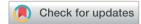
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Can the Stockholm convention address the spectrum of chemicals currently under regulatory scrutiny? Advocating a more prominent role for modeling in POP screening assessment

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Frameworks for chemical regulation are based on the science at the time they were written. Today some regulations are being applied to a much broader spectrum of chemicals than we had knowledge of when the regulations were written. This entails a risk that the regulations are being used outside of their chemical application domain. This question is explored using the POP screening assessment in the Stockholm convention, which was developed 20 years ago. Using perfluorinated alkyl acids (PFAAs) as an example, it is shown that the assessment can lead to false negative conclusions. A second case study using octamethylcyclotetrasiloxane (D4) illustrates that there is also a risk of false positives. The risk for false negative classification of PFAAs is due to the inclusion of a screening criterion – bioaccumulation – that is not a requirement for adverse effects of chemicals in remote regions. For D4 the risk of false positive classification stems from the four screening criteria (persistence, bioaccumulation, long-range transport, and adverse effects) applying to different environmental media/compartments. The major lesson is that applying the POP screening procedure to the broad spectrum of chemicals in modern commerce will require that we rely less on the individual screening criteria and more on the comparison of estimated exposure and the thresholds for effects stipulated in Annex D, paragraph 2 of the convention. Models have an important role to play in this context and should become more strongly integrated into the POP screening process.

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Environmental significance

This paper illustrates some limitations of the Stockholm convention, one of the most important tools for regulation of chemicals at the global scale. It shows that the criteria to screen for new POPs can lead to false negative and false positive conclusions when applied to chemicals that lie outside of the chemical domain of the screening procedure. This problem is clearly attributed to breaking down the complex processes of chemical transport, fate and exposure into simple indicators, a strategy which cannot be successful across a wide spectrum of chemicals. Integrated transport, fate and exposure models are advocated as a solution.

Introduction

Frameworks for environmental regulation of chemicals are initiated in response to a societal concern and constructed based on the understanding of contaminant science at the time they are formulated. Some of the regulatory frameworks we are currently working with are more than 20 years old. They were developed based on our experience with a limited set of perhaps several hundred environmental contaminants. Today societal concerns have evolved and we are applying these frameworks to tens of thousands of chemicals with a much broader spectrum of uses, modes of emission, and physical chemical properties. It is possible that some of these chemicals do not fit within these frameworks, which would imply a higher risk of false positive and false negative regulatory decisions. Borrowing on modeling terminology, we can say that a regulation has a chemical application domain arising from the initial societal concern and rooted in the state of the science at the time of its formulation. Are we adhering to these domains in our efforts to regulate more diverse chemicals? Can our regulatory frameworks for chemicals deal with the diversity of chemicals that we are managing today and intend to regulate tomorrow? The answer to this question has significant consequences for future research needs in contaminant science. In the following this question will be explored using the Stockholm convention on persistent organic pollutants.

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The Stockholm convention

The objective of the Stockholm convention is to "protect human health and the environment from persistent organic pollutants" (Stockholm convention, 2009).¹ It was adopted in 2001 and initially specified international action on 12 persistent organic pollutants (POPs). An important component of the convention was criteria and a procedure for identifying further POPs. This component is based on the work of the Criteria Expert Group, which completed its task in 1999.² The procedure for identifying further POPs is a two stage process. In the first stage the candidate chemical is assessed against four screening criteria. If it passes this stage, a risk profile of the chemical is constructed, the purpose of which is "to evaluate whether the chemical is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and/or environmental effects".¹

The four screening criteria in the first stage of this process are persistence, bioaccumulation, potential for long range transport in the environment, and adverse effects. An historical perspective on the origin of these criteria and how similar concepts have been employed in other regulations is provided by Matthies et al.3 At the time the POP screening criteria were derived, contaminant science, and in particular those parts of it dealing with contamination in remote areas, was focused on semi-volatile organic chemicals, many of them chlorinated aromatic compounds. The concerns with these chemicals had to do with their bioaccumulation in top predators to levels that were considered potentially toxic, particularly in marine mammals and human populations that eat marine mammals. Some comments on the purpose, historical context, and evaluation of each of the criteria are provided below as background to the assessment of the application domain of the screening procedure.

Persistence is a criterion that is indirectly related to exposure levels, as a persistent chemical will have higher concentrations in the environment than a non-persistent chemical emitted at the same rate. However, the inclusion of persistence among the screening criteria is much more strongly motivated by its relevance as an indicator of reversibility. The ability to reverse exposure is essential if we wish to be able to manage contaminant problems affecting human health or the environment in the future. Given that our understanding of possible adverse effects is almost always incomplete, it is essential that society maintain the possibility to manage contaminant problems. At least as early as 1982 it was recognized that the reversibility of environmental contamination is the most important criterion for assessing the hazard of a chemical.4 In light of this, one could formulate the goal of the POP screening stage as "We want to avoid poorly reversible exposure of humans and the environment in remote regions to chemicals at levels that could be harmful". Persistence is defined in the convention as a halflife >2 months in water, >6 months in soil, or >6 months in sediment.1

Bioaccumulation, like persistence, is a property that can increase exposure, but it is not a condition for exposure. Its

inclusion as a screening criterion is a reflection of the concern in the 1990s about adverse effects in top predators. At that time, most organic chemicals of concern in remote regions bio-accumulated. However, the effect of making bioaccumulation a criterion for passing the first stage of the evaluation was that chemicals that do not bioaccumulate will not be of concern. Bioaccumulation is defined in the convention as a bio-concentration factor in fish >5000.1

The long-range transport criterion reflects the global nature of the convention. Three transport media are named: air, water, and migratory species. To fulfill the long-range transport criterion the convention requires either measured levels of the chemical in remote environments at levels of concern or other evidence showing potential for or occurrence of long-range transport plus potential for transfer to a receiving environment.¹

The last criterion requires evidence of adverse effects on health or the environment, or toxicity or ecotoxicity data that indicate the potential for such adverse effects. This criterion is also a reflection of the focus in the 1990s on contaminant effects in humans and top predators. Potential effects on non-biological systems (*e.g.*, the atmosphere) are not included. Of the four screening criteria, adverse effects is the least specific; no guidance is provided on how severe adverse effects should be or at what exposure levels they should be evaluated. However, the convention does require that the screening evaluation include a comparison between the measured or estimated exposure and toxicity or ecotoxicity data – if possible. 1

Since the adoption of the Stockholm convention, 16 further chemicals have been classified as POPs and listed in the convention's annexes. All but one of the 16 are chlorinated or brominated, and most of these are semivolatile organic compounds.6 However, today our regulatory ambition encompasses a much broader spectrum of chemicals, with tens of thousands of chemicals under scrutiny in different jurisdictions. Despite this expansion in the chemical spectrum in focus, only one chemical far outside of the original chemical domain has been listed in the convention, perfluorooctane sulfonic acid (PFOS). This may be an indication that the convention's screening procedure is not effective at identifying POPs that are different from the original 12 POPs. If indeed the screening procedure is poorly suited for working with a broader spectrum of chemicals, there is a risk that it will lead to both false negative and false positive results. In the following we will examine an example of each.

False negative classification

Perfluorinated alkyl acids (PFAAs) are an example of a group of chemicals that are subject to false negative classification. These chemicals are highly persistent in water, subject to long range transport in water and air, present in biota, and some have been shown to elicit a range of adverse effects. However, they are not bioaccumulative as defined in the convention.

One PFAA, namely PFOS, has been listed as a POP in the convention.⁶ In the risk profile for PFOS it is acknowledged that the bioaccumulation criterion of a BCF in fish >5000 L kg⁻¹ is

not met. Instead, it is argued that bioaccumulation should be assessed based on biomagnification, and although PFOS has not been found to clearly biomagnify in fish, it does biomagnify in air-breathing top predators. To further support the bioaccumulation assessment, it is argued that PFOS has been found at high concentrations in biota in remote regions.⁷ This argumentation was successful, presumably because there was a consensus that PFOS causes poorly reversible exposure of humans and the environment in remote regions at levels that could be harmful, and PFOS was listed as a POP.

A second PFAA, perfluorooctanoic acid (PFOA), is currently a candidate for listing as a POP and a risk profile has been prepared. Therein it is once again acknowledged that the bioaccumulation criteria for $K_{\rm OW}$ and fish BCF are not met. It is again argued that bioaccumulation should be judged based on biomagnification, but it is acknowledged that the available results vary widely, with some studies showing biomagnification and others not. Although the evidence is weaker than for PFOS, it is concluded that PFOA is bioaccumulative based on selected studies showing bioaccumulation in airbreathing organisms and PFOA presence in air-breathing aquatic species and terrestrial species.8

The difficulties encountered with the regulation of PFOS and PFOA, although they are clearly global threats to the environment and human health, have exposed problems with the bioaccumulation criterion. PFOA is an example of a chemical for which drinking water can be the primary source of exposure. When this is the case, bioconcentration in fish and biomagnification, the metrics primarily used to assess bioaccumulation, are of no relevance. Relying instead on tissue levels in humans or top predators as a substitute for bioaccumulation metrics can be problematic, as chemicals can be rapidly metabolized or excreted and still have adverse effects. In such cases modifying the requirements to fulfill the bioaccumulation criterion, as was done for PFOS and PFOA, would not suffice; it would be necessary to waive the criterion.

Bioaccumulation is not a requirement for exposures that can cause adverse effects. Motivated by these concerns, researchers are now questioning the relevance of bioaccumulation as a criterion in chemical screening.9 The German Environment Agency has proposed to use persistence, mobility and toxicity instead of persistence, bioaccumulation and toxicity as screening criteria for the regulation of chemicals in water.¹⁰ While their concept focuses on water resource management, there are conceptual parallels to POP screening.

False positive classification

Octamethylcyclotetrasiloxane (D4) provides a plausible case study to explore how application of the Stockholm convention to a broader set of chemicals may lead to false positive classifications. D4 is an important intermediate in the production of PDMS (polydimethylsiloxane) and has a wide range of direct uses. According to information available in 2009 the major releases of D4 to the European environment are leakage of residual D4 monomers in PDMS to air (940 tonnes per year) and release to air and water via use of personal care products (490

and 54 tonnes per year, respectively).11 The physical chemical properties of D4 are distinctly different than those of classical POPs as illustrated by comparison with PCB 180 in Table 1. It is much less persistent in all surface media, especially in water and soil where degradation is 600 and 8000 times faster than for PCB 180. The differences are even greater for the partitioning behaviour, the air-water partition coefficient of D4 being 5 orders of magnitude higher and the organic carbon/air partition coefficient being almost 8 orders of magnitude lower. Compared to classical POPs, D4 is extremely volatile.

An initial assessment of D4 against the screening criteria of the Stockholm convention (without considering transformation products) yields the following. It has a half-life in sediment of 242-365 d,13 and thus satisfies the persistence criterion. It has a bioconcentration factor in fish of 12 400 L kg⁻¹, 11 and thus satisfies the bioaccumulation criterion. The D4 concentrations in Arctic (Svalbard) air during the winter are similar to the concentrations in air in southern Sweden,14,15 indicating that long-range atmospheric transport occurs. Finally, adverse effects of D4 have been observed in fish and daphnia above concentrations of 5 μ g L⁻¹, indicating that there is a potential for adverse effects in the environment.13 Thus, an initial assessment indicates that D4 fulfills the POP screening criteria.

The classification is less clear if one does an integrated assessment using a model. Xu and Wania used a global environmental fate model to compare the behaviour of D4 with a classical POP, PCB 180. They emitted each chemical into the global atmosphere at a constant rate and predicted the concentrations in different media in the model compartments over time. After 30 years of global emissions at 1 000 000 kg per year, ~200 000 kg of PCB 180 had accumulated in the Arctic while the corresponding value for D4 was \sim 0.5 kg. 12 The propensity of D4 to accumulate in the remote environment was nearly one million times lower than that of the classic POP.

Why do the POP screening criteria not capture the much smaller tendency of D4 to accumulate in remote regions? Xu and Wania explain that the difference in behaviour is partly due to degradation of volatile methylsiloxanes in air.12 In addition, D4 is hydrolyzed rapidly in water, so that very little chemical is left by the time that it reaches the medium where it is relatively persistent, sediment. Here chemical persistence as defined in

Table 1 Comparison of the partitioning properties and degradation half-lives of D4 and PCB 180°

	D4	PCB 180
$K_{\rm OC}$ (L kg ⁻¹)	1.7×10^{4}	5.0×10^{6}
K _{AW}	490	0.0033
$K_{\rm OC/A}$ (L kg ⁻¹)	34	1.5×10^{9}
t ₅₀ air (h)	250	2600
<i>t</i> ₅₀ water (h)	94	$5.5 imes 10^4$
t_{50} sediment (h)	$8.8 imes 10^3$	$1.7 imes 10^5$
<i>t</i> ₅₀ soil (h)	130	$1.0 imes 10^6$

^a All properties from the model-based comparative assessment of D4 and PCB 180 by Xu and Wania¹² with the exception of $K_{\text{OC/A}}$ which was calculated as the quotient of K_{OC} and K_{AW} .

the convention has no predictive power for environmental exposure in remote regions, since the medium where the chemical is persistent is a medium that only a small portion of the chemical ever reaches. A second reason for the large discrepancy between D4 and PCB 180 is the much higher volatility of D4.12 The much lower tendency to partition from air to either water or organic carbon (Table 1) means that a much smaller portion of the D4 enters surface media. As a consequence, the criteria that have traditionally been used for characterizing the tendency of a POP to accumulate in remote environments, namely long-range atmospheric transport and persistence in any one surface medium, are not sufficient for

In drafting the screening criteria for the convention, the Criteria Expert Group had the foresight to include stipulations that address this problem. In the text for long-range transport they required evidence for "potential for transfer to a receiving environment". Models have an important role to play in evaluating this potential, and model-based indicators have been developed for this purpose. Xu and Wania employed two of these indicators in their work, transfer efficiency (calculated by the OECD Pov and LRTP Screening Tool)16 and the Arctic contamination potential (calculated using the Globo-POP model).17 Both of these indicated that the transfer to receiving environments is much lower for D4 than for established POPs.12

Another interesting issue in assessing D4 is the link between environmental levels and bioaccumulation. Is bioaccumulation relevant if it occurs in a compartment where exposure is low? For classical POPs this question did not arise, as they accumulate in aquatic systems and the bioaccumulation criterion is defined for fish. For D4 in remote regions contaminated via long-range transport, concentrations will be highest in the air and much lower in surface media as discussed above. Chemical activities are also expected to be lower in the aquatic environment than in the air since air is the source of the chemical to water and D4 hydrolyses quite rapidly in water. Is bioaccumulation in water breathing organisms relevant for such a chemical? Interestingly, while D4 is bioaccumulative in fish, it does not bioaccumulate in mammals.11 Should D4 therefore be classified as nonbioaccumulative because it does not bioaccumulate in the medium with high exposure? This question can and should be addressed by exposure modeling in which fate models and bioaccumulation models are coupled to produce exposure estimates in different organisms that can be compared. However, while such a comparison would tell us which medium is most relevant for exposure, it would not yield a bioaccumulation metric. Here we are reminded of the question that arose in the discussion of false negative classification: is bioaccumulation a relevant metric for classification of POPs? The D4 example also suggests that we should be looking at exposure directly rather than at a surrogate for exposure (such as BCF in fish).

D4 also adds a new facet to the adverse effects criterion. Adverse effects have only been reported for aquatic organisms, and the threshold above which they have been observed is about 5 μ g L⁻¹. The water solubility of D4 is 56 μ g L⁻¹, ii so the threshold for effects is about 10% of the water solubility. Is it conceivably possible to achieve a concentration in water equal

to 10% of the water solubility in a remote region exposed by atmospheric long-range transport? Even if we saturated the atmosphere with D4 in source regions, would not so much be degraded during atmospheric transport and subsequently via hydrolysis in water that it would not be possible to attain a concentration of 10% of the solubility? If this is not possible, can D4 be a POP? This question did not arise for classical POPs as their toxicity thresholds were not close to saturation and their environmental degradation was low compared to D4. To address this question, multimedia fate models are the obvious tool of choice.

For classical POPs the screening criteria are effective at eliciting the potential for adverse effects in remote regions, but this is not the case for D4. The persistence criterion does not predict exposure levels, the long-range transport criterion requires an assessment of deposition to surface media, the bioaccumulation criterion is disconnected from the environmental medium with high exposure and thus does not predict organism exposure, and the exposure threshold for effects, although a low concentration, may not be physically achievable in remote environments. To do a meaningful screening assessment of D4, it is necessary to prepare an estimate of the exposure of susceptible organisms in remote regions and compare this with best estimates of effects. This is possible within the framework of the convention, as Annex D stipulates that the screening evaluation should include a comparison between the measured or estimated exposure and toxicity or ecotoxicity data. Models that link long-range transport, fate in remote regions, and exposure to wildlife and humans would be very helpful for conducting such an evaluation.

As discussed above, reversibility of exposure is an important component of the screening assessment of chemicals, as it is a prerequisite for being able to manage the chemical should adverse effects be identified in the future. Although not specified as a goal in the Stockholm convention, it is implicit in the definition of persistence as a screening criterion. Is the persistence criterion a good indicator of the reversibility of exposure for D4? Xu and Wania simulated the global fate of D4 for a scenario in which emissions were stopped after having been constant for 40 years. The amount of D4 in the global environment decreased by 2.5 orders of magnitude in 6 months.¹² This is consistent with other modeling work showing that hypothetical chemicals with environmental degradation halflives equal to the REACH thresholds for persistence and partitioning properties similar to D4 will be 95% removed from the environment within 1-2.5 years.18 Xu and Wania found a slower half-life of 1 year for elimination from sediment, whereby the levels in sediment were largely the result of local emissions to water in their model scenario.12 As discussed above, D4 accumulation in sediment in remote regions is expected to be lower due to degradation during long-range atmospheric transport and in water before deposition to sediment. Here we again have a potential issue of misalignment of environmental media; the medium where the chemical is persistent may not be the medium where exposure is potentially problematic. This issue was not encountered with classical POPs; it too can be addressed using models.

The role of modeling

Clearly problems can be encountered when the screening procedure in the Stockholm convention is applied to chemicals that lie outside of the property domain of semivolatile organic compounds. The lessons from the examples discussed above are two-fold. First, there can be flaws in the construction of the screening procedure that lead to incorrect decisions. The PFAA case study illustrated that having bioaccumulation as a criterion can result in potentially problematic chemicals not being screened in. Second, the four screening criteria may not be satisfied in the same environmental media or compartments. Some degree of alignment between the criteria and environmental media/compartments is necessary if the chemical is to be a POP (i.e., can lead to significant adverse human health and/ or environmental effects as a result of long-range transport). Classical POPs were clearly aligned; they were transported to remote aquatic systems, persistent in aquatic systems, bioaccumulated in aquatic systems and toxic to aquatic organisms. D4 is transported largely to air, persistent in sediment but not in water, bioaccumulates in aquatic organisms and is toxic to pelagic organisms. This lack of compartment/media coherence between the criteria can result in chemicals incorrectly being screened in. Compared to incorrectly screening out chemicals, incorrectly screening in is principally less problematic (the incorrect decision can be corrected at the risk profile stage), but it nevertheless creates work for the convention partners that prevents them from addressing more relevant concerns and it generates uncertainty about the future of the chemical that can have economic consequences.

These problems can be resolved in different ways. For the first class of problems it may be necessary to change the convention or the interpretation thereof (e.g., by waiving criteria for specific chemicals). The second class of problems must be addressed by taking an integrated approach to assessing longrange transport and fate, bioaccumulation, toxicity, and reversibility. For a diverse population of chemicals it is not possible to break this complex problem down into a handful of independent criteria. Thankfully there is room to work within the framework of the convention to achieve this, but it would require an adjustment of current practice. If the convention is to be applied to a broader range of chemicals, it will be necessary to rely less on the individual criteria (Annex D, par. 1) and more on the "screening risk estimate" (Annex D, par. 2). In Annex D, paragraph 2 the convention defines the information requirements for the "screening risk estimate" as "comparison of toxicity and ecotoxicity data with detected or predicted levels of a chemical resulting or anticipated from its long-range environmental transport". How this comparison is to be done is not further detailed.

I maintain that models are key for this task, as only models can integrate the diverse information required for such a screening risk estimate. Models also have an important role to play in fostering comparability in the treatment of different chemicals and increasing the transparency of the evaluation. Models should become more strongly integrated into the POP

screening process. Care will be required to ensure that the models are applicable to the chemical of interest, as models, like chemical regulations, have an application domain.

Diverse modeling approaches will be needed depending on the chemical under consideration. However, tools that are certain to be of value will be models that link long-range transport, fate in remote environments, and exposure, as well as models (perhaps the same ones) that can assess the reversibility of exposure. For instance, if the work of Xu and Wania modeling D4 levels in the Arctic environment as a result of long range transport was linked to an exposure model that predicted the exposure of Arctic aquatic organisms, the modeled exposure could be compared to aquatic ecotoxicity data to establish if it is conceivable that long range transport of D4 could cause harm to the environment. If portions of the environment were identified that could conceivably be harmed, then dynamic models such as those employed by Xu and Wania could be used to establish whether the exposure in these portions of the environment is reversible.

Conflicts of interest

Over the past 10 years the author has received funding to study PFAAs from the Swedish Research Council Formas and funding to study cyclic volatile methylsiloxanes from Unilever, the Long-Range Research Initiative of the European Chemical Industry Council, the Centre Européen des Silicones and various Scandinavian government organizations. He testified for the Canadian government in the hearings of the Siloxane D5 Board of Review. There was no external funding for the work presented here.

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