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Toward a Consistent Evaluative Framework for POP Risk Characterization†

JON A. ARNOT,*,‡ JAMES M. ARMITAGE,§ LYNN S. MCCARTY,⊥ FRANK WANIA,‡ IAN T. COUSINS,§ AND LIISA TOOSE-REID∥

University of Toronto Scarborough, Department of Physical and Environmental Sciences, 1265 Military Trail, Toronto, ON, Canada, M1C 1A4, Stockholm University, Department of Applied Environmental Science (ITM), Stockholm SE-106 91, Sweden, LS McCarty Scientific Research & Consulting, 1115 Quaker Trail, Newmarket, ON, Canada, L3X 3E2, and Canadian Centre for Environmental Modelling and Chemistry, Trent University, 1600 West Bank Drive, Peterborough, ON, Canada

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The purpose of Annex E in the Stockholm Convention (SC) on Persistent Organic Pollutants (POPs) is to assess whether a chemical is likely, as a result of its long-range environmental transport, to lead to significant adverse human health or environmental effects, such that global action is warranted. To date, risk profiles for nominated POPs have not consistently selected assessment endpoints or completed mandated risk characterizations. An assessment endpoint hierarchy is proposed to facilitate risk characterization for the implementation of the SC. The framework is illustrated for a nominated POP, hexabromocyclododecane (HBCD), using three risk estimation methods. Based on current monitoring and toxicity data, the screening-level results indicate that humans and ecological receptors in remote regions such as the Arctic are unlikely to experience significant adverse effects (i.e., low risk) due to long-range environmental transport of HBCD. The results for birds are more uncertain than the results for fish and mammals due to the paucity of avian toxicity data. Risk characterization results for HBCD and for some listed POPs are compared to illustrate how the proposed methods can further assist decision-making and chemical management.

Introduction

The Stockholm Convention (SC) is a global treaty intended to protect human health and the environment from chemicals referred to as Persistent Organic Pollutants (POPs) (*1*). The SC is the result of research in recent decades largely focused on 12 chlorinated chemicals or groups of chemicals, referred to as the "dirty dozen". The SC was brought into force in 2004 and the "dirty dozen" were listed as POPs under Annex A (Elimination), Annex B (Restriction), and/or Annex C (Unintentional Production). Nine chemicals (including "groups" and "precursors") have been added to the SC since 2004 and three chemicals are currently being evaluated (see Supporting Information, SI-S1). Chemicals are nominated as POP candidates to be listed under Annex A, B, and/or C by a Party of the Convention and are first evaluated against screening criteria outlined in Annex D of the SC by the POP Review Committee (POPRC). If the POPRC deems that the documentation provided in the nomination is adequate and that some, or all, of the screening criteria are met, then the evaluation proceeds to Annex E. The POPRC evaluates the data included in Annex E (a risk profile) and decides whether a chemical proceeds to Annex F (risk management) (*1*). Annex E and F form the basis for deciding whether or not a chemical is listed under the SC (i.e., Annex A, B, and/or C) (*1*).

The primary objective of Annex E is to develop a risk profile to evaluate whether "the chemical is likely, as a result of its long-range environmental transport, to lead to significant adverse human health or environmental effects, such that global action is warranted" (*1*). According to general SC guidance, risk profiles are to synthesize information "in the form of a risk characterization, with emphasis on information that leads to the conclusive statement" thus addressing the primary objective (*2*). A risk-based framework is recommended to evaluate the potential for significant adverse effects (SAE) since the magnitude of a possible effect is a function of exposure and toxicity. Risk profiles were not completed under the SC for the "dirty dozen"; however, risk estimates for certain "dirty dozen" chemicals are available (*3*–*5*). An independent review commissioned by the SC Secretariat (*6*) and other studies (*7*) have found inconsistencies in the development of risk profiles for ten recently assessed POPs. In particular, the selected assessment endpoints were varied, risk characterization was not always included, and when risk characterization was included various methods were used. One reason for these inconsistencies is that Annex E is only semiprescriptive and there are no specific guidelines to determine the potential of SAE (*1, 6*). More chemicals are expected to be nominated as POPs in the future (*8*). There are no guarantees that replacement chemicals have less potential for SAE, thus reinforcing the need for a risk-based framework for comparative evaluations. Considering the implications of listing chemicals under the SC, a clear and consistent framework is needed.

This policy analysis proposes a hierarchical framework for effect (toxicity) data to evaluate the potential for SAE and provide greater consistency in the development of POP risk profiles. The myriad of effects data are categorized into three tiers to facilitate the interpretation of risk characterization results for decision-making. A case study illustrates the hierarchical approach and comparative risk evaluation. Hexabromocyclododecane (HBCD) is a flame retardant primarily used in building insulation and textiles and has been recently nominated as a POP (*9*). Three risk estimation methods are used to assess the likelihood of SAE as a result of long-range transport for HBCD. Risk characterization results for HBCD and for some listed POPs are compared incorporating the proposed hierarchical approach for assessment endpoints.

Risk Characterization

Methods and detailed guidance for risk characterization and risk assessment are documented in other regulatory programs (*10*–*13*). Briefly, the four general stages of risk assessment

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* Corresponding author phone: +1-416-287-7506; fax: +1-416-287-7279; e-mail: jon.arnot@utoronto.ca.
‡ University of Toronto Scarborough.
§ Stockholm University.
⊥ LS McCarty Scientific Research & Consulting.
∥ Canadian Centre for Environmental Modelling and Chemistry, Trent University.

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include (i) problem formulation, (ii) effect characterization (exposure−response assessment), (iii) exposure characterization (assessment), and (iv) risk characterization. Problem formulation is the process in which assessment objectives are developed into an assessment strategy including the selection of appropriate assessment (effect) endpoints. Risk characterization integrates information from the first three steps for risk estimation and risk description to inform and support risk management objectives and decisions (*13*). Risk estimation is a quantitative analysis of exposures and effects. Risk description provides an interpretation of the results of the risk estimate for risk managers (i.e., POPRC).

Annex E provides a general context for problem formulation by stating an objective (i.e., potential for SAE); however, specific assessment endpoints have not been defined. Without defining or characterizing assessment endpoints with respect to the primary objective, a consistent framework for POP risk profiles and decision-making cannot be established because the assessment endpoint(s) provide the foundation for the interpretation of the risk estimates and thus the potential for SAE.

Tiered Approach for Characterizing Assessment Endpoints

The current ambiguity in evaluating the potential for SAE is addressed here by outlining a hierarchical framework to characterize the myriad of effects data so that they can be used to interpret risk estimate results. The focus of the proposed approach is on noncancer effect endpoints. An assessment endpoint consists of an entity (e.g., species, population, or ecosystem) and an attribute (e.g., survival, growth, or reproduction) and should be selected based on the assessment objectives (*13*). Ideally, chemicals should be evaluated for a variety of endpoints to better understand and describe the potential risks, and effects data should be critically examined for reliability, relevance, and adequacy (*14*). The current spectrum of effects ranges from lethality to subtle biochemical changes or adaptations. This spectrum also approximates the relative uncertainty associated with the "significance" or "relevance" of an adverse effect. For example, mortality is well-defined with respect to its significance as an adverse effect on an organism, whereas subcellular changes in an in vitro test are often poorly defined in this respect. The proposed three-tiered hierarchy reflects the applicability of the data within the context of determining the likelihood of a SAE. These categories are loosely affiliated with levels of biological organization and also reflect the confidence with which the exposure−response relationship of available assessment endpoint data can be applied for assessing SAE.

Tier 1 assessment endpoints can be directly linked to an effect, or lack of effect, in survival (mortality), growth, or reproduction of organisms or populations of organisms either in controlled testing or in the field. Such endpoints may not necessarily be significantly adverse; however, these key types of effects are relatively well understood for assessing SAE compared to other types of effects data. Tier 1 data are the most generally accepted and typically applied endpoints in ecological risk assessment (*7, 15*) having relatively well-defined attributes and adequate exposure−response relationships to evaluate the potential for SAE. There is comparatively little debate in the scientific community as to the potential significance of Tier 1 assessment endpoints and thus there is relatively "low uncertainty" associated with applying these endpoints to assess the likelihood of SAE.

Tier 2 assessment endpoints include some alterations in organism or suborganism level structure or function such as changes in organ mass, alterations in behavior, and changes in various biochemical parameters and activities. Tier 2 assessment endpoints have adequate exposure−response relationships; however, well-defined linkages between these effects and their significance to survival, growth, or reproduction are not established. Tier 2 effects may be adverse in the sense that they may represent an "undesirable change"; however, they may also be adaptive (e.g., enzyme induction). Compared to Tier 1 data there is less scientific consensus as to the potential significance or adversity of the effect and thus there is "moderate uncertainty" associated with applying these endpoints to assess SAE. Tier 2 assessment endpoint data may be best used in a supporting role for decision-making.

Tier 3 effects data are not presently useable for risk characterization because there are no adequate exposure−response relationships and/or linkages between these effects and their significance are not well established. Tier 3 data include observed effects in the field; however, available exposure estimates cannot be linked to a particular stressor (chemical) and thus the exposure−response relationship cannot be established. Tier 3 data also include effects data that are not obtained from exposures of whole organisms, but rather exposures of isolated preparations of organs, tissues, or cells in vitro. These data may be conceptually and statistically sound for the purposes for which they were developed and they may be helpful in understanding mechanisms by which key effects are caused. However, it is difficult to establish exposure−response relationships for comparisons with exposure assessments and the potential significance of these effects at higher levels of biological organization are not well established. Tier 3 data are generally inapplicable ("highly uncertain") for quantifying the likelihood of SAE and were not used in this case study.

Case Study Using HBCD and Selected POPs

Three risk estimation methods are presented for HBCD and then the screening-level risk characterization results for HBCD are compared with results for some listed POPs. The exposure and effects data used in this case study are summarized in the SI. Monitoring data from remote regions (i.e., Arctic) are used to address the primary objective of Annex E. Data suggest HBCD is neither carcinogenic nor mutagenic (*16*).

Risk is estimated using risk characterization ratios (RCR) (*17*):

$$\text{RCR} = \text{Exposure}/\text{Effect} \quad (1)$$

where the exposure and effect (or no-effect) values share the same units (e.g., mmol·kg-body weight^{-1}). RCRs are sometimes referred to as risk quotients (RQs) and predicted environmental concentration/predicted no effect concentration (PEC/PNEC) ratios. These deterministic screening-level RCRs provide an indication of the likelihood of an effect occurring for risk estimation; however, they are surrogate parameters since they do not capture the "incidence and severity" and uncertainty of adverse effects (*17*). RCRs and the tiered assessment endpoints can provide some context for the risk estimate and risk description. For example, a RCR of 10 for a Tier 1 assessment endpoint indicates a high likelihood of a "low uncertainty" SAE, whereas a RCR of 10^{-6} for a Tier 2 assessment endpoint indicates a low likelihood of an "uncertain" SAE. Uncertainty (application or safety) factors were not employed because there is no conclusive scientific evidence or consensus for their application (*15*) and there is no policy in the SC for quantifying uncertainty.

Method 1: Environmental Concentrations

Risks can be estimated by comparing exposure concentrations in physical compartments of the environment (e.g.,

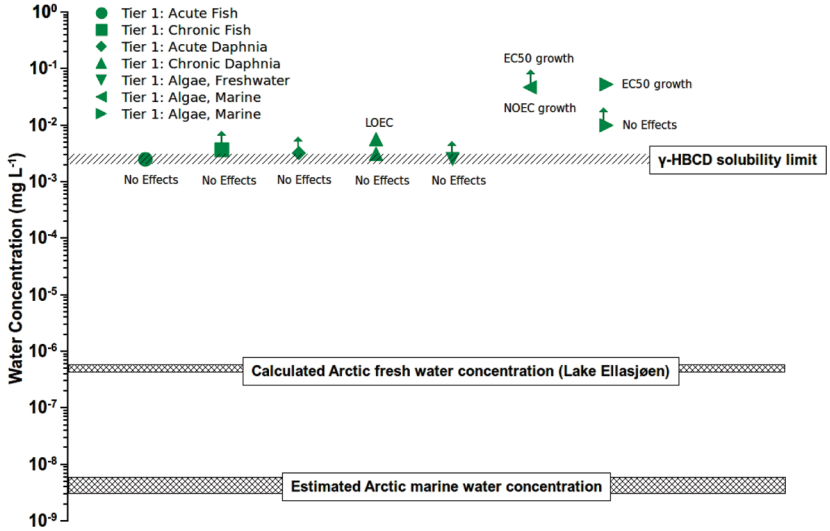

FIGURE 1. Risk characterization results for HBCD using the environmental concentrations method. Arrows indicate concentrations that were reported as ">".

water) with effect or estimated no-effect assessment endpoints derived using exposure media (e.g., water) in laboratory studies (*11, 17*). Commercial and technical HBCD is primarily a mixture of three isomers: α and β, 3−30%, and γ, 70−95% (*9*). Figure 1 shows that based on available data there are no observed acute or chronic effects of HBCD in aquatic species for Tier 1 assessment endpoints up to the water solubility limit for γ-HBCD (~2 $\mu g \cdot L^{-1}$), the predominant isomer of technical HBCD (SI; S2). To estimate risk in remote regions using this method some water-borne exposure estimates are needed; however, water concentrations of HBCD in remote regions (Arctic) have not been reported in freshwater or marine systems. Current method detection limits for HBCD in water are ~3 $pg \cdot L^{-1}$ (*18*). Freely dissolved concentrations were estimated to be below current method detection limits (<1 $pg \cdot L^{-1}$) in the Arctic marine environment (SI; S3). The RCR is approximately 10^{-6} assuming water concentrations of HBCD in the Arctic marine environment are near detection limits (~3 $pg \cdot L^{-1}$) and selecting the No-Observed-Effect-Concentration (NOEC) of 3.1 $\mu g \cdot L^{-1}$ as a Tier 1 assessment endpoint (SI; S4). Reported sediment concentrations in a high Arctic lake (normalized for organic carbon) and the octanol−water partition coefficient were used to estimate freely dissolved freshwater concentrations (400−600 $pg \cdot L^{-1}$) (SI; S3). The sediment data and the estimated freshwater HBCD concentrations are uncertain (see SI; S3); however, these data provide some preliminary, conservative values in the absence of measured freshwater data. The RCR for this particular lake using the NOEC of 3.1 $\mu g \cdot L^{-1}$ is approximately 10^{-4}. This suggests that current exposures of HBCD to aquatic biota in the Arctic are unlikely to cause SAE.

Water-borne effect endpoints (e.g., LC50s) are routinely included in SC assessments (Annex D and E) despite fundamental concerns for directly using these data for POP assessments. Sparingly soluble substances such as HBCD and many listed POPs pose technical challenges for water-borne testing and for data interpretation (*7, 19*). Nominated POPs typically show bioaccumulation potential (Annex D screening) and substances that biomagnify in the food web will have higher concentrations at higher trophic levels. Thus, exposures to higher trophic level organisms are predominantly the result of dietary intake and water-borne effect endpoints alone cannot account for dietary exposures. For these reasons, methods such as those outlined below are strongly recommended to more rigorously assess POP candidates (*20, 21*).

Method 2: Tolerable Daily Intake (TDI)

The first recommended approach for assessing the potential risks of POP candidates compares estimates of total chemical daily intake rates with estimates of daily intakes obtained from laboratory tests associated with effects or no effects (typically expressed as $mg \cdot (kg\text{-}bw \cdot d)^{-1}$). For upper trophic level Arctic species, HBCD intake occurs predominantly through the diet (>99%) and can thus be estimated from organism body weight, feeding rate, diet composition, and chemical concentrations in the diet. Polar bears (*Ursus maritimus*) are apex predators in the Arctic and feed almost exclusively on seals and were therefore selected for the TDI method. Following a recent effects assessment, a feeding rate of 3 kg of seal blubber per day was assumed for a 200-kg bear (*5*). Figure 2 shows that based on this feeding rate and the maximum concentration of ΣHBCD reported in Arctic ringed seal (*Pusa hispida*) blubber (34.5 $\mu g \cdot kg\text{-}lipid^{-1}$, ~31.0 $\mu g \cdot kg\text{-}wet\ weight^{-1}$), the total daily intake estimate is 4.6×10^{-4} $mg \cdot (kg\text{-}bw \cdot d)^{-1}$.

No-Observed-Effect-Levels (NOELs) for Tier 1 and 2 assessment endpoints were derived from mammalian testing data (SI; S5). The lowest, most conservative, Tier 1 NOEL of 10.2 $mg \cdot (kg\text{-}bw \cdot d)^{-1}$ corresponds with the value used previously in the European Union risk assessment as a reproductive effect endpoint (*16*). This effect endpoint and the total daily intake of 4.6×10^{-4} $mg \cdot (kg\text{-}bw \cdot d)^{-1}$ result in a RCR of 4.6×10^{-5}. The lowest, most conservative, Tier 2 NOEL effect endpoint is 0.056 $mg \cdot (kg\text{-}bw \cdot d)^{-1}$ based on tests for various effects including changes in trabecular bone mineral density and the corresponding RCR is 8.3×10^{-3}. This suggests that current dietary exposures of HBCD to Arctic biota are unlikely to cause SAE.

Although the focus of this case study is on ecological receptors, the TDI risk estimation method was also used to calculate screening-level risk estimates for humans living in remote regions (see details in SI; S6). The "worst case" scenario assumes that an adult Arctic resident consumes 410 g of marine mammal blubber every day and that the concentration of HBCD in the blubber is the maximum reported concentration from the Arctic (i.e., 34.5 $\mu g \cdot kg\text{-}lipid^{-1}$ in ringed seal). The HBCD concentration for this ringed seal is about 1 order of magnitude greater than other currently reported concentrations for marine mammals consumed by Arctic residents, i.e., seal, narwhal, walrus, whales (SI; S6). The total daily intake estimate is 2.0×10^{-4} $mg \cdot (kg\text{-}bw \cdot d)^{-1}$ and the corresponding screening-level RCRs are 2.0×10^{-5}

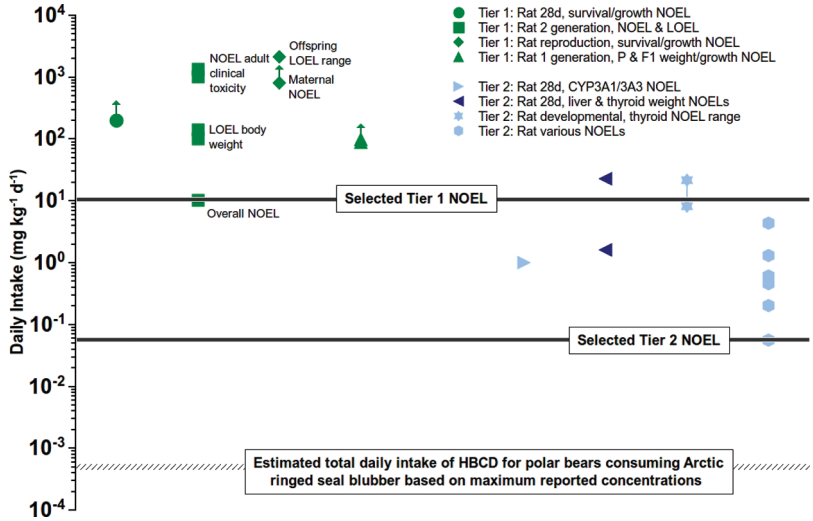

FIGURE 2. Risk characterization results for HBCD using the tolerable daily intake (TDI) method. Arrows indicate concentrations that were reported as ">".

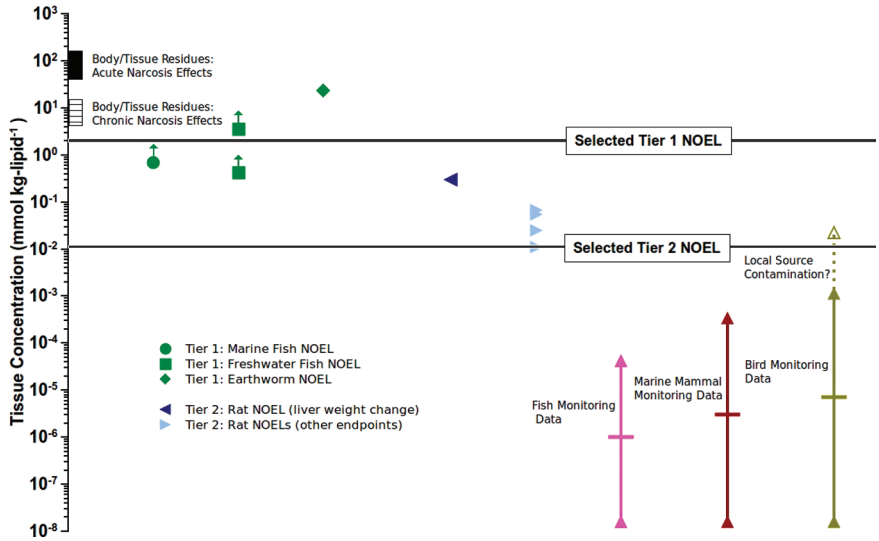

FIGURE 3. Risk characterization results for HBCD using the body/tissue residue method. The ranges (columns) and medians (horizontal bars) reflect monitoring concentrations. The dashed line for birds represents monitoring data collected from a refuse dump site and therefore likely reflects some point source exposures rather than exposures that are only the result of long-range environmental transport.

and 3.6×10^{-3} for the Tier 1 and Tier 2 assessment endpoints, respectively. These RCRs are more than a factor of 2 below those estimated for the polar bear. This suggests that current dietary exposures of HBCD to Arctic residents are unlikely to cause SAE.

Method 3: Body or Tissue Residues

Another recommended risk estimation method for POP assessment compares whole-body or tissue concentrations with measured effect or estimated no-effect whole body or tissue concentrations (e.g., mmol·kg^{-1}). Compared to the first two methods, method 3 provides estimates of chemical concentrations closest to the site(s) of toxic action in organisms and is therefore a preferred method to estimate risk. The majority of the monitoring data and mammalian tissue-residue effects data for HBCD are reported on a lipid weight basis; therefore, reported wet weight data were lipid normalized to facilitate comparisons. Figure 3 illustrates the range of HBCD lipid weight concentrations measured in Arctic fish, marine mammals, and birds relative to selected Tier 1 and 2 assessment endpoints. The bird monitoring data include glaucous gull (*Larus hyperboreus*) samples from a refuse dump site in the Svalbard archipelago with concentrations ~20 times higher than other reported concentrations of HBCD in Arctic birds. This suggests that some of their body burden is the result of point source contamination from the dump site and brings into question the relevance and applicability of these data for assessing potential SAE as a result of long-range transport. To address this issue screening-level RCRs were calculated using maximum and estimated median concentrations either including or excluding the dump site data (SI; S6).

A Tier 1 NOEL assessment endpoint of 2 mmol·kg-lipid^{-1} was established just below the lower end of the chronic toxicity residue range associated with baseline narcosis. This value is supported by the available Tier 1 data for HBCD from vertebrate species (i.e., no effects on survival, growth, or reproduction) and corresponds well with the selected Tier 1 assessment endpoint used in method 2 (SI; S6). Residue–toxicity relationships for baseline narcosis provide further guidance for interpreting the available data and selecting the Tier 1 assessment endpoint. The Tier 1 RCRs based on the maximum concentrations are 2.1×10^{-5}, 1.7×10^{-4}, and 1.1×10^{-2} for fish, marine mammals, and birds, respectively.

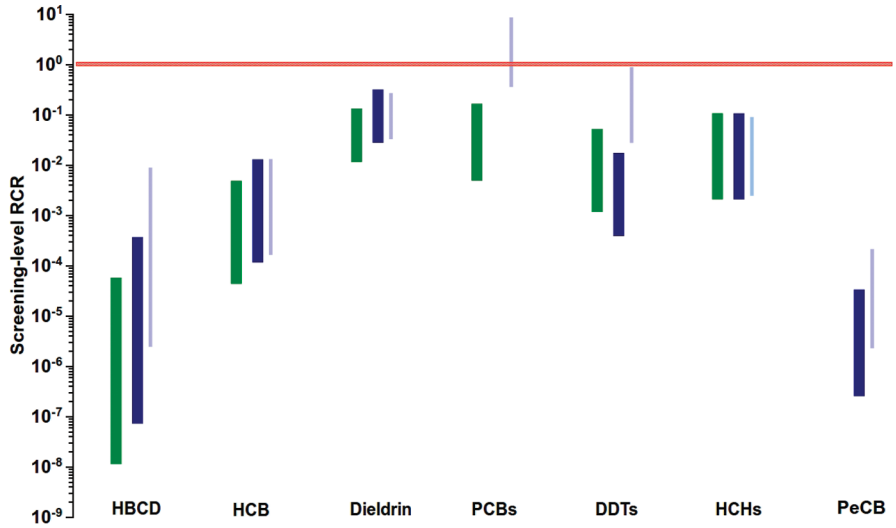

FIGURE 4. Risk characterization comparisons for HBCD and some listed POPs. Risk characterization ratios (RCRs) are displayed as a range using the minimum and maximum measured concentrations in Arctic ringed seal blubber. The green columns provide comparisons of Tier 1 assessment endpoints. The navy columns provide direct comparisons of specific Tier 2 assessment endpoints (organ weight change). The light blue columns provide indirect comparisons of general Tier 2 assessment endpoints. A RCR of 1 is indicated by the red horizontal line. HBCD: Σhexabromocyclododecane isomers; HCB: hexachlorobenzene; PCBs: Σpolychlorinated biphenyl congeners; DDTs: dichlorodiphenyldichloroethylene (*p,p′*-DDE) and dichlorodiphenyldichloroethane (*p,p′*-DDT); HCHs: Σhexachlorocyclohexane isomers; PeCB: pentachlorobenzene and tetrachlorobenzene.

The Tier 1 RCR for birds using the maximum reported concentrations but excluding the dump site data is 5.7×10^{-4}. The Tier 1 RCRs based on the estimated median concentrations are 5.0×10^{-7}, 1.5×10^{-6}, and 3.5×10^{-6} for fish, marine mammals, and birds, respectively.

The lowest, most conservative Tier 2 NOEL is 0.011 mmol·kg-lipid^{-1}, which is an assessment endpoint from tests for various effects including changes in trabecular bone mineral density and auditory impairment in mammals. The Tier 2 RCRs based on the maximum monitoring concentrations are 3.8×10^{-3}, 3.1×10^{-2}, and 2.1 for Arctic fish, marine mammals, and birds, respectively. The Tier 2 RCR for birds excluding the dump site data is 0.10. The Tier 2 RCRs based on the estimated median concentrations are 9.1×10^{-5}, 2.7×10^{-4}, and 6.4×10^{-4} for Arctic fish, marine mammals, and birds, respectively.

Method 3 RCRs using available Tier 1 assessment endpoint data indicate that SAE from current exposures to HBCD as a result of long-range transport to the Arctic are unlikely. The RCRs for fish and marine mammals using Tier 2 assessment endpoint data also indicate that effects from current exposures to HBCD are unlikely. The RCRs for Arctic birds using Tier 2 assessment endpoint data indicate that some current exposures are near NOELs associated with certain effects in mammals such as trabecular bone mineral density and auditory impairment. A more comprehensive risk evaluation may be appropriate to consider the potential significance of these mammalian Tier 2 assessment endpoints for birds. Tier 1 and Tier 2 HBCD toxicity data for birds are not currently available thus requiring the use of nonavian toxicity data as surrogate estimates. An assessment of current HBCD and polybrominated diphenyl ether levels in the eggs of Arctic birds indicated "low risk" of reproductive effects using data from captive American kestrels (*Falco sparverius*) (*4*), which supports the general findings in the present screening-level assessment.

Bird and marine mammal RCRs are larger than fish RCRs, reflecting higher relative risk potential for upper trophic level organisms compared to lower trophic level organisms as a result of food web biomagnification. These results support the use of either method 2 or 3 for POP risk characterization rather than method 1.

Comparative Risk Evaluations

Benchmarking has been proposed for assessing and comparing POP candidates with listed POPs with respect to overall persistence (P_{OV}), long-range transport potential (LRTP) (*22*), and exposure potential (*23*). Comparative risk evaluations can be useful for benchmarking RCRs for nominated POPs against those of listed POPs and for comparing the relative risks of different chemicals with similar commercial uses such as possible replacement chemicals. For example, a listed POP with surfactant properties may be replaced by another chemical with surfactant properties. The ultimate use, exposure, toxicity, and potential risk of a replacement chemical may be comparable to, or greater than, the listed POP. Comparative risk evaluations provide quantitative guidance that can be used in concert with other information such as cost−benefit analyses for informed risk management decisions.

Figure 4 compares RCRs for HBCD with those of listed POPs following the previously described TDI risk estimation method (polar bear eating ringed seal). Exposure data for remote regions (Arctic) are from recent reviews and POP risk profiles and the selected NOELs are recommended by regulatory agencies, unless otherwise indicated (see SI; S8). The columns reflect the range of RCRs as estimated by the range of reported detectable measurements (minimum−maximum monitoring data) for the lowest, most conservative, Tier 1 (green) and Tier 2 (light blue) assessment endpoints included in this case study. The navy blue columns compare RCRs calculated using NOELs for organ weight change (Tier 2). Ideally, risk comparisons should use consistent endpoints such as lethality (Tier 1) or a specific organ mass change normalized for body size (Tier 2). Despite not meeting the ideal requirements in all cases, the RCR comparisons in Figure 4 still provide useful information in the context of the SC.

The RCRs for Tier 1 and Tier 2 assessment endpoints calculated from maximum exposure measurements span approximately 5 orders of magnitude. For Tier 1 assessment endpoints the screening-level RCRs for the listed POPs and

HBCD are <1. Tier 1 HBCD RCRs are approximately 1.5−3.5 orders of magnitude lower than those for the listed POPs (no Tier 1 data available for pentachlorobenzene). For Tier 2 assessment endpoints only the RCR for polychlorinated biphenyls (PCBs) exceeds 1; however, ΣDDTs and dieldrin RCRs are close to 1. For the organ weight change assessment endpoint (Tier 2), all RCRs are <1 (no data available for PCBs). For this endpoint, the HBCD risk estimate is 35−870 times lower than estimates for listed POPs except for pentachlorobenzene for which it is ∼10 times higher. If all Tier 2 endpoints are considered (i.e., not based on a directly comparable, consistent endpoint), HBCD exhibits RCRs comparable to some of the listed POPs.

The present comparison is limited because more effect endpoints were collected and reviewed for HBCD than for the listed POPs (SI; S7). This may bias the general Tier 2 assessment endpoint comparisons for HBCD because highly sensitive effect endpoints such as auditory impairment and changes to trabecular bone mineral density were not available for the listed POPs. As noted above, the relevance (and reliability) of these particular endpoints as indicators of SAE could be considered further as a part of more comprehensive risk evaluations. The exposure concentrations for the listed POPs are recent (since the late 1990s) and do not reflect higher historical levels. Furthermore, for substances with multiple congeners and mixtures, congener/chemical-specific toxicity data and exposure comparisons are preferable if the data are available.

Further Considerations for Risk Characterization

It has been argued that the need to quantify risk is the fundamental reason for monitoring chemicals in the environment and conducting laboratory toxicity tests (*24*). There are enormous costs (money, time, animals) associated with obtaining these data, the value of which is drastically diminished if this information is not used in a systematic framework for evaluation and decision-making. Chemical detection in remote regions is a function of the sensitivity of the analytical methods and emissions and thus does not provide definitive evidence of persistence, long-range transport potential, or the likelihood of SAE (*25*). Detection limits have been lowered from parts-per-million levels in the 1970s (10^{-6}) to parts-per-quadrillion levels (10^{-15}) in recent years (*24*) and the ability to detect chemicals in the environment is expected to further improve in the future. In this context a systematic risk-based framework provides a transparent foundation for consistent evaluations for the potential of SAE, minimizing subjectivity in judgment and maximizing the available scientific data for decision-making.

The SC advocates the use of risk characterization; however, this activity is not being adequately conducted in current risk profiles prepared for nominated POPs, thereby reducing the role of science and limiting the utility of available, valuable scientific data to support decision-making. The proposed assessment endpoint hierarchy strives to facilitate the development of POP risk profiles and the implementation of the SC by providing guidance to risk managers for evaluating the potential for SAE to humans and the environment. The value of the monitoring data for assessing exposures is thus realized because these data include key properties of the chemical that are often difficult to determine independently; namely, actual emissions to the environment, environmental persistence, long-range environmental transport, and bioaccumulation. All of the available monitoring data were included for transparency in these results (i.e., including uncertain dump-site and sediment core data). A tiered approach to evaluate the relevance and applicability of the monitoring and exposure data could also be considered.

The main objective here is to illustrate how quantitative risk-based methods using the proposed hierarchy for assessment endpoints can be applied to support decision-making and fully implement the mandate of the SC. Other factors for consideration are the potential for mixture toxicity, the magnitude of emissions, persistence, long-range transport, bioaccumulation, and toxicity, and the uncertainty in the data and the RCRs. The calculated screening-level RCRs in this analysis used "no effect" data. More comprehensive evaluations could consider using "lowest effect" data to better quantify the uncertainty associated with the effect endpoint. Mass balance models can be used to corroborate emission estimates with the monitoring data and to predict changes in exposures and the potential for SAE as a result of increases or decreases in emission rates (*23*). In general, changes in exposure are directly proportional to changes in emissions due to the linearity of the models. Increased emissions are thus expected to result in increased exposures and proximity to a possible SAE and vice versa. Some modeling has been conducted to simulate changes in environmental concentrations and multimedia response times based on reduced emissions of HBCD and some listed POPs (*26*). Model simulations such as these could be further developed to consider risk management options for nominated and listed POPs. Finally, a risk-based mass balance modeling framework can provide guidance for data collection thereby reducing uncertainty in the assessments and unnecessary costs while also providing information related to chemical properties and use patterns that result in SAE thus promoting sustainable, "green" chemistry.

Acknowledgments

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Supporting Information Available

Listed and nominated SC chemicals and summary information used to conduct the risk estimation for HBCD and comparative assessments. This material is available free of charge via the Internet at http://pubs.acs.org.

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