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How many persistent organic pollutants should we expect?

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ABSTRACT

Under the Stockholm Convention on Persistent Organic Pollutants (POPs), currently 22 chemicals or groups of chemicals are regulated as POPs. However, various screening exercises performed on large sets of chemicals indicate that the number of substances fulfilling the screening criteria defined in Annex D of the Stockholm Convention might be much higher. Most of these screening studies searched for highly persistent and bioaccumulative chemicals, but did not include the long-range transport potential, which is a key criterion under the Stockholm Convention. We apply the screening criteria for persistence, bioaccumulation and long-range transport potential of the Stockholm Convention to a set of 93 144 organic chemicals. Because no toxicity threshold is defined under the Stockholm Convention, we use the toxicity threshold of REACH, the chemicals regulation of the European Union. For the vast majority of the chemicals, the property data required for the assessment had to be estimated from the chemical structure. Assessment results for the acknowledged POPs and for POP candidates currently under review are discussed. Beyond these well-known substances, we find 510 chemicals that exceed all four critieria and can be considered potential POPs. Ninety eight percent of these chemicals are halogenated; frequent types of chemicals are halogenated aromatic compounds, including polychlorinated diphenylethers, tetrachloro benzyltoluenes, brominated and fluorinated naphthalenes and biphenyls; and highly or fully chlorinated and fluorinated alkanes (cyclic, linear, branched). Non-halogenated substances are highly branched alkanes and nitroaromatic compounds. Ten substances are high-production volume chemicals and 249 are pre-registered in the EU. We used uncertainty ranges of the chemical property data to estimate a lower and upper bound of the number of potential POPs; these bounds are at 190 and 1 200 chemicals. These results imply that several tens of potential POPs may have to be expected for future evaluation under the Stockholm Convention.

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1. Introduction

Persistent organic chemicals are a group of priority chemicals in chemical hazard and risk assessment. Because they are persistent, these chemicals "have time" to be transported over long distances and to reach remote regions in all parts of the world. Depending on their other properties such as octanol-water partition coefficient, bioaccumulation factor and toxicity, they have the potential to bioconcentrate and biomagnify along the food chain, to cause chronic exposure and, finally, to exert toxic effects in wildlife and humans. This concern is reflected by the concept of PBT assessment (persistence, bioaccumulation, toxicity), which is employed in several national chemical regulations, including the European regulation REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (EU, 2006). At the global level, the concern about persistent organic chemicals is addressed by the Stockholm Convention on Persistent Organic Pollutants (POPs), which entered into force in 2004 (UNEP, 2012). Currently, there are 22 chemicals or groups of chemicals that are listed as POPs under the Convention and another five are currently under review by the POP Review Committee (POPRC) of the Convention (UNEP, 2012). A key question for the future work under the Stockholm Convention is how many additional POPs are to be expected, given the fact that there are tens of thousands of chemicals on the market globally. In other words, concepts and tools are needed that make it possible to screen large numbers of chemicals for substances with POP properties.

In the recent years, various lists of priority chemicals or chemicals of concern have been published (Muir and Howard, 2006; Brown and Wania, 2008; Howard and Muir, 2010; Nendza et al., 2010; OSPAR, 2012; SIN, 2012; ETUC, 2012; Öberg and Iqbal, 2012). An important aspect of these priority lists of chemicals is that they differ considerably in their focus. For example, Strempel et al. (2012) found that the SIN list (SIN, 2012) contains only 5% of potential PBT chemicals, whereas in the list of priority substances of the OSPAR convention (OSPAR, 2012) almost 50% are potential PBT substances. This finding is not unexpected, because the different lists are based on different criteria, such as PBT criteria (excluding long-range transport potential), POPs criteria (including long-range transport potential), or criteria for carcinogenicity, mutagenicity and toxicity for reproduction (CMR). Even when the same criteria are used, the threshold values often differ; for example, the US EPA PBT criteria use a bioconcentration factor of 1 000, whereas the REACH PBT criteria use 2 000, and the Stockholm Convention uses 5 000, see overview in Table 1 of Muir and Howard (2006). In addition, most lists do not include half-life in air, which is the criterion for long-range transport under the Stockholm Convention.

To exactly address the definition of POPs used under the Stockholm Convention, it is necessary to employ the POP screening criteria defined in Annex D of the Convention. Muir and Howard (2006) used these criteria to screen more than 10 000 substances from the Canadian Domestic Substances List; on their list of the top

30 substances with PBT and LRT characteristics (their Table 3), 19 substances exceeded all three Stockholm Convention thresholds. Two of these substances, tetra- and pentabromo diphenylether, were included in the Stockholm Convention in 2009; one substance, hexabromocyclododecane, is currently under review by the POPRC.

Rorije et al. (2011) identified, in a set of 65 000 industrial chemicals, pharmaceuticals, pesticides and biocides, almost 2 000 substances that may fulfill the persistence and bioaccumulation criteria of the Stockholm Convention. Similarly, Strempel et al. (2012) identified 3 000 to 5 000 potential PBT chemicals in a set of 95 000 industrial chemicals. These high numbers indicate that the number of potential POPs may be higher than the 19 substances reported by Muir and Howard (2006). Rorije et al. (2011) explicitly addressed the need for a POPs list and explicitly mention the Stockholm Convention, but used a score based on overall persistence and biomagnification, did not explicitly consider long-range transport potential, and excluded toxicity. Öberg and Iqbal (2012) also identified potential POPs, but they used overall persistence (Pov) and LRTP calculated with the OECD Pov and LRTP Tool (Wegmann et al., 2009) and applied threshold values of 195 days for Pov and 5 000 km for LRTP instead of the Annex D criteria of the Stockholm Convention. Furthermore, they did not include toxicity as a screening criterion. Finally, Lambert et al. (2011) used a different approach and searched for potential POPs in a list of 83 chemicals that have been detected in field samples from the Arctic and Antarctic.

Here we apply the POP screening criteria defined in Annex D of the Stockholm Convention to a set of 93 144 industrial chemicals and identify the substances that exceed these criteria.

2. Methods

2.1. Assessment criteria

In Annex D of the Stockholm Convention, threshold values are defined for three of the four screening criteria: a degradation half-life of 60 days (water) or 180 days (soil, sediment) for persistence (P); a bioconcentration factor (BCF) or a bioaccumulation factor (BAF) of 5 000 for bioaccumulation (B); and a half-life in air of 2 days for long-range transport potential (LRTP); the latter corresponds to a transport distance of 690 km if an average wind speed of 4 m/s is assumed. For toxicity (T), Annex D refers to evidence of adverse effects to human health or the environment but does not specify a threshold value. This implies that in screening exercises the toxicity dimension is left out or a threshold from a different regulation has to be used.

To identify potential POPs, we defined two groups of chemicals. The “POP group” consists of chemicals that exceed a biodegradation half-life in water of 60 days, a BCF or BAF of 5 000, a half-life for reaction with OH radicals in air of 2 days, and have toxic effect concentrations below 0.1 mg/L (acute) or 0.01 mg/L (chronic). These toxicity thresholds were taken from the REACH regulation (EU, 2006) and refer to marine or freshwater species (aquatic toxicity). The second group is the “very-POP group” and was defined by a biodegradation half-life in water exceeding 180 days, a BCF or BAF exceeding 20 000, and a half-life in air exceeding 10 days; the toxicity thresholds are the same as in the POP group.

It is important to note that Annex D of the Stockholm Convention specifies for all four properties that other evidence can also be used for the assessment of whether or not a chemical exceeds the screening criteria. For the B dimension, this has been discussed in detail by Kitano (2007).

2.2. Selection of chemicals

The minimum information about a chemical that is needed for a screening exercise based on estimated property data is the CAS number and the SMILES code (Daylight, 2008; CAS, 2012). The CAS number specifies the identity of the chemical and the SMILES code describes the chemical structure. We collected CAS numbers and SMILES codes from two large databases: the SMILECAS database, which is included in the EPI Suite software (US EPA, 2012), and includes CAS, names and SMILES for 115 346 chemicals (Syracuse, 2012) and a database provided by the Joint Research Centre of the European Commission (JRC) that includes CAS and SMILES for 72 561 of the 100 204 chemicals in EINECS, the “European Inventory of Existing Commercial Chemical Substances” (JRC, 2012). We merged the two sets and obtained a set of approximately 135 000 entries. We then removed incorrect or ambiguous CAS and SMILES, which reduced the set to approximately 122 000 chemicals for which a correct CAS and unique SMILES was available.

Next, we removed several 100 individual congeners of polychlorinated biphenyls (PCBs), polychlorinated naphthalenes (PCNs), polychlorinated dibenzodioxins and -furans (PCDD/Fs), polybrominated diphenylethers (PBDEs), and polychlorinated diphenylethers (PCDEs), because these individual congeners of chemicals with POP properties would have given too much weight to acknowledged POPs. PCBs, PCNs, PCDD/Fs, PBDEs and PCDEs are represented in our database as homologues with different degrees of halogenation.

We also removed approximately 20 000 inorganic and metallorganic substances and salts, because the property estimation methods described in Section 2.3 cannot be applied to these substances. Another 10 000 organic substances were removed because they are also outside the applicability domains of the property estimation methods (chemicals with molecular weight above 1 000 g/mol; chemicals for which only the molecular weight was used to estimate the degradation half-life by the method BIOWIN3). After all these steps, we obtained a set of 93 144 chemicals for which we estimated property data for P, B, LRTP and T. Approximately 50% of these 93 144 chemicals have been pre-registered in the EU under REACH (ECHA, 2010). Details of the compilation of this database of organic chemicals are provided in the Supporting Material (SM) and by Strempel et al. (2012).

2.3. Chemical property data

Because for the majority of chemicals no measured data for P, B, LRTP and T are available, we had to use property estimation methods. We used the collection of estimation tools of Epi Suite (US EPA, 2012), which are freely available and cover all properties needed for the assessment: BIOWIN3 for ultimate biodegradation (aerobic), BCFBAF for BCF and BAF, AOPWIN for half-life in air, and ECOSAR for aquatic toxicity.

BIOWIN3 (Boethling et al., 1994) yields scores between 0 and 5 that indicate the order of magnitude of the half-life of ultimate aerobic biodegradation. A score of 5 stands for a half-life on the order of hours, 4 indicates days, 3 weeks, 2 months, and 1 stands for “recalcitrant”. In the Epi Suite User Guide for the Level-III fugacity model that is also part of Epi Suite, half-life values corresponding to these scores are provided (from 0.17 days for a score of 5 to 180 days for scores below 1.75). We fitted a straight line through the pairs of suggested half-lives and the corresponding BIOWIN3 scores and used the resulting relationship, $\log t_{1/2} = -0.80\ s + 3.51$, to convert the BIOWIN3 output into degradation half-lives (s is the BIOWIN3 score and $t_{1/2}$ the half-life in days). We interpreted the half-lives obtained from the BIOWIN3 score as half-lives in water and compared them to the threshold of 60 days.

Table 1. *Number of chemicals for which at least one measured data point of the five properties listed was found (first row) and uncertainty factors derived from a comparison of the available measured data with estimated data (second row)*

	Biodegradation half-life	BCF	2nd-order rate constant for reaction with OH radicals	Acute aquatic toxicity	Chronic aquatic toxicity
Number of chemicals	216	995	1 025	2 198	241
Uncertainty factor	4	4	2	45	100

BCFBAF yields two main outputs when it is run in batch mode, a BCF derived from a relationship between BCF and K_{ow} and chemical-specific correlation factors, and a BAF based on the Arnot-Gobas upper trophic level model (Arnot and Gobas, 2003). We recorded both BCF and BAF for the further screening.

AOPWIN calculates 2nd-order rate constants for the reaction of organic chemicals with OH radicals in the gas phase (Atkinson, 1988). The program then estimates 1st-order rate constants, k^{OH}, by multiplying the 2nd-order constants by an average OH radical concentration of 7.5×10^5 molecules/cm^3 and calculating the half-life as $t_{1/2} = \ln 2/k^{OH}$. The rate constant, k^{OH}, represents reaction with OH radicals in the gas phase, but for chemicals with low vapor pressure (below 1 Pa, so-called semivolatile organic chemicals), a significant portion may be adsorbed to or absorbed into atmospheric aerosol particles. This includes many POP-like substances. It is generally assumed that the particle-bound fraction is not (fully) available for reaction with OH radicals (Scheringer, 1997). This implies that actual half-lives in air of semivolatile organic chemicals are often higher than the estimates from AOPWIN. In addition, AOPWIN has been found to yield uncertain and probably too high rate constants for complex and highly chlorinated chemicals (Franklin et al., 2000; Krüger and Zetzsch, 2001).

ECOSAR (US EPA, 2009) estimates the toxicity of organic chemicals in aquatic species; depending on the chemical structure, it uses different relationships to derive the toxic effect concentration from the chemical properties, mainly K_{ow}, and information about functional groups in the chemical (Moore et al., 2003). We used ECOSAR in the batch mode; in this case, ECOSAR looks up the results for all chemicals of the batch in a built-in database without actually running any QSARs. From all results listed for a given chemical, we recorded the lowest estimated acute and chronic toxicity concentrations (if both were available). This approach can be applied independently of the water solubility of the chemicals; Mayer and Reichenberg (2006) reported that even chemicals with high K_{ow} exert a significant baseline toxicity and that their low water solubility does not make them non-toxic.

In addition to the estimated property data, we also collected measured property data from more than 10 public-domain databases, as listed in the Supporting Material. Data were retrieved by either downloading them as a file or by setting up a computer program that submitted property queries for all individual CAS numbers. The data points were then checked for consistency and plausibility; for example, we removed BCF values for which the test duration was so short that it was unlikely that steady-state was reached. The number of chemicals for which experimental data were found are remarkably small; they range from two hundred for P to around 2 000 for acute toxicity, see Table 1.

Finally, for each property and for all chemicals for which measured data were available, we combined the estimated and measured data points. In doing so, we gave equal weight to measured and estimated data. For P, B and LRTP, we created a set of all individual data points for a given property and chemical, and calculated the geometric mean of the data points in this set. For T, we used the "most-vulnerable-species" approach and selected the lowest toxicity value, whether experimental or calculated by ECOSAR. This was done separately for acute and chronic toxicity.

After this combination of measured and estimated data, the degradation half-lives for water (P) were compared to the 60-d threshold; both the BCF and BAF were compared to the threshold of 5 000 and if either of them was above the threshold the chemical was classified as B; the half-life in air was compared to the threshold of two days; and the acute and chronic effect concentrations were compared to the REACH thresholds of 0.1 mg/L and 0.01 mg/L; if either of them was below the threshold, the chemical was classified as T. Substances for which all four criteria were fulfilled were included in the POP group. The same was done with the criteria for the very-POP group.

2.4. Uncertainty analysis

For the limited number of chemicals for which experimental data were found, these measured data points can be compared to the estimated values of the same property. This provides an opportunity to estimate the uncertainty of the estimated property data: we plotted the estimated data against the experimental data for the same property and fitted a regression line through these pairs of data points. We then determined the range around the regression line that includes 68% of all data points. A fraction of 68% was used because, for distributions similar to a normal distribution, approximately 68% of the data points lie within one standard deviation around the mean. This means that, for example, the estimated BCF is within a factor of 4 around the measured BCF for 68% of the data points (see Table 1). The factor that spans this range was then used as the uncertainty factor of the respective property (see second row in Table 1).

The factors in Table 1 reflect uncertainties as they can be expressed quantitatively on the basis of the available empirical data. The actual uncertainties surrounding the chemical property data may be higher than these factors, but this additional uncertainty cannot be quantified.

3. Results

Application of this POPs screening method to the set of 93 144 organic chemicals yields 574 chemicals that exceed the Annex D thresholds and 193 chemicals that are in the "very POP" group. The 574 chemicals in our group of potential POPs are listed in the Supporting Material. As we point out in the discussion section, this list is associated with uncertainties; the list can be refined when improved property estimation tools are available and/or priority chemicals can be selected for in-depth investigations, including measurements of chemical properties.

3.1. Acknowledged POPs

Specifically, there are several acknowledged POPs in the group of chemicals exceeding the Annex D criteria, including

- PCBs (8 homologues ranging from trichloro to decachloro),
- PCDD/Fs (6 homologues ranging from trichloro to octachloro),
- the insecticides DDT, chlordane, toxaphene, chlordecone,

Table 2. *Thresholds for POP properties that are exceeded (yes) or not exceeded (no) for several acknowledged POPs. In general, results are based on combinations of estimated and measured property data*

Chemical	Half-life of aerobic biodegradation > 60 d	BCF or BAF > 5 000	Half-life of reaction with OH radicals in air > 2 d
Aldrin	Yes	Yes	**No**
Heptachlor	Yes	Yes	**No**
α-HCH	Yes	**No**	Yes
β-HCH	Yes	**No**	Yes
γ-HCH	Yes	**No**	Yes
PFOS	Yes	**No** [a]	Yes
Endosulfan	Yes	**No**	**No**

[a] *Estimated property data exceed the threshold but the combination of estimated and measured data is below the threshold.*

Table 3. *Thresholds for POP properties that are exceeded (yes) or not exceeded (no) for chemicals currently under review by the POPRC. In general, results are based on combinations of estimated and measured property data*

Chemical	Half-life of aerobic biodegradation > 60 d	BCF or BAF > 5 000	Half-life of reaction with OH radicals in air > 2 d
PCN (tri- to octachloro)	Yes	Yes	Yes
Hexabromocyclododecane	Yes	Yes	Yes
Hexachlorobutadiene	Yes	Yes	Yes
Pentachlorophenol	**No** [a]	**No**	Yes
Pentachloroanisole	Yes	Yes	Yes
SCCPs, 60% and 61% Cl	Yes	Yes	Yes
SCCPs, 51% and 54% Cl	Yes	Yes	**No** (Yes)
SCCP, 46% Cl	Yes	Yes	**No**
SCCP, 40% Cl	**No**	Yes	N**o**

[a] *Estimated property data exceed the threshold but the combination of estimated and measured data is below the threshold.*

- pentachlorobenzene, hexachlorobenzene and hexabromobiphenyl,
- PBDEs (tetra- to heptabromo and in addition also octa- and nonabromo, which are not included in the PBDEs regulated by the Stockholm Convention),
- three precursors of PFOS, namely perfluorooctane sulfonyl fluoride, PFOSF (CAS 307-35-7), perfluorooctane sulfonamide, FOSA (CAS 754-91-6), and N-methyl FOSA (CAS 31506-32-8).

Three of the acknowledged POPs are not included in our database (dieldrin, endrin, mirex). Results for the other acknowledged POPs for which not all thresholds are exceeded are listed in Table 2 (toxicity is not included, because no toxicity threshold is defined in the Stockholm Convention).

Low values of estimated atmospheric half-lives (below 2 days) of aldrin and heptachlor are known to be highly uncertain (Bidleman et al., 1990). Howard (1991) states, "aldrin in the atmosphere is expected to be adsorbed to particulate matter and no rate can be estimated for the reaction of adsorbed aldrin with hydroxyl radicals". Accordingly, atmospheric half-lives of these substances may be well above the threshold of 2 days if it is assumed that reaction with OH radicals is impeded for chemical sorbed to aerosol particles. This aspect is discussed in detail by Scheringer (1997). In addition, AOPWIN results for these highly chlorinated substances are generally uncertain (Franklin et al., 2000; Krüger and Zetzsch, 2001).

The BCF values below 5 000 of the three HCH isomers and PFOS and reasons why these chemicals are still considered as fulfilling the B screening criteria of the Stockholm Convention have been discussed by Kitano (2007).

For endosulfan, significant bioconcentration in terrestrial organisms was the reason that endosulfan was considered as a bioconcentrating chemical under the Stockholm Convention (UNEP, 2009); BCFBAF, which deals with aquatic bioconcentration, does not cover this aspect. Concerning the half-lives in air estimated with AOPWIN for endosulfan, Becker et al. (2011) found evidence that these half-lives are too low. Again, this is in line with the known uncertainty in AOPWIN results for complex molecules (Krüger and Zetzsch, 2001).

3.2. Chemicals under review by the POP review committee

The five POP candidates currently under review by the POPRC are present in the group of potential POPs, including PCNs (6 homologues ranging from trichloro to octachloro), hexabromocyclododecane (HBCD), hexachlorobutadiene (HCBD), pentachloroanisole (pentachlorophenol itself is not present in the POP group), and several short-chain chlorinated paraffins (SCCPs). Details are provided in Table 3 (toxicity is not included, because no toxicity threshold is defined in the Stockholm Convention).

SCCPs are represented in our database by six individual chemicals that are in the range of 40% to 70% chlorine (by weight) and have between 10 and 13 carbon atoms; these substances are $C_{10}H_{18}Cl_4$ (51% chlorine, CAS 102880-00-2); $C_{10}H_{16}Cl_6$ (61% chlorine, CAS 108171-26-2); $C_{11}H_{19}Cl_5$ (54% chlorine, CAS 140899-23-6); $C_{12}H_{23}Cl_3$ (40% chlorine, CAS 71011-12-6); $C_{12}H_{22}Cl_4$ (46% chlorine, CAS 60836-00-2); and $C_{12}H_{19}Cl_7$ (60% chlorine, CAS 63449-39-8). For the two compounds with 60% and 61% chlorine, all thresholds are exceeded; the two compounds with 51% and 54% chlorine exceed the P and B thresholds and are just below the 2-d threshold in air (1.9 and 1.8 days). As mentioned above for aldrin, heptachlor, and endosulfan, sorption to aerosol particles may increase the half-life of reaction with OH radicals in air significantly (Bidleman et al., 1990; Scheringer, 1997). Because the octanol-air partition coefficient of these compounds is high, significant sorption to aerosols can be expected and the half-life in air is probably higher than 2 days (indicated by "(yes)" in Table 3). Finally, for the two SCCPs with 46% and 40% chlorine, AOPWIN yields half-lives for reaction with OH radicals that are below the 2-d threshold (0.83 days and 1.31 days, respectively); in addition, the SCCP with 40% chlorine is below the P threshold.

Table 4. *Most important classes of chemicals present in the group of substances exceeding the Annex D criteria of the Stockholm Convention*

Class	Examples
Halogenated monoaromatic compounds	Tetrachlorobenzene and many mixed-halogenated (fluorinated, chlorinated, brominated) benzenes; 2,3-dibromopropyl-2,4,6-tribromophenyl ether (DPTE), a brominated flame retardant (CAS 35109-60-5); tri-, tetra- and pentabromobenzene
Chlorinated terphenyls and quaterphenyls	
Chlorinated azobenzenes	Tetrachloroazobenzene, a degradation product of chloranilide herbicides, such as diuron
Chlorinated bisphenols	
Organochlorine insecticides	Various isomers of dicofol, nonachlor
Perchlorinated alkanes	perchloroisobutane
Perfluorinated alkanes	Linear: perfluoro hexane, heptane, octane, nonane, dodecane; Branched: perfluoro-2-methylpentane; Cyclic: perfluoro(1,4-dimethylcyclohexane), perfluorodecalin, perfluoro(methyldecalin)
Polyfluorinated alkanes	Nonafluoro octane, octafluoro decane
Polyfluorinated alkyl substances (PFASs)	8:2, 10:2 and 12:2 fluorotelomer alcohol, perfluorodecanoic acid, perfluorododecanoic acid, perfluorododecane sulfonic acid
Polychlorinated diphenyl ethers (PCDEs)	Eight homologues ranging from trichloro to decachloro and several hydroxy- and methoxy-PCDEs
Polyfluorinated and polybrominated dibenzodioxins and -furans	
Polyfluorinated and polybrominated biphenyls; several hydroxy-PCBs	
Polyfluorinated, polybrominated and polyiodinated naphthalenes	
Halogenated pyrenes	Tetrachloro and tetrabromo pyrene
Triazines with fluorinated or chlorinated substituents	Tris(perfluoroethyl) triazine, tris(perfluorobutyl) triazine
Tetrachlorobenzyl toluene (ugilec-141)	
Non-halogenated compounds	Octamethyl octane, 2,4,6-tri-t-butyl nitrobenzene

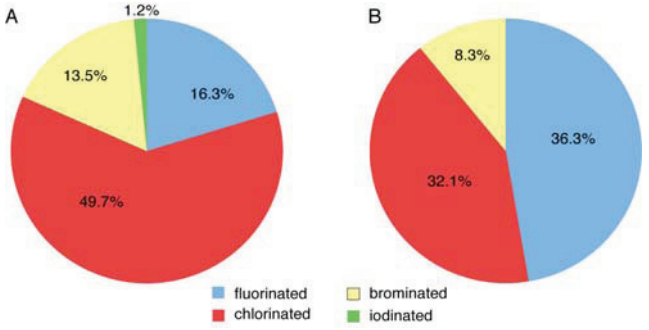

Figure 1. *Percentages of chemicals with different halogenation within the halogenated substances in the POP group* ***(A)*** *and in the very-POP group* ***(B)****. Included are only chemicals with "pure" halogenation; in addition there are 19% of chemicals with mixed halogenation in the POP group and 23% in the very-POP group. 1.4% of substances in the POP group are not halogenated.*

3.3. Additional chemicals: potential POPs

In addition to the acknowledged POPs and the chemicals currently under review by the POPRC, there are approximately 510 chemicals in our group of potential POPs that have not been evaluated under the Stockholm Convention. The vast majority of these chemicals (98%) are halogenated; the percentages of chemicals with only fluorine, chlorine, bromine and iodine are shown in Figure 1A; in addition there are 19% of chemicals with mixed halogenation (not included in Figure 1A). An overview of the most prominent classes of chemicals in the group of potential POPs is provided in Table 4. A full list of all chemicals in the group of potential POPs is provided in the Supporting Material.

The "very POP" group only contains halogenated substances (193 in total), including:

- hexachlorobenzene;
- polychlorinated biphenyls (six homologues from pentachloro to decachloro);
- PCDD/Fs (hexachloro to octachloro);
- polybrominated diphenyl ethers (pentabromo to octabromo);
- polybrominated biphenyls (pentabromo to octabromo); octafluoro biphenyl; 4,4'-dibromooctafluoro biphenyl (CAS 10386-84-2);
- polychlorinated naphthalenes (hexachloro to octachloro) and hexabromo naphthalene;
- polychlorinated diphenyl ethers (pentachloro to decachloro);
- triazines with fluorinated or chlorinated substituents;
- 1,3-dichloro-6-(trifluoromethyl)phenanthrene-9-carbonyl chloride (CAS 94133-67-2);
- perfluorinated alkanes (linear, branched, and cyclic);
- perfluorinated alkyl ethers (linear, branched, and cyclic).

The percentages of purely fluorinated, chlorinated and brominated chemicals are shown in Figure 1B (in addition there are 23% chemicals with mixed halogenation, which are not included in Figure 1B). Remarkable is the high fraction of fluorinated chemicals (36.3% compared to 16.3% in the POP group). This high fraction of fluorinated chemicals is in contrast to the fact that there is currently only one fluorinated chemical in the acknowledged POPs (PFOS). A list of all substances in the "very POP" group is provided in the Supporting Material.

Approximately 45% of the substances in the POP group have been pre-registered in the EU (ECHA, 2010). A total of 15 substances in the POP group are listed as high-production-volume chemicals (HPVCs), five of these are acknowledged POPs or POP candidates currently under review (DDT, HCB, PFOSF, HBCD, octa-BDE). The other 10 are listed in Table 5. Also included in Table 5 are two substances that have been identified for registration under REACH by 31 May 2013 (ECHA, 2012), perfluorotripropylamine (perfluamine) and 1,2,3,4-tetrachlorohexafluorobutane.

Table 5. *Potential POPs identified in this work that are either HPVCs or identified for registration under REACH*

CAS	Name	Relevance
115-32-2	Dicofol	HPVC
128-63-2	Tetrabromopyrene	HPVC
133-49-3	Pentachlorothiophenol	HPVC
77-47-4	Hexachlorocyclopentadiene	HPVC
95-94-3	1,2,4,5-tetrachlorobenzene	HPVC
2043-53-0	1-iodo-1H,1H,2H,2H-perfluorodecane	HPVC
2043-57-4	1-iodo-1H,1H,2H,2H-perfluorooctane	HPVC
678-39-7	8:2 fluorotelomer alcohol	HPVC
311-89-7	Perfluorotributylamine	HPVC
52184-19-7	6-[(2-nitrophenyl)azo]-2,4-di-tert-pentylphenol	HPVC
338-83-0	Perfluorotripropylamine	REACH
375-45-1	1,2,3,4-tetrachlorohexafluorobutane	REACH

3.4. Uncertainty

Application of the uncertainty factors defined in the methods section leads to a lower bound and an upper bound of the number of chemicals in the POP and very-POP group. For the POP group, the lower bound is 191 substances and the upper bound is 1 201 chemicals; for the very-POP group, the bounds are 70 and 326 chemicals. Compared to the best estimates of 574 and 193 chemicals, these are factors of 0.33 and 2.1 (uncertainty of the number of chemicals in the POP group) and factors of 0.36 and 1.7 (uncertainty of number of chemicals in the very-POP group).

4. Discussion

Our list of potential POPs is the result of a screening exercise and provides starting points for more detailed assessments. In particular, even when uncertainty ranges of the chemical property data are included, the number of potential POPs is still around 190. A first main conclusion is therefore that several tens to approximately 100 potential POPs may be expected for future evaluation under the Stockholm Convention.

A screening assessment as performed here may create false-negative and false-positive results. False positives occur when estimates of the chemical property data are too high. For P, this is possible for chemicals that undergo hydrolysis, which is not recognized by BIOWIN; examples are carbonyl chlorides and anhydrides (Muir and Howard, 2006). On the other hand, it may be expected that the degradation process comes to a halt after the hydrolysis step if the hydrolysis products themselves are recalcitrant. This is well possible if the initial anhydride or carbonyl chloride is highly halogenated. In other words, it is important to capture persistent transformation products that are formed in a relatively fast initial reaction. Concepts for this have been presented by Fenner et al. (2000) and further advanced by Ng et al. (2011).

Regarding B, false positives may occur if either BCF or BAF is overestimated or the biotransformation rate constant, k_m, is underestimated. It is known that the Arnot-Gobas bioaccumulation model, which is the underlying BAF model in BCFBAF, tends to overestimate the BAF. The explanation for this bias is the model calibration by Arnot and Gobas (2003); this is discussed in detail by Arnot and Gobas (2003).

Inspection of Figure 14 in Arnot and Gobas (2006) shows that for chemicals with log K_{ow} values between 3 and 5 it is possible that the (measured and estimated) BCF is below 5 000, the estimated BAF above 5 000, but the measured BAF below 5 000. For these chemicals, the estimated BAF would create false-positive results; in our POP group, there are 18 substances of this type (listed in the Supporting Material).

In addition, it is possible that underestimation of biotransformation causes overestimation of BAF for some chemicals, especially when they are outside the chemical property ranges that represent the training set of the biotransformation QSAR in BCFBAF. This may apply to brominated aromatic compounds (Nyholm et al., 2009); in our group of potential POPs there are 17 brominated aromatic compounds with BAF values above 5 000 for which the K_{ow} exceeds the upper bound of log K_{ow} = 8.7 indicated for the biotransformation QSAR in BCFBAF.

On the other hand, false negatives may occur if either BCF or BAF is underestimated, or if k_m is overestimated. Regarding the first case, BCF models are known to generate some false negatives, as discussed by Arnot and Gobas (2006), but this is in part compensated for by the simultaneous consideration of BAF, which is unlikely to underestimate B, as discussed above. In terms of k_m, the performance of the QSAR used to predict k_m has been assessed by Arnot et al. (2009) and shown to have no particular bias to either over- or underestimate biotransformation.

Furthermore, BCFBAF may underestimate the BCF of chemicals that bind to proteins, such as perfluorinated alkyl substances (PFOS) or cyclic acid anhydrides (tetrachlorophthalic anhydride). However, the number of these chemicals in our database is difficult to quantify.

AOPWIN has been found to underestimate half-lives in air of complex molecules (Krüger and Zetsch, 2001; Becker et al., 2011). In addition, AOPWIN does not take into account the effect of sorption to aerosol particles (the particle-bound fraction is probably not fully available for reaction with OH radicals). Again, this effect is difficult to quantify.

Another limitation in the context of false negatives is that our database of 93 144 substances does not contain all relevant types of chemicals. For example, many pesticides, biocides and pharmaceuticals are not included. These groups have been explicitly addressed by Rorije et al. (2011). Another type of chemicals not included is siloxanes; for example, Öberg and Iqbal (2012) identified 1,3-bis-(dichloromethyl)-1,1,3,3-tetramethyl-disiloxane (CAS No. 2943-70-6, not included in our database) as a potential POP.

Table 6. *Results for five compounds listed by Öberg and Iqbal (2012) as potential POPs, but not in the POP group in this study*

CAS	Name or Chemical Class	Threshold exceeded?			
		P	B	LRTP	T
87-83-2	Pentabromotoluene	Yes	**No**	Yes	Yes
328-70-1	3,5-bis(trifluoromethyl) bromobenzene	Yes	**No**	Yes	Yes
2641-34-1	Perfluorinated alkyl ether, carbonyl fluoride	Yes	Yes	Yes	**No**
84041-66-7	Perfluorinated cyclic alkyl ether	Yes	Yes	Yes	**No**
84613-97-8	1,2-dichloro-3-(trichloromethyl)benzene	Yes	Yes	Yes	**No**

Table 7. *Results for seven compounds listed by Muir and Howard (2006) as potential POPs, but not in the POP group in this study*

CAS	Chemical name	Threshold exceeded?			
		P	B	LRTP	T
87-84-3	Cyclohexane, pentabromo-6-chloro	Yes	**No**	Yes	Yes
117-08-8	Tetrachlorophthalic anhydride	Yes	**No**	Yes	Yes
145-39-1	1-tert-butyl-3,4,5-trimethyl-2,6-dinitrobenzene	Yes	**No**	Yes	Yes
944-61-6	1,2,3,4-tetrachloro-5,6- dimethoxybenzene	Yes	Yes	Yes	**No**
30554-72-4	Cyclohexane, tetrabromodichloro	Yes	**No**	Yes	Yes
30554-73-5	Cyclohexane, tribromotrichloro	Yes	**No**	Yes	Yes
73398-87-5	4-(4-chloro-3-propylphenyl) pyridine	**No**	**No**	**No**	Yes

Finally, the Stockholm Convention explicitly mentions the possibility that substances may be considered as POPs because of additional evidence, even if they do not exceed the threshold-based criteria for P, B, und LRT. This implies that substances not fulfilling the P, B, LRTP and T criteria according to our method might still be categorized as POPs due to environmental measurements and other considerations. This is especially important for substances accumulating in terrestrial organisms, which might not be captured by our approach, because we evaluated only aquatic bioconcentration and bioaccumulation and toxicity.

Comparison to other lists of potential POPs. Forty six of the 68 potential POPs listed by Öberg and Iqbal (2012) in their Table 4 are present in our database. Nine chemicals of the 22 that are not in our database are congeners of PCBs or PCNs that are represented by the corresponding homologues in our database, which means that the actual number of chemicals missing in our database is 13. Forty one of the 46 chemicals that our database has in common with the list of Öberg and Iqbal (2012) are also in our POP group, 16 even in the very-POP group. The five substances that were identified by Öberg and Iqbal (2012) as potential POPs but are not in our POP group are listed in Table 6.

Pentabromotoluene is below the B threshold because of measured BCF data. For 3,5-bis(trifluoromethyl) bromobenzene, BCFBAF yields a BAF of 4 989, which may have been rounded to 5 000 by Öberg and Iqbal (2012). The last three compounds exceed the thresholds for LRTP, P and B, but are less toxic than indicated by the toxicity threshold of REACH. Because our system includes a quantitative toxicity threshold, it is in this respect more restrictive than that by Öberg and Iqbal (2012). But, on the other hand, the numerical criteria used by Öberg and Iqbal (2012) are more stringent than those in Annex D of the Stockholm Convention and used here: an overall persistence of 195 days and a characteristic travel distance of 5 097 km, corresponding to a half-life in air of 14.5 days if an average wind speed of 4 m/s is assumed. Another reason why we identified a larger number of potential POPs than Öberg and Iqbal (2012) is that our total set of chemicals is larger (not limited to chemicals pre-registered in the EU).

Table 3 of Muir and Howard (2006) contains 30 top P and LRTP chemicals that also have bioaccumulation potential; 19 of these exceed the P, B and LRTP criteria of the Stockholm Convention. Of these 19 chemicals, 14 are present in our database, and seven of these are in our POP group; the seven that are not in our POP group are listed in Table 7.

For six of these seven chemicals, our estimate for B is below the threshold. This is most likely caused by the fact that Muir and Howard (2006) used, in addition to BCFWIN (the precursor of the BCFBAF tool used here), a BCF estimation method that yields higher BCF in particular for chemicals with log K_{ow} below 4.5 (BCFmax developed by Dimitrov et al., 2003). In the remaining case, 1,2,3,4-tetrachloro-5,6-dimethoxybenzene, it is again the toxicity threshold in our screening criteria that leads to exclusion of the chemical.

Concerning the B assessment of tetrachlorophthalic anhydride, the WHO (2009) reports "that cyclic acid anhydrides bind to plasma proteins and hemoglobin and that the primary binding amino acid appears to be lysine" (WHO 2009). Therefore, B from BCFBAF may be too low for this compound, see above discussion of false negatives. On the other hand, tetrachlorophthalic anhydride undergoes hydrolysis, which is not covered by BIOWIN3, which means that it is probably not P (Muir and Howard, 2006), but see above, discussion of persistent transformation products.

Finally, for 4-(4-chloro-3-propylphenyl) pyridine (CAS 73398-87-5), the main difference from the results reported by Muir and Howard (2006) is in the B value, which again is caused by using two different BCF estimation methods, BCFBAF in our case and BCFmax by Muir and Howard (2006). P and LRTP are very close to the threshold values and the different classifications result from rounding errors.

How can our list of potential POPs be used by scientists and regulators, in particular the POPRC? First, our results confirm that the five substances or groups of substances currently under review by the POPRC are likely to have POP properties. The results for SCCPs indicate a gradual transition to less pronounced POP properties with decreasing degree of chlorination, but overall a large portion of the substances present in the mixture called SCCPs fulfils the POPs screening criteria.

Secondly, the number of chemicals identified in this work as potential POPs is too high to be processed by the assessment procedure of the Stockholm Convention. A possible starting point is to focus on the chemicals in our very-POP group, because for these chemicals it is probably not contentious that they exceed the screening criteria of the Stockholm Convention. Another option is to compile additional information on uses and emissions in order to identify a smaller set of high-priority potential POPs; for these substances, the estimates for P, B, LRTP and T need to be refined by inclusion of more measured data. Here a particular challenge is that measured data on chemical properties and on levels in remote regions are very limited or missing altogether for many chemicals. Additional measurements and field campaigns will be inevitable. New measured chemical property data will be beneficial in two ways: they will improve the body of empirical property data and help to understand the trends, ranges, and uncertainties of these data. Additionally, more measured data will provide a broader basis for the development and/or improvement of QSARs and QSPRs.

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Supporting Material Available

Procedure of chemical selection, sources of experimental property data, and lists of potential POPs. This information is

available free of charge via the Internet at http://www.atmospolres.com.

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