be depleted in HBCD-exposed organisms, which would increase peripheral tissue uptake of thyroid hormones.[97]

In addition to affecting the thyroid axis by increasing hormone turnover rates, HBCD affects interactions between thyroid hormones and their receptors. Using human cervical carcinoma cells Yamada-Okabe et al.[87] (Figure 2: Study No. 6) showed HBCD activated the thyroid receptor in the presence of T3. Affinity for the receptor was noted even in the absence of T3 (ref 98, Figure 2 Study No. 7). Hyperthyroidal effects were observed in the T-screen assay where HBCD induced growth of the rat pituitary tumor GH3 cell line in the absence of T3, and to a greater extent in the presence of T3 (ref 99, Figure 2 Study No. 14).

Schriks et al. (ref 88 Figure 2 Study No. 9) investigated the ability of HBCD to affect GH3 cells cultured from the rat pituitary. In the absence of T3, HBCD had no effect on GH3 cell proliferation indicating that HBCD did not directly interact with the thyroid receptor. However, in the presence of T3, HBCD potentiated GH3 cell proliferation. The inhibitory effect of HBCD in the presence and absence of T3 (ref 85, Figure 2 Study No. 10) has been examined on regression of tadpole tail tips in an ex vivo culture system. Collectively, these studies indicate the agonistic activity of HBCD toward T3-mediated effects.

7.2. Toxicity Concerns at Current Environmental Concentrations/Exposures. The studies reviewed indicate HBCD is not acutely toxic to terrestrial organisms, aquatic organisms and lower trophic organisms including algae (SI Section 10.1). There are insufficient data to assess the carcinogenic potential of HBCD, but carcinogenic initiation is not likely to occur via mutagenesis. Oral, dermal and inhalation toxicity is low in mammalian models.[77] Acute toxicity of HBCD is not a general concern for aquatic organisms owing to the compound's limited solubility (2−3 μg L^{-1} at 25 °C).[16] Several studies report no toxicity to algae, aquatic invertebrates or fish at nominal exposure concentrations that exceed the limit of HBCD solubility.[77] However, several chronic effects arising from exposure to HBCD are consistently noted, with similar responses reported in vivo and/or in vitro using animal models or cell lines, respectively. Activation of the PXR/CAR complex, altered thyroid and lipid metabolism, potential reproductive effects, nervous system damage and oxidative stress, have all been observed.

Deriving a sense of the potential for HBCD to affect end points in biota from urban, rural and remote locations is hampered by several factors. Few toxicological studies have examined tissue concentrations to relate to their measured end points. Nominal doses or exposures are given but toxicological bioavailability is not quantified. Concentrations of HBCD reported for biota from the environment are often determined as "whole animal" or in tissues (e.g., muscle, adipose tissue), but which may have less relevance for determining effects (e.g., liver, thyroid, nervous tissue). Units of HBCD reported differ between studies and often cannot be compared without conversion, introducing a measure of uncertainty.

Despite these limitations, there are available toxicological and environmental data on which to generally assess the potential for biological effects in wild fish, birds and mammals. Among the most sensitive end points are effects on the mammalian nervous system. Thresholds from in vitro exposures[100,101] and in vivo exposures[102] note lowest observable effects at low μM concentrations (approximately 1000−20 000 ng g^{-1}). Thyroid function alterations appear to be the most universally noted effect of HBCD across biological levels of organization. In vitro cell culture work indicates HBCD can bind to thyroid receptors,[84,87] affect T3 mediated cellular events[84,85,88,97] and gene expression of thyroid binding proteins[92] and increase expression of genes that can increase turnover rates of thyroid hormones.[81] In vivo thyroid axis effects have also been noted at liver tissue concentrations of >40 000 ng g^{-1} in mammals[86] and as low as ∼2600 ng g^{-1} in fish.[89] Consideration of these collective data, with a primary focus on observed whole organism effects, against environmental concentrations noted in Figure 2 suggest that adverse effect thresholds may be exceeded in biota from some point source and source locations, but that biota in remote locations are below known adverse effect thresholds.

Given the wide variety of experimental HBCD toxicity data available, development of a weight of evidence scheme for differentiating between measurable changes and toxicologically significant adverse effects would facilitate technical input into regulatory assessments. A framework for POP risk characterization has recently been proposed including a case study for HBCD.[115]

8. RECOMMENDATIONS

In assessing the overall state of HBCD science globally, we make the following recommendations for future assessments:

1 Comprehensive studies on bioisomerization and biotransformation of HBCD diastereomers in various species are needed.
2 Studies to better understand the apparent variability in BMFs and TMFs are required.
3 Studies of the isomer-specific susceptibility of HBCD to degradation are required to improve our understanding of the isomer-specific fate of HBCD, which in turn will provide insights into behavior of this compound in biota.
4 Investigate global variation in dietary exposure and exposure through air and dust.
5 Additional laboratory intercalibration studies are required for HBCD.
6 There is a requirement for reference materials with certified values for HBCDs.
7 A formal decision-making framework for weighing and classifying technical evidence is needed to aid in distinguishing between measurable effects and toxicologically significant adverse effects.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Detailed information regarding criteria used in the assessment of HBCD persistence, bioaccumulation

toxicity and long-range transport. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone: 905-319-6919 (C. M. T.); 204-983-5167 (G. T. T.). E-mail: chris.marvin@ec.gc.ca (C. M. T.); gregg.tomy@dfo-mpo.gc.ca (G. T. T.).

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REFERENCES

(1) Janák, K.; Covaci, A.; Voorspoels, S.; Becher, G. Hexabromocyclododecane in marine species from the western Scheldt estuary: Diastereoisomer- and enantiomer-specific accumulation. *Environ. Sci. Technol.* **2005**, *39*, 1987–1994.

(2) Arsenault, G.; Konstantinov, A.; Marvin, C. H.; MacInnis, G.; McAlees, A.; McCrindle, R.; Riddell, N.; Tomy, G. T.; Yeo, B. Synthesis of the two minor isomers, $\delta-$ and $\varepsilon-$1,2,5,6,9,10-hexabromocyclododecane, present in commercial hexabromocyclododecane. *Chemosphere* **2007**, *68*, 887–892.

(3) Law, R. J.; Kohler, M.; Heeb, N. V.; Gerecke, A. C.; Schmid, P. P.; Voorspoels, S.; Covaci, A.; Becher, G.; Janák, K.; Thomsen, C. Hexabromocyclododecane challenges scientist and regulators. *Environ. Sci. Technol.* **2005**, *39*, 281A–287A.

(4) Covaci, A.; Gerecke, A. C.; Law, R. J.; Voorspoels, S.; Kohler, M.; Heeb, N. V.; Leslie, H. A.; Allchin, C. R.; de Boer, J. Hexabromocyclododecane (HBCDs) in the environment and humans—A review. *Environ. Sci. Technol.* **2006**, *40*, 3679–3688.

(5) Becher, G. The stereochemistry of 1,2,5,6,9,10-hexabromocyclododecane and its graphic representation. *Chemosphere* **2005**, *58*, 989–991.

(6) Harrad, S. J.; Abdallah, M. A.-E.; Covaci, A. Causes of variability in concentrations and diasteromer patterns of hexabromocyclododecanes in indoor dust. *Environ. Int.* **2009**, *35*, 573–579.

(7) Heeb, N. V.; Schweizer, W. B.; Mattrel, P.; Haag, W. R.; Gerecke, A. C.; Schmid, P. P.; Zennegg, M.; Vonmont, H. Regio- and stereoselective isomerization of hexabromocyclododecanes (HBCDs):kinetics and mechanisms of $\gamma-$ to α-HBCD isomerization. *Chemosphere* **2008**, *73*, 1201–1210.

(8) Koppen, R.; Becker, P. R.; Jung, C.; Nehls, I. On thermally induced isomerization of hexabromocyclododecane stereoisomers. *Chemosphere.* **2008**, *71*, 656–662.

(9) Law, K.; Palace, V. P.; Halldorson, T. H. J.; Danell, R. W.; Wautier, K.; Evans, R. E.; Alaee, M.; Marvin, C. H.; Tomy, G. T. Dietary accumulation of hexabromocyclododecane diastereoisomers in juvenile rainbow trout (*Oncorhynchus mykiss*) I: bioaccumulation parameters and evidence of bioisomerization. *Environ. Toxicol. Chem.* **2006**, *25*, 1757–1761.

(10) Schenker, U.; MacLeod, M.; Scheringer, M.; Hungerbuhler, K. Improving data quality for environmental fate models: A least-squares adjustment procedure for harmonizing physicochemical properties of organic compounds. *Environ. Sci. Technol.* **2005**, *39*, 8434–8441.

(11) *Final act of the conference of plenipotentiaries on the Stockholm Convention on persistent organic pollutants*; United Nations Environment Programme: Geneva, Switzerland, 2001.

(12) Schaefer, E.; Haberlein, D. *Hexabromocyclododecane (HBCD): Closed Bottle Test*; 439E-102; Wildlife International Ltd.: Easton, MD, 1996.

(13) Davis, J. W.; Gonsior, S. J.; Marty, G.; Ariano, J. M. The transformation of hexabromocyclododecane in aerobic and anaerobic soils and aquatic sediments. *Water Res.* **2005**, *39*, 1075–1084.

(14) Davis, J. W.; Gonsior, S.; Markham, D. A.; Friederich, U.; Hunziker, R. W.; Ariano, J. Biodegradation and product identifiaction of [^{14}C]hexabromocyclododecane in wastewater sludge and freshwater aquatic sediment. *Environ. Sci. Technol.* **2006**, *40*, 5395–5401.

(15) Gerecke, A. C.; Giger, W.; Hartmann, P. C.; Heeb, N. V.; Kohler, H.-P. E.; Schmid, P. P.; Zennegg, M.; Kohler, M. Anaerobic degradation of brominated flame retardants in sewage sludge. *Chemosphere* **2006**, *64*, 311–317.

(16) Arnot, J.; McCarty, L.; Armitage, J. M.; Toose-Reid, L.; Wania, F.; Cousins, I. T. *An Evaluation of Hexabromocyclododecane (HBCD) for Persistent Organic Pollutant Properties and the Potential for Adverse Effects in the Environment*; European Brominated Flame Retardant Industry Panel (EBFRIP): Brussels, 2009.

(17) Arnot, J.; Gouin, T.; Mackay, D. *Practical Methods for Estimating Environmental Biodegradation Rates*, CEMN2005003; Canadian Environmental Modeling Network: Peterborough, Ontario, 2005.

(18) Aronson, D.; Boethling, R.; Howard, P.; Stiteler, W. Estimating biodegradation half-lives for use in chemical screening. *Chemosphere* **2006**, *63* (11), 1953–1960.

(19) *Hexabromocyclododecane As a Possible Global POP*; Nordic Chemical Group: Copenhagen, Norway, 2008.

(20) Law, K.; Halldorson, T. H. J.; Danell, R. W.; Stern, G. A.; Gerwutz, S.; Alaee, M.; Marvin, C.; Whittle, D. M.; Tomy, G. T. Bioaccumulation and trophic transfer of some brominated flame retardants in a Lake Winnipeg (Canada) food web. *Environ. Toxicol. Chem.* **2006**, *25*, 2177–2186.

(21) Harrad, S. J.; Abdallah, M. A.-E.; Rose, N. L.; Turner, S. D.; Davidson, T. A. Current-use brominated flame retardants in water, sediment, and fish from English Lakes. *Environ. Sci. Technol.* **2009**, *43*, 9077–9083.

(22) Harrad, S.; de Wit, C. A.; Abdallah, M. A. E.; Bergh, C.; Bjorklund, J. A.; Covaci, A.; Darnerud, P. O.; de Boer, J.; Diamond, M.; Huber, S.; Leonards, P.; Mandalakis, M.; Oestman, C.; Haug, L. S.; Thomsen, C.; Webster, T. F. Indoor contamination with hexabromocyclododecanes, polybrominated diphenyl ethers, and perfluoroalkyl compounds: An important exposure pathway for people? *Environ. Sci. Technol.* **2010**, *44* (9), 3221–3231.

(23) Tomy, G. T.; Budakowski, W. R.; Halldorson, T. H. J.; Whittle, D. M.; Keir, M. J.; MacInnis, G.; Alaee, M. Biomagnification of α- and γ-hexabromocyclododecane (HBCD) isomers in a Lake Ontario food web. *Environ. Sci. Technol.* **2004**, *38*, 2298–2303.

(24) Sørmo, E. G.; Salmer, M. P.; Jenssen, B.; Hop, H.; Baek, K.; Kovacs, K. M.; Lydersen, C.; Falk-Petersen, S.; Gabrielsen, G. W.; Lie, E.; Skaare, J. U. Biomagnification of polybrominated diphenyl ether and hexabromocyclododecane flame retardants in the polar bear food chain in Svalbard, Norway. *Environ. Toxicol. Chem.* **2006**, *25*, 2502–2511.

(25) Tomy, G. T.; Pleskach, K.; Ferguson, S. H.; Hare, J.; Stern, G. A.; MacInnis, G.; Marvin, C. H.; Loseto, L. L. Trophodynamics of some PFCs and BFRs in a Western Canadian Arctic Marine Food Web. *Environ. Sci. Technol.* **2009**, *43*, 4076–4081.

(26) Law, K.; Halldorson, T. H. J.; Danell, R. W.; Stern, G. A.; Gewurtz, S.; Alaee, M.; Marvin, C. H.; Tomy, G. T. Erratum: Bioaccumulation and trophic transfer of some brominated flame retardants in a Lake Winnipeg (Canada) food-web. *Environ. Toxicol. Chem.* **2007**, *26*, 190.

(27) Wu, J. P.; Guan, Y. T.; Zhang, Y.; Luo, X. J.; Zhi, H.; Chen, S. J.; Mai, B. X. Trophodynamics of hexabromocyclododecanes and several other non-PBDE brominated flame retardants in a freshwater food web. *Environ. Sci. Technol.* **2010**, *44*, 5490–5495.

(28) Tomy, G. T.; Pleskach, K.; Oswald, T.; Halldorson, T. H. J.; Helm, P. A.; Marvin, C. H.; MacInnis, G. Enantioselective bioaccumulation of hexabromocyclododecane and congener-specific accumulation of brominated diphenyl ethers in an Eastern Canadian Arctic marine food web. *Environ. Sci. Technol.* **2008**, *42*, 3634–3639.

(29) Gobas, F. A. P. C.; De Wolf, W.; Burkhard, L. P.; Verbruggen, E.; Plotzke, K. Revisiting bioaccumulation criteria for POPs and PBT assessments. *Integr. Environ. Assess. Manage.* **2009**, *5*, 624–637.

(30) Klecka, G. M.; Muir, D. C. G.; Dohmen, P.; Eisenreich, S. J.; Gobas, F. A. P. C.; Jones, K. C.; Mackay, D.; Tarazona, J. V.; van Wijk, D.

Introduction to special series: Science-based guidance and framework for the evaluation and identification of PBTs and POPs. *Integr. Environ. Assess. Manage.* **2009**, *5*, 535–538.

(31) Wu, R. S. S.; Chan, A. K. Y.; Richardson, B. J.; Au, D. W. T.; Fang, J. K. H.; Lam, P. K. S.; Giesy, J. P. Measuring and monitoring persistent organic pollutants in the context of risk assessment. *Mar. Pollut. Bul.* **2008**, *57* (6−12), 236–244.

(32) Covaci, A.; Voorspoels, S.; Ramos, L.; Neels, H.; Blust, R. Recent developments in the analysis of brominated flame retardants and brominated natural compounds. *J. Chromatogr., A* **2007**, *1153*, 145–171.

(33) Abdallah, M. A.-E.; Harrad, S. J.; Covaci, A. Hexabromcyclododecanes and tetrabromobisphenol-A in indoor air and dust in Birmingham, UK: Implications for human exposure. *Environ. Sci. Technol.* **2008**, *42*, 6855–6861.

(34) Eljarrat, E.; Guerra, P.; Martínez, E.; Farré, M.; Alvarez, J. G.; López-Teijón, M.; Barceló, D. Hexabromocyclododecane in human breast milk: levels and enantiomeric patterns. *Environ. Sci. Technol.* **2009**, *43*, 1940–1946.

(35) Frederiksen, M.; Vorkamp, K.; Bossi, R.; Riget, F.; Dam, M.; Svensmark, B. Method development for simultaneous analysis of HBCD, TBBPA, and dimethyl-TBBPA in marine biota from Greenland and the Faroe Islands. *Int. J. Environ. Anal. Chem.* **2007**, *87*, 1095–1109.

(36) Garcia-Valcarcel, A. I.; Tadeo, J. L. Determination of hexabromocyclododecane isomers in sewage sludge by LC-MS/MS. *J. Sep. Sci.* **2009**, *32*, 3890–3897.

(37) Vilaplana, F.; Karlsson, P.; Ribes-Greus, A.; Ivarsson, P.; Karlsson, S. Analysis of brominated flame retardants in styrenic polymers - Comparison of the extraction efficiency of ultrasonication, microwave-assisted extraction and pressurised liquid extraction. *J. Chromatogr., A* **2008**, *1196−1197*, 139–146.

(38) Kajiwara, N.; Sueoka, M.; Ohiwa, T.; Takigami, H. Determination of flame-retardant hexabromocyclododecane diastereomers in textiles. *Chemosphere* **2009**, *74*, 1485–1489.

(39) Marvin, C. H.; MacInnis, G.; Alaee, M.; Arsenault, G.; Tomy, G. T. Factors influencing enantiomeric fractions of hexabromocyclododecane measured using liquid chromatography/tandem mass spectrometry. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 1925–1930.

(40) Guerra, P.; De la Torre, A.; Martinez, M. A.; Eljarrat, E.; Barcelo, D. Identification and trace level determination of brominated flame retardants by liquid chromatography/quadrupole linear ion trap mass spectrometry. *Rapid Commun. Mass Spectrom.* **2008**, *22*, 916–924.

(41) Zhou, S. N.; Reiner, E. J.; Marvin, C.; Helm, P.; Riddell, N.; Dorman, F.; Misselwitz, M.; Shen, L.; Crozier, P.; MacPherson, K.; Brindle, I. D. Development of liquid chromatography atmospheric pressure chemical ionization tandem mass spectrometry for analysis of halogenated flame retardants in wastewater. *Anal. Bioanal. Chem.* **2010**, *396*, 1311–1320.

(42) Zhou, S. N.; Reiner, E. J.; Marvin, C.; Kolic, T.; Riddell, N.; Helm, P.; Dorman, F.; Misselwitz, M.; Brindle, I. D. Liquid chromatography-atmospheric pressure photoionization tandem mass spectrometry for analysis of 36 halogenated flame retardants in fish. *J. Chromatogr., A* **2010**, *1217*, 633–641.

(43) Haug, L. S.; Thomsen, C.; Liane, V. H.; Becher, G. Comparison of GC and LC determinations of hexabromocyclododecane in biological samples—Results from two interlaboratory comparison studies. *Chemosphere* **2008**, *71*, 1087–1092.

(44) Heeb, N. V.; Schweizer, W. B.; Mattrel, P.; Haag, R.; Gerecke, A. C.; Kohler, M.; Schmid, P.; Zennegg, M.; Wolfensberger, M. Solid-state conformations and absolute configurations of (+) and (−)alpha-, beta-, and gamma-hexabromocyclododecanes (HBCDs). *Chemosphere* **2007**, *68*, 940–950.

(45) Dodder, N. G.; Peck, A. M.; Kucklick, J. R.; Sander, l. C. Analysis of hexabromocyclododecane diastereomers and enantiomers by liquid chromatography-tandem mass spectrometry: chromatographic selectivity and ionization matrix effects. *J. Chromatogr., A* **2006**, *1135*, 36–42.

(46) Guerra, P.; Eljarrat, E.; Barceló, D. Enantiomeric specific determinatino of hexabromocyclododecane by liquid chromatography-quadrupole linear ion trap mass spectrometry in sediment samples. *J. Chromatogr., A* **2008**, *1203*, 81–87.

(47) Vorkamp, K.; Thomsen, M.; Falk, K.; Leslie, H.; Møller, S.; Sørensen, P. B. Temporal development of brominated flame retardants in Peregrine Flacon (*Falco peregrinus*) eggs from south Greenland (1986−2003). *Environ. Sci. Technol.* **2005**, *39*, 8199–8206.

(48) Vorkamp, K.; Riget, F. F.; Bossi, R.; Dietz, R. Temporal trends of hexabromocyclododecane, polybrominated diphenyl ethers and polychlorinated biphenyls in ringed seals from East Greenland. *Environ. Sci. Technol.* **2011**, *45*, 1243–1249.

(49) Ismail, N.; Gewurtz, S.; Pleskach, K.; Whittle, D. M.; Helm, P. A.; Marvin, C. H.; Tomy, G. T. Brominated and chlorinated flame retardants in Lake Ontario Lake trout between 1979 and 2004 and possible influences of food web changes. *Environ. Toxicol. Chem.* **2009**, *28*, 910–920.

(50) Fängström, B.; Athanasiadou, I.; Odsjö, T.; Norén, K. Bergman, Å. Temporal trends of polybrominated diphenyl ethers and hexabromocyclododecane in milk form Stockholm mothers, 1980−2004. *Mol. Nutr. Food Res.* **2008**, *52*, 187–193.

(51) Knutsen, H. K.; Kvalem, H. E.; Thomsen, C.; Froshaug, M.; Haugen, M.; Becher, G.; Alexander, J.; Meltzer, H. M. Dietary exposure to brominated flame retardants correlates with male blood levels in a selected group of Norwegians with a wide range of seafood consumption. *Mol. Nutr. Food Res.* **2008**, *52*, 217–227.

(52) Harrad, S.; Goosey, E.; Desborough, J.; Abdallah, M. A. E.; Roosens, L.; Covaci, A. Dust from UK primary school classrooms and daycare centers: The significance of dust as a pathway of exposure of young UK children to brominated flame retardants and polychlorinated biphenyls. *Environ. Sci. Technol.* **2010**, *44*, 4198–4202.

(53) *European Commission Risk Assessment Hexabromocyclododecane*, EINECS No.: 247-148-4; Scientific Committee on Health and Environmental Risks: Brussels, Belgium, 2008.

(54) *Arctic Pollution*; Arctic Monitoring Assessment Program: Oslo, Norway, 2009.

(55) Thomsen, C.; Molander, P.; Daae, H. L.; Janák, K.; Froshaug, M.; Liane, V. H.; Thorud, S.; Becher, G.; Dybing, E. Occupational exposure to hexabromocyclododecane at an industrial plant. *Environ. Sci. Technol.* **2007**, *41*, 5210–5216.

(56) Stapleton, H. M.; Allen, J. G.; Kelly, S. M.; Konstantinov, A.; Klosterhaus, S.; Watkins, D.; Mcclean, M. D.; Webster, T. F. Alternate and new brominated flame retardants detected in U.S. house dust. *Environ. Sci. Technol.* **2008**, *42*, 6910–6916.

(57) Abdallah, M. A.-E.; Harrad, S. J. Personal exposure to HBCDs and its degradation products via ingestion of indoor dust. *Environ. Internat.* **2009**, *35*, 870–876.

(58) Shi, Z.-X.; Wu, Y.-N.; Li, J.-G.; Zhao, Y.-F.; Feng, J.-F. Dietary exposure assessment of Chinese adults and nursing infants to tetrabromobisphenol-A and hexabromocyclododecanes: occurrence measurements in foods and human milk. *Environ. Sci. Technol.* **2009**, *43*, 4314–4319.

(59) Roosens, L.; Abdallah, M. A. E.; Harrad, S.; Neels, H.; Covaci, A. Exposure to hexabromocyclododecanes (HBCDs) via dust ingestion, but not diet, correlates with concentrations in human serum: Preliminary results. *Environ. Health Perspect.* **2009**, *117*, 1707–1712.

(60) Driffield, M.; Harmer, N.; Bradley, E.; Fernandes, A. R.; Rose, M.; Mortimer, D.; Dicks, P. Determination of brominated flame retardants in food by LC-MS/MS: diastereoisomer-specific hexabromocyclododecane and tetrabromobisphenol A. *Food Addit. Contam.* **2008**, *25*, 895–903.

(61) Thomsen, C.; Knutsen, H. K.; Liane, V. H.; Froshaug, M.; Kvalem, H. E.; Haugen, M.; Meltzer, H. M.; Alexander, J.; Becher, G. Consumption of fish from a contaminated lake strongly affects the concentrations of polybrominated diphenyl ethers and hexabromocyclododecane in serum. *Mol. Nutr. Food Res.* **2008**, *52*, 228–237.

(62) Kupper, T.; de Alencastro, L. F.; Gatsigazi, R.; Furrer, R.; Grandjean, D.; Tarradellas, J. Concentrations and specific loads of brominated flame retardants in sewage sludge. *Chemosphere* **2008**, *71*, 1173–1180.

(63) Schecter, A.; Harris, T. R.; Shah, N.; Musurnbal, A.; Papke, O. Brominated flame retardants in U.S. food. *Mol. Nutr. Food Res.* **2008**, *52*, 266–272.

(64) Abdallah, M. A. E.; Harrad, S.; Covaci, A. Hexabromocyclododecanes and tetrabromobisphenol-A in indoor air and dust in Birmingham, UK: Implications for human exposure. *Environ. Sci. Technol.* **2008**, *42*, 6855–6861.

(65) Abdallah, M. A.-E.; Harrad, S. J.; Ibarra, C.; Diamond, M.; Melymuk, L.; Robson, M.; Covaci, A. Hexabromocyclododecanes in indoor dust from Canada, the United Kingdom, and the United States. *Environ. Sci. Technol.* **2008**, *42*, 459–464.

(66) Antignac, J. P.; Cariou, R.; Maume, D.; Marchand, P.; Monteau, F.; Zalko, D.; Berrebi, A.; Cravedi, J. P.; Andre, F.; Le Bizec, B. Exposure assessment of fetus and newborn to brominated flame retardants in France: preliminary data. *Mol. Nutr. Food Res.* **2008**, *52*, 258–265.

(67) Meijer, L.; Weiss, J.; Van Velzen, M.; Brouwer, A.; Bergman, A.; Sauerf, P. J. J. Serum concentrations of neutral and phenolic organohalogens in pregnant women and some of their infants in the Netherlands. *Environ. Sci. Technol.* **2008**, *42*, 3428–3433.

(68) Lignell, S.; Aune, M.; Darnerud, P. O.; Cnattingius, S.; Glynn, A. Persistent organochlorine and organobromine compounds in mother's milk from Sweden 1996−2006: compound-specific temporal trends. *Environ. Res.* **2009**, *109*, 760–767.

(69) Polder, A.; Thomsen, C.; Lindström, G.; LØken, K. B.; Skaare, J. U. Levels and temporal trends of chlorinated pesticides, polychlorinated biphenyls and brominated flame retardants in individual human breast milk samples from Northern and Southern Norway. *Chemosphere* **2008**, *73*, 14–23.

(70) Kakimoto, K.; Akutsu, K.; Konishi, Y.; Tanaka, Y. Time trend of hexabromocyclododecane in the breast milk of Japanese women. *Chemosphere* **2008**, *71*, 1110–1114.

(71) Malarvannan, G.; Kunisue, T.; Isobe, T.; Sudaryanto, A.; Takahashi, S.; Prudente, M.; Subramanian, A.; Tanabe, S. Organohalogen compounds in human breast milk from mothers living in Payatas and Malate, the Philippines: Levels, accumulation kinetics and infant health risk. *Environ. Pollut.* **2009**, *157*, 1924–1932.

(72) Tue, N. M.; Sudaryanto, A.; Tu, B. M.; Isobe, T.; Takahashi, S.; Pham, H. V.; Tanabe, S. Accumulation of polychlorinated biphenyls and brominated flame retardants in breast milk from women living in Vietnamese e-waste recycling sites. *Sci. Total Environ.* **2010**, *408*, 2155–2162.

(73) Polder, A.; Gabrielsen, G. W.; Odland, J. O.; Savinova, T. N.; Tkachev, A.; Loken, K. B.; Skaare, J. U. Spatial and temporal changes of chlorinated pesticides, PCBs, dioxins (PCDDs/PCDFs) and brominated flame retardants in human breast milk from Northern Russia. *Sci. Total Environ.* **2008**, *391*, 41–54.

(74) *Risk Assessment: Hexabromocyclododecane*; Swedish National Chemicals Inspectorate, 2003.

(75) Roosens, L.; Cornelis, C.; D'Hollander, W.; Bervoets, L.; Reynders, H.; Van Campenhout, K.; Van Den Heuvel, R.; Neels, H.; Covaci, A. Exposure of the Flemish population to brominated flame retardants: Model and risk assessment. *Environ. Int.* **2010**, *36*, 368–376.

(76) Birnbaum, L. S.; Staskal, D. F. Brominated flame retardants: cause for concern? *Environ. Health Perspect.* **2004**, *112*, 9–17.

(77) *Data Summary and test plan for hexabromocyclododecane (HBCD)*; AR201-13459A; American Chemistry Council: Arlington, VA, 2001.

(78) Darnerud, P. O. Toxic effects of brominated flame retardants in man and in wildlife. *Environ. Int.* **2003**, *29*, 583–624.

(79) Canton, R. F.; Peijnenburg, A. A. C. M.; Hoogenboom, R. L. A. P.; Piersma, A. H.; van der Ven, L. T. M.; van den Berg, M.; Heneweer, M. Subacute effects of hexabromocyclododecane (HBCD) on hepatic gene expression profiles in rats. *Toxicol. Appl. Pharmacol.* **2008**, *231*, 267–272.

(80) Ema, M.; Fujii, S.; Hirata-Koizumi, M.; Matsumoto, M. Two-generation reproductive toxicity study of the flame retardant hexabromocyclododecane in rats. *Reprod. Toxicol.* **2008**, *25*, 335–351.

(81) Fery, Y.; Buschauer, I.; Salzig, C.; Lang, P.; Schrenk, D. Technical pentabromodiphenyl ether and hexabromocyclododecane as activators of the pregnane-X-receptor (PXR). *Toxicology* **2009**, *264*, 45–51.

(82) Germer, S.; Piersma, A. H.; van der Ven, L.; Kamyschnikow, A.; Fery, Y.; Schmitz, H. J.; Schrenk, D. Subacute effects of the brominated flame retardants hexabromocyclododecane and tetrabromobisphenol A on hepatic cytochrome P450 levels in rats. *Toxicology* **2006**, *218*, 229–236.

(83) Saegusa, Y.; Fujimoto, H.; Woo, G. H.; Inoue, K.; Takahashi, M.; Mitsumori, K.; Hirose, M.; Nishikawa, A.; Shibutani, M. m. t. a. j. Developmental toxicity of brominated flame retardants, tetrabromobisphenol A and 1,2,5,6,9,10-hexabromocyclododecane, in rat offspring after maternal exposure from mid-gestation through lactation. *Reprod. Toxicol.* **2009**, *28*, 456–467.

(84) Schriks, M.; Roessig, J. M.; Murk, A. J.; Furlow, J. D. Thyroid hormone receptor isoform selectivity of thyroid hormone disrupting compounds quantified with an in vitro reporter gene assay. *Environ. Toxicol. Pharmacol.* **2007**, *23*, 302–307.

(85) Schriks, M.; Zvinavashe, E.; Furlow, J. D.; Murk, A. J. Disruption of thyroid hormone-mediated Xenopus laevis tadpole tail tip regression by hexabromocyclododecane (HBCD) and 2,2 ',3,3 ',4,4 ', 5,5 ',6-nona brominated diphenyl ether (BDE206). *Chemosphere* **2006**, *65*, 1904–1908.

(86) van der Ven, L. T. M.; van de Kuil, T.; Leonards, P. E. G.; Slob, W.; Lilienthal, H.; Litens, S.; Herlin, M.; Hakansson, H.; Canton, R. F.; van den Berg, M.; Visser, T. J.; van Loveren, H.; Vos, J. G.; Piersma, A. H. Endocrine effects of hexabromocyclododecane (HBCD) in a one-generation reproduction study in Wistar rats. *Toxicol. Lett.* **2009**, *185*, 51–62.

(87) Yamada-Okabe, T.; Sakai, H.; Kashima, Y.; Yamada-Okabe, H. Modulation at a cellular level of the thyroid hormone receptor-mediated gene expression by 1,2,5,6,9,10-hexabromocyclododecane (HBCD), 4,4 '-diiodobiphenyl (DIB), and nitrofen (NIP). *Toxicol. Lett.* **2005**, *155*, 127–133.

(88) Schriks, M.; Vrabie, C. M.; Gutleb, A. C.; Faassen, E. J.; Rietjens, I. M. C. M.; Murk, A. J. T-screen to quantify functional potentiating, antagonistic and thyroid hormone-like activities of poly halogenated aromatic hydrocarbons (PHAHs). *Toxicol. In Vitro.* **2006**, *20*, 490–498.

(89) Palace, V. P.; Pleskach, K.; Halldorson, T. H. J.; Danell, R. W.; Wautier, K.; Evans, B.; Alaee, M.; Marvin, C. H.; Tomy, G. T. Biotransformation enzymes and thyroid axis disruption in juvenile rainbow trout (*Oncorhynchus mykiss*) exposed to hexabromocyclododecane diastereoisomers. *Environ. Sci. Technol.* **2008**.

(90) Lower, N.; Moore, A. The impact of a brominated flame retardant on smoltification and olfactory function in Atlantic salmon (Salmo salar L.) smolts. *Mar Freshwater Behav. Physiol.* **2007**, *40*, 267–284.

(91) Palace, V.; Park, B.; Pleskach, K.; Gemmill, B.; Tomy, G. Altered thyroxine metabolism in rainbow trout (*Oncorhynchus mykiss*) exposed to hexabromocyclododecane (HBCD). *Chemosphere* **2010**, *80*, 165–169.

(92) Crump, D.; Chiu, S.; Egloff, C.; Kennedy, S. W. Effects of Hexabromocyclododecane and polybrominated diphenyl ethers on mRNA expression in chicken (*Gallus domesticus*) hepatocytes. *Toxicol. Sci.* **2008**, *106*, 479–487.

(93) Marteinson, S. C.; Kimmins, S.; Letcher, R. J.; Palace, V. P.; Bird, D. M.; Ritchie, I. J.; Fernie, K. J. Diet exposure to technical hexabromocyclododecane (HBCD) affects testes and circulating testosterone levels in American Kestrels (*Falco sparverius*). *Environ. Sci. Technol.* **2011**.

(94) Zhang, X. L.; Yang, F. X.; Xu, C.; Liu, W. P.; Wen, S.; Xu, Y. Cytotoxicity evaluation of three pairs of hexabromocyclododecane (HBCD) enantiomers on Hep G2 cell. *Toxicol. In Vitro.* **2008**, *22*, 1520–1527.

(95) Kuiper, R. V.; Canton, R. F.; Leonards, P. E. G.; Jenssen, B. M.; Dubbeldam, M.; Wester, P. W.; van den Berg, M.; Vos, J. G.; Vethaak, A. D. Long-term exposure of European flounder (*Platichthys flesus*) to the flame-retardants tetrabromobisphenol A (TBBPA) and hexabromocyclododecane (HBCD). *Ecotoxicol. Environ. Saf.* **2007**, *67*, 349–360.

(96) Ronisz, D.; Finne, E. F.; Karlsson, H.; Forlin, L. Effects of the brominated flame retardants hexabromocyclododecane (HBCDD), and tetrabromobisphenol A (TBBPA), on hepatic enzymes and other biomarkers in juvenile rainbow trout and feral eelpout. *Aquat. Toxicol.* **2004**, *69*, 229–245.

(97) Kamstra, J. H.; Du, T.; Visser, T. J.; van der Ven, T. M.; Murk, A. J.; Hamers, T. *In vitro induction of organic anion transporting polypeptides (OATPs) as a possible mechanism for thyroid hormone disruption by hexabromocyclododecane (HBCD)*; Fourth International BFR Workshop: The Netherlands, 2007.

(98) Sakai, H.; Yamada-Okabe, T.; Kashima, Y.; Matsui, M.; Aono, T.; Aoyagi, M.; Hasegawa, J. Effects of brominated flame retardants on transcruiptional activation mediated by thyroid hormone receptor. *Organohalogen Compd.* **2003**, *61*, 215–218.

(99) Hamers, T.; Kamstra, J. H.; Sonneveld, E.; Murk, A. J.; Kester, M. H. A.; Andersson, P. L.; Legler, J.; Brouwer, A. In vitro profiling of the endocrine-disrupting potency of brominated flame retardants. *Toxicol. Sci.* **2006**, *92*, 157–173.

(100) Mariussen, E.; Fonnum, F. The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. *Neurochem. Internat.* **2003**, *43*, 533–542.

(101) Dingemans, M. M. L.; Heusinkveld, H. J.; de Groot, A.; Bergman, Å.; van den Berg, M.; Westerlink, R. H. S. Hexabromocyclododecane inhibits depolarization-induced increase in intracellular calcium levels and neurotransmitter release in PC12 cells. *Toxicol. Sci.* **2009**, *107*, 490–497.

(102) Lilienthal, H.; van der Ven, L. T. M.; Piersma, A. H.; Vos, J. G. Effects of the brominated flame retardant hexabromocyclododecane (HBCD) on dopamine-dependent behavior and brainstem auditory evoked potentials in a one-generation reproduction study in Wistar rats. *Toxicol. Lett.* **2009**, *185*, 63–72.

(103) Braune, B. M.; Mallory, M. L.; Gilchrist, H. G.; Letcher, R. J.; Drouillard, K. G. Levels and trends of organochlorines and brominated flame retardants in Ivory Gull eggs from the Canadian Arctic, 1976 to 2004. *Sci. Total Environ.* **2007**, *378*, 403–417.

(104) Knudsen, L. B.; Gabrielsen, G. W.; Verreault, J.; Barrett, R.; Skaare, J. U.; Polder, A.; Lie, E. *Temporal trends of brominated flame retardants, cyclododeca-1,5,9-triene and mercury in eggs of four seabird species from Northern Norway and Svalbard*; 942/2005; Norwegian Polar Institute: Tromso, Norway, 2005.

(105) Law, R. J.; Bersuder, P.; Allchin, C. R.; Barry, J. Levels of the flame retardants hexabromocyclododecane and tetrabromobisphenol A in the blubber of Harbor porpoises (*Phocoena phocoena*) stranded or bycaught in the U.K., with evidence for an increase in HBCD concentrations in recent years. *Environ. Sci. Technol.* **2008**, *40*, 2177–2183.

(106) Law, R. J.; Bersuder, P.; Barry, J.; Wilford, B. H.; Allchin, C. R.; Jepson, P. D. A significant downturn in levels of hexabromocyclododecane in the blubber of harbor porpoises (*Phocoena phocoena*) stranded or bycaught in the UK: an update to 2006. *Environ. Sci. Technol.* **2008**, *42*, 9104–9109.

(107) van der Ven, L. T. M.; Verhoef, A.; van de Kuil, T.; Sloub, W.; Leonards, P. E. G.; Visser, T. J.; Hamers, T.; Herlin, M.; Hakansson, H.; Olausson, H.; Piersma, A. H.; Vos, J. G. A 28-day oral dose toxicity study enhanced to detect endrocine effects of hexabromocyclododecane in Wistar rats. *Toxicol. Sci.* **2006**, *94*, 281–292.

(108) Aniagu, S. O.; William, T. D.; Chipman, J. K. Changes in gene expression and assessment of DNA methylation in primary human hepatocytes and HepG2 cells exposed to the environmental contaminants - hexabromocyclododecane and 17-b estradiol. *Toxicol.* **2009**, *256*, 143–151.

(109) Reistad, T.; Fonnum, F.; Mariussen, E. Neurotoxicity of the pentabrominated diphenyl ether mixture, DE-71, and hexabromocyclododecane (HBCD) in rat cerebellar granule cells in vitro. *Arch. Toxicol.* **2006**, *80*, 785–796.

(110) Hu, J.; Liang, Y.; Chen, M.; Wang, X. Assessing the toxicity of TBBPA and HBCD by zebrafish embryo toxicity assay and biomarker analysis. *Environ. Toxicol.* **2009**, *24*, 334–342.

(111) Zhang, X. L.; Yang, F. X.; Xu, C.; Liu, W. P.; Wen, S.; Xu, Y. Cytotoxicity evaluation of three pairs of hexabromocyclododecane (HBCD) enantiomers on Hep G2 cell. *Toxicol.in Vitro.* **2008**, *22* (6), 1520–1527.

(112) *6-Week Administration Study of 1,2,5,6,9,10-Hexabromocyclododecane for Avian Reproduction Toxicity under Long-Day Conditions Using Japanese Quail*, Study No: 08-013; Chemicals Evaluation Office, Policy Planning Division, Environmental Health Department, Ministry of the Environment: Japan, 2009.

(113) Deng, J.; Yu, L.; Liu, C.; Yu, K.; Shi, X.; Yeung, L. W. Y.; Lam, P. K. S.; Wu, R. S. S.; Zhou, B. Hexabromocyclododecane-induced developmental toxicity and apoptosis in zebrafish embryos. *Aquat. Toxicol.* **2009**, *93*, 29–36.

(114) Eriksson, P.; Fischer, C.; Wallin, M.; Jakobsson, E.; Fredriksson, A. Impaired behaviour, learning and memory, in adult mice neonatally exposed to hexabromocyclododecane (HBCDD). *Environ. Toxicol. Pharmacol.* **2006**, *21*, 317–322.

(115) Arnot, J. A.; Armitage, J. M.; McCarty, L. S.; Wania, F.; Cousins, I. T.; Toose-Reid, L. Toward a consistent evaluative framework for POP risk characterization. *Environ. Sci. Technol.* **2011**, *45*, 97–103.