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Article

Screening New Persistent and Bioaccumulative Organics in China's Inventory of Industrial Chemicals

Xianming Zhang,* Xiangfei Sun, Ruifen Jiang, Eddy Y. Zeng, Elsie M. Sunderland, and Derek C. G. Muir*

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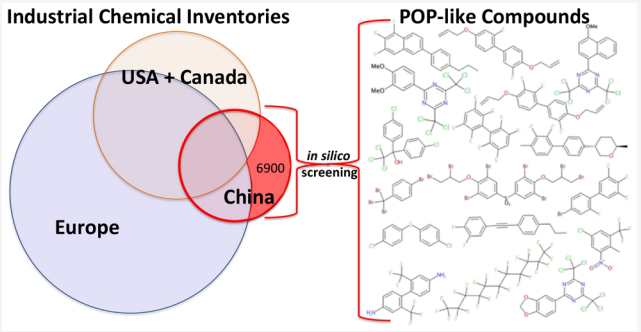
ABSTRACT: Over a third of the world's annual chemical production and sales occur in China. Thus, knowledge of the properties of the substances produced and emitted there is important from a global perspective. The chemical Inventory of Existing Chemical Substances of China (IECSC) lists over 45 000 chemicals. When compared to the North American and European chemical inventories, 6916 substances were found to be unique to the IECSC. We retrieved structural information for 14 938 organic chemicals in the IECSC and determined their overall environmental persistence , bioaccumulation factor (BAF), and long-range transport potential (transfer efficiency) using in silico approaches with the goal of identifying new chemicals with properties that might lead to global contamination issues. Overall, 10% of the 14 938 chemicals were unique to the IECSC and their environmental persistence and BAF were statistically higher than the values for the rest of the IECSC chemicals. We prioritized 27 neutral organic compounds predicted to have prolonged environmental persistence, and high potential for bioaccumulation and long-range transport when compared with polychlorinated biphenyls as a benchmark. We also identified 69 organofluorine compounds with three or more perfluorinated moieties, unique to the IECSC. Screening approaches and results from this study help to identify and prioritize those to be considered in further environmental modeling and monitoring assessments.



INTRODUCTION

The global chemical industry has grown rapidly over the past several decades.[1] The number of chemicals registered in the Chemical Abstract Service (CAS) database exceeded 160 million registered substances as of 2020[2] and approximately half of these chemicals were added to the CAS Registry within the past five years. Among the large number of CAS registered chemicals, an estimated 350 000 are industrial chemicals in commerce.[3] Less than 10% of these substances account for more than 99% of the total global chemical production volume.[1,4]

Growth in the global chemical industry in recent decades has predominantly been driven by China. Between 2007 and 2017, China's chemical production grew by 11% annually and its share of global chemical manufacturing and sales rose from 15% to 37%.[4] The rapid development and large volume of China's chemical industry has led to calls for effective management of the chemicals produced and used.[5] China's Ministry of Environmental Protection identified environmental and health related risks associated with chemical substances as a knowledge gap.[6] Prioritizing chemical substances based on potential environmental fate and exposure is challenging given limited information on uses, emissions, physicochemical properties and toxicity of most industrial chemicals in commerce. Cost-effective modeling simulations (in silico approaches) provide an alternative starting point for tiered chemical risk assessment approaches when such data are limited.

A wide range of in silico screening systems have been developed to prioritize and assess risk of chemicals.[7] Over the past 12 years these in silico approaches have been applied to large lists of substances included in European and North American chemical inventories to identify those potentially a concern for environmental and/or human exposure.[8−15] Most screening efforts[8−13] have focused on chemicals that meet the criteria used to regulate chemicals under programs such as the Stockholm Convention for persistent organic pollutants (POPs), namely: chemical persistence (P), bioaccumulation (B), and long-range transport potential (LRTP).[16] Chemical screening activities have generally used publicly available chemical inventory databases such as the U.S. Toxic

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Substances Control Act Inventory (TSCAI),[17] the Canadian Domestic Substances List (DSL),[18] and the registered or pre-registered substances under the European chemical regulation framework REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) for lists of substances that should be considered.[19] Other screening efforts using chemical inventories have focused on specific toxicological properties such as endocrine disruption,[20] carcinogenicity, mutagenicity, and developmental toxicity.[21] Comprehensive screening for hazards of chemicals is challenging due to insufficient data and lack of modeling tools that address all end points of different modes of action, thus most first-tier chemical risk screening focuses on environmental persistence and exposure potential rather than toxicity.[22]

China established a chemical regulatory system under the legislation entitled "Measures on the Environmental Administration of New Chemical Substances" in 2003.[23] Similar to TSCA and REACH, China's chemical regulatory system included development of an inventory of "existing" substances in use in China ca. 2003. The inventory, referred to as the Inventory of Existing Chemical Substances of China (IECSC),[6] consists of 45 612 substances, 81.3% of which are associated with Chemical Abstracts Service registry numbers (CASRNs). Chemical substances subject to other existing laws and regulations (pharmaceuticals, pesticides, cosmetics, and food additives) are generally not in the IECSC unless they are also used as industrial chemicals.[24] Efforts to prioritize chemicals in the IECSC for environmental management in China were made by Yu et al.[5] but such screening was only considered for a small subset (0.6%) of the IECSC.

The main objective of this study was to identify chemicals that are unique to China and with POP-like environmental fate characteristics including persistence, bioaccumulation, and long-range transport potential. We compared the ICESC to North American and European chemical inventories and compiled chemical structures for most individual organic chemicals. We omitted polymers, UVCBs (unknown or variable composition, complex reaction products or biologicals) and organometallics. We characterized persistence, bioaccumulation, and long-range transport potential of the chemicals using in silico approaches and prioritized them for further assessment.

METHODS

Retrieval of Chemical Information. Records of 45 612 substances in the IECSC (last updated on January 31, 2013, Supporting Information (SI) Table S1) were retrieved as open data from the Ministry of Environmental Protection of China Web site[6] and classified using the R script provided in the SI. All the records contained both Chinese and English names for each substance. Based on the names, we determined the presence of each element in the periodic table and the number of substances belonging to the following categories: Polymers (including resins, cellulose, rubber, and starch), halogenated compounds, salts, polycyclic aromatic compounds, azo compounds, oil, organosilicons, dyes, mixtures of different carbon chain length, reaction products, extracts, petroleum products, organophosphates, paraffins, and musks.

CASRNs were available for 37 103 records in the IECSC (SI Table S1).[6] We checked the CASRN against the CAS digit verification method.[25] A total of 52 CASRN were incorrect and we were able to correct 32 of them. After removing 24 duplicated CASRNs, there were 37 080 unique CASRNs in the IECSC. These CASRNs were then compared with those in the TSCAI (U.S. list),[17] the DSL (Canadian list),[18] and chemicals registered or pre-registered under REACH (EU list)[19]

To derive structural information on substances in the IECSC, we searched the CASRNs in (1) the EPISuite built-in database,[26] (2) CASRNs and simplified molecular-input line-entry system (SMILES) strings compiled for the DSL and the TSCA inventory,[27] (3) PubChem database,[28] (4) ChemSpider,[29] and (5) the U.S. EPA Chemicals Dashboard[30] and obtained their SMILES strings. In addition, SMILES strings were also determined by parsing the chemical names (in IUPAC format) using OPSIN.[31] Merging the SMILES retrieved from the different sources, we obtained structural information for 26 645 substances in the IECSC (SI Table S1).

Estimation of Physicochemical Properties and Environmental Fate. Among chemicals with structural information, we excluded 11 631 substances because they did not fall within the applicability domains of the in silico tools.[12] These included inorganics, organometallics, salts, peroxides, disulfides, epoxides, sulfonic acids, phosphonic acids, carboxylic acids, carbonyl halides, phosphonyl halides, or sulfonyl halides and chemicals with molecular weight over 1000 using the substructure search function in rcdk (v3.4.7).[32] Fluoroalkyl sulfonic acids and carboxylic acids were reviewed separately as described below. For the remaining 14 938 organic chemicals (SI Table S2), we applied EPISuite[26] to derive their physical chemical properties including octanol−water, air−water, and octanol−air partition coefficients (K_{OW}, K_{AW}, and K_{OA})derived with KOWWIN, HENRYWIN, and KOAWIN, respectively, half-lives of reaction with hydroxyl radicals and ozone in the air (HL_a) derived with AOPWIN, half-lives of degradation in soil and water predicted with BIOWIN (HL_w) and bioaccumulation factors (BAF) predicted with BCFBAFWIN. We used BAF rather than bioconcentration factor (BCF) because BAF considers multiple exposure and elimination pathways.[33] If measured values of the properties were available, they were preferentially chosen over the predicted ones. We derived and used internally consistent K_{OW}, K_{AW}, and K_{OA} values following the approach detailed by Schenker et al.[34] because due to measurement or prediction errors the physicochemical properties of K_{OW}, K_{AW}, and K_{OA} or predicted by KOWWIN, HENRYWIN, and KOAWIN in EPISuite[26] were not always thermodynamically consistent, that is, K_{OW} did not equal the product of K_{AW}, and K_{OA}.,

Prioritization of Chemicals Based on Their Structures and Environmental Fate. Physicochemical properties for each chemical were used as the input to the OECD (Organization for Economic Cooperation and Development) screening model to predict the persistence and long-range transport of the chemicals.[35,36] The OECD screening model is a generic three-compartment global evaluative environment representing air, water, and soil/sediment.[35,36] Using the model, we calculated overall persistence (P_{OV}) and transfer efficiency (TE), two indicators of environmental fate. P_{OV} considers phase distributions and degradation potential in each environmental compartment. The calculated P_{OV} value was based on emission scenarios (to air, water, and soil) that result in the highest persistence, whereas TE, which measures propensity for long-range atmospheric transport and deposition, was included to characterize potential impacts on distant receptors. Because Pov, BAF, and TE differ in magnitude and distribution pattern, differences need to be eliminated in order to avoid the influence of an extreme value in one of the

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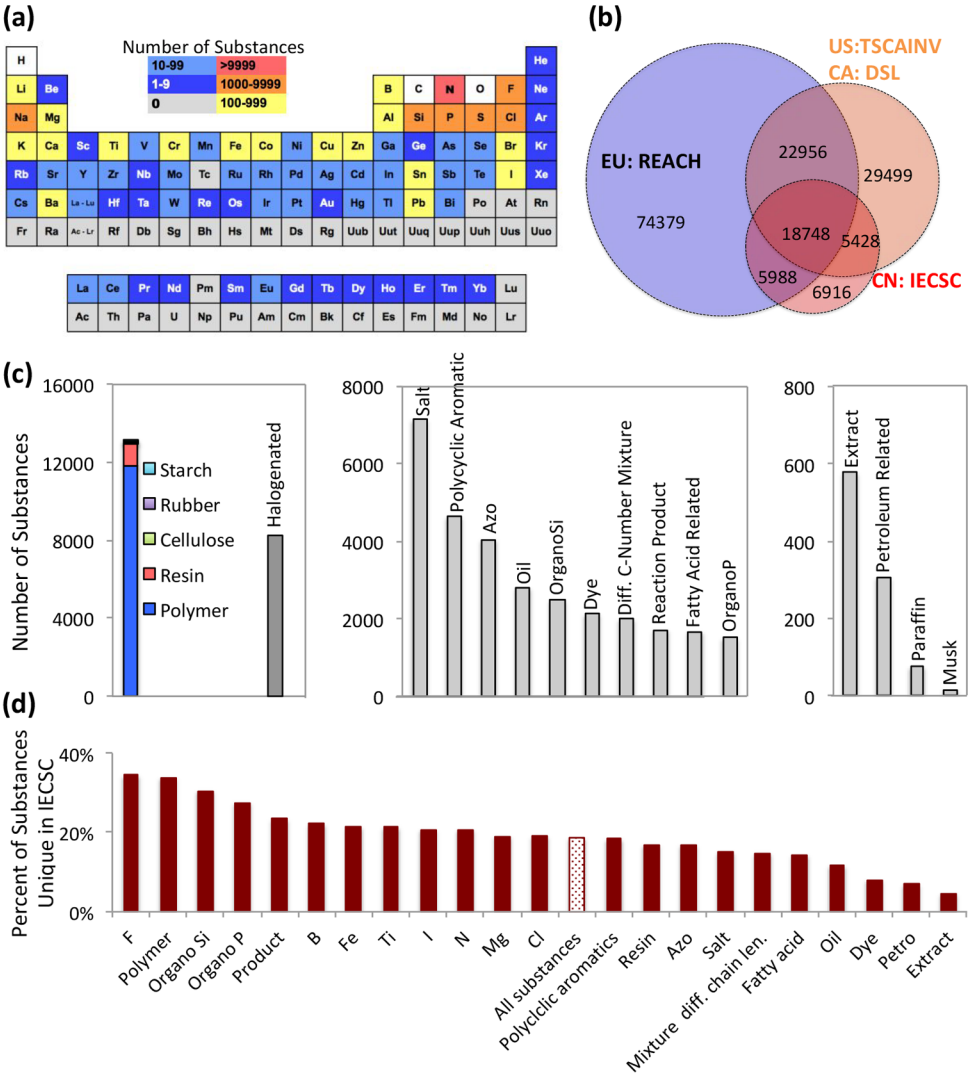

Figure 1. An overview on the Inventory of Existing Chemical Substances Produced or Imported in China (IECSC): (a) Elemental distributions (b) Comparisons of CASRNs with the U.S. Toxic Substances Control Act Inventory (TSCAInv), the Canadian Domestic Substance List (DSL), and chemicals registered and pre-registered under the EU REACH legislation; (c) Classes of substances in IECSC derived from their common names listed in the inventory; (d) Percent of each group of substances that are unique to IECSC.

indicators in a scoring/ranking system that integrates the three predicted parameters. Therefore, we normalized and scaled the indicator values by calculating z-scores of logP_{OV}, logBAF (L kg^{-1} ww), and logTE and then defined an integrated persistence−bioaccumulation−long range transport (P−B−LRT) score as the sum of the three z-scores.[37]

We used the Arctic POP score developed by Brown and Wania[9] as a second scoring approach to evaluate and rank the chemicals. This score was based on structural features of known POPs detected in the Arctic environment. Methods used to calculate it and a comparison with the P−B−LRT score are presented in the SI.

We also evaluated POP-like characteristics of the IECSC chemicals based on K_{OA}−K_{AW} values.[38] Ranges of concern were identified by Czub et al.[38] using a global chemical transport model[39] and an Arctic food web model.[40] Chemicals with elevated Arctic contamination and bioaccumulation potential (ACBAP) tend to undergo long-range transport and accumulate in Arctic food webs (behavior of POPs) if they have specific combinations of values identified by Czub et al.:[38] $\log K_{OA} + \log K_{AW} \geq 3.5$ and $\log K_{OA} \geq 6$ and $0.5 \geq \log K_{AW} \geq -7$ and $\log K_{AW} \leq -1.78 \times \log K_{OA} + 14.56$.

We prioritized chemicals based on three partitioning and fate criteria:

(I) logK_{AW} and logK_{OA} in the ACBAP region;

(II) $HL_a \geq 2$ d (criterion used by the Stockholm Convention[41] and the Canadian Toxic Substances Management Policy[42]), $HL_w \geq 40$ d, BAF or BCF $\geq$ 2000 L/kg (REACH PBT criteria).

(III) The P−B−LRT score and the Arctic POP score within the ranges or higher than that of polychlorinated biphenyls (PCBs).

Emerging poly- and perfluoroalkyl substances (PFAS) are a priority for further assessment given the severe environmental and public health impacts associated with releases of legacy compounds.[43] PFAS, particularly the perfluoroalkyl acids (PFAAs), have unique physicochemical properties and fall outside of the applicability domains of most in silico screening tools. Some neutral precursors can also be degraded to

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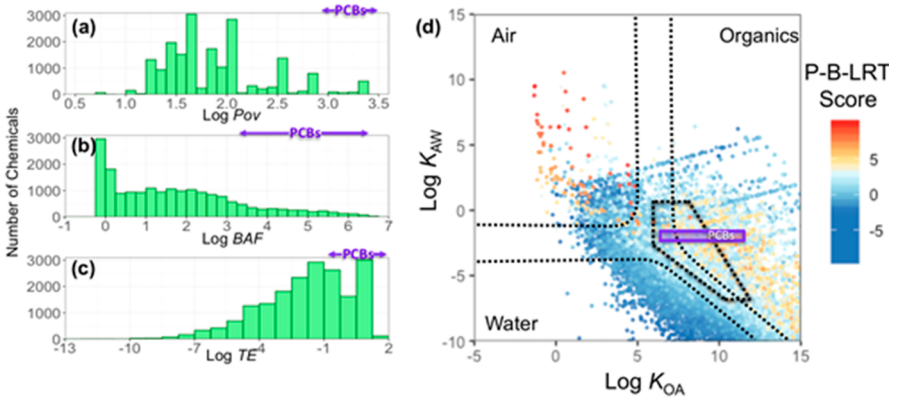

Figure 2. Environmental fate and exposure indicators including: (a) overall environmental persistence (P_{OV}), (b) bioaccumulation factor (BAF, mid trophic level), and (c) transfer efficiency (TE) of the organic chemicals in the Inventory of Existing Chemical Substances Produced or Imported in China (IECSC). Persistence-bioaccumulation-long range transport (P−B−LRT) scores are shown by color dots on the octanol−air and air−water partition coefficients (K_{OA}−K_{AW}) chemical space (panel d), where dotted lines separate regions where the equilibrium distribution of chemicals (>90%) is in air, water, and the organic phases (soil, vegetation). The region within the dash lines represent chemicals with higher Arctic contamination and bioaccumulation potential (ACBAP). Polychlorinated biphenyls (PCBs) are a class of legacy persistent organic pollutants (POPs) commonly used as a benchmark for PBT properties and are shown within the purple region of panel (d).

persistent PFAAs, and, to our knowledge, there is no in silico tool to predict their degradation pathways and products. As such, prioritization of PFAS was based on our review of the similarity of their structural features to legacy PFAAs that have been associated with adverse health effects rather than in silico derived environmental parameters.

RESULTS AND DISCUSSION

Overview of Chemicals in the IECSC. Elemental distributions derived based on the English and Chinese names of the 45 612 substances in the IECSC are shown in Figure 1a. Other than carbon, hydrogen, and oxygen, nitrogen and sulfur are the two most frequently occurring elements. They are present in 35% and 16% of the IECSC substances. Chlorine is the third most frequently occurring element and is present in 9% of the IECSC substances. Fluorine and bromine are also frequently occurring halogens, which are present in 5% and 2% of the IECSC substances, respectively. Sodium and potassium occur in many salts in the IECSC inventory. They are present in 8% and 1% of the IECSC substances. The top 10 most widely present elements also include silicon and phosphate. They are present in 6% and 4% of the IECSC substances. Of the silicon and phosphate containing substances, 95% and 87% respectively, are organic compounds such as siloxanes, silanes, and organophosphates.

CASRNs of chemical substances in the IECSC were compared with those in TSCAI, the DSL, and chemicals registered and pre-registered under REACH (Figure 1b). Of the 37 080 substances with CASRNs in the IECSC, 18 747 (51%) overlap with the combined European and North American chemical inventories; 6916 (19%) are unique in the IECSC (i.e., listed with no CASRNs or with CASRNs not in TSCAI, DSL, or REACH). In addition, 5428 (15%) and 5988 (16%) of the IECSC CASRNs overlap with the North American and European inventories, respectively.

Four thousand IECSC substances are UVCBs and 13 100 are polymers (including resin, rubber, cellulose, and starch), which together contribute to 29% of the IECSC substances (Figure 1c). Halogenated compounds represent the largest in number (7564) of nonpolymeric substances, and account for 17% of the IECSC substances. Of the halogenated compounds, 499 (7%) are heterohalogens (i.e., contain more than one halogen atoms). Among heterohalogens, fluorochloro-compounds are most abundant (305) followed by chlorobromo- (90) and fluorobromo-compounds (56). Halogenated organics comprise all of the POPs listed in the Stockholm Convention and half of the persistent and bioaccumulative chemicals screened from over 22 000 substances in the Canadian and U.S. chemical inventories.[27] Therefore, we mainly focused on the environmental fate and partitioning properties of the halogenated compounds, especially those unique to the IECSC.

Elemental profiles and chemical categories of all 37 080 substances with CASRNs were compared with those of the 6916 substances that are not in the North American or European inventories (Figure 1d). While 19% of all the substances were unique to IECSC, a larger portion (35%) of the 2352 chemicals containing fluorine (mostly organofluorines) were unique to the IECSC. Similarly, substances classified as polymers, organosilicons, organophosphates, reaction products, and those containing the elements of boron, iron, titanium, iodine, nitrogen, magnesium, and chlorine also made up a higher percentage (20−34%) of substances unique to the IECSC than the average for all the substances (Figure 1d).

POP-Like Indicators for IECSC Chemicals. Figure 2 shows the simulated values for persistence, bioaccumulation, and long-range transport potential of the 14 938 organic chemicals in the IECSC. Median (interquartile ranges) of Pov, logBAF, and TE are 67 (34−108) d, 1.8 (0.4−2.8), and 0.03% (0.001−0.70%) respectively (panel a−c of Figure 2). About 10% (1546) of the compounds have CASRNs unique to the IECSC when compared to the North American or European chemical inventories. The Pov, BAF, and TE values for the 1546 unique organics were generally greater than for the larger data set; median (interquartile ranges) of Pov, logBAF, and TE are 104 (43−249) d, 2.2 (0.6−3.5), and 0.04% (0.002−0.54%).

Chemicals unique to the IECSC have significantly higher predicted persistence and bioaccumulation than the other IECSC substances that are also present in the North American and European chemical inventories[17−19] (Wilcoxon rank sum

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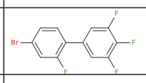
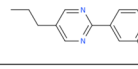
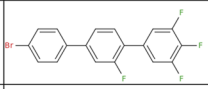
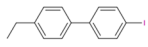
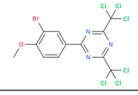
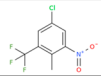
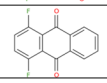
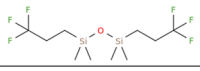
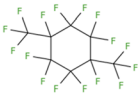
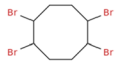
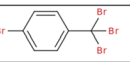
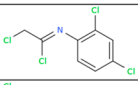
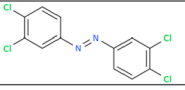
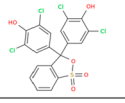
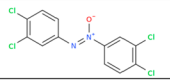
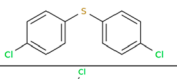
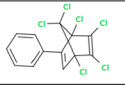
Table 1. Halogenated Organic Chemicals of Concern Screened from the Inventory of Existing Chemical Substances Produced or Imported in China (IECSC) that are Not in U.S., Canada or European (REACH) Registered or Pre-Registered Lists

IECSC ID	CASRN	Names	Structure	Uses	Criteria I, II, III [a]
36262	187804779	4-bromo-2,3',4',5'-tetrafluoro-1,1'-biphenyl		Intermediate for synthesizing poly-substituted biphenyl and cyclohexyl biphenyl liquid crystal monomers. [45, 46]	Y, Y, Y
7681	107392358	5-propyl-2-(3,4-Difluorophenyl)-pyrimidine		Nematic liquid crystal component used liquid crystal and electrophotosensitive materials.	Y, N, N
36263	n/a[b]	4''-bromo-2',3,4,5-tetrafluoro-[1,1':4',1''-terphenyl]		Nematic liquid crystal component. [73, 74]	N, Y, N
38440	17078761	4-ethyl-4'-iodo-1,1'-biphenyl		Intermediate to produce phenanthrylenediamine based electrophotosensitive material[75] and carbazole derivative luminescent compounds.[76] Predicted to be particle bound.	Y, Y, N
36059	172600805	2-(3-bromo-4-methoxyphenyl)-4,6-bis(trichloromethyl)-1,3,5-triazine		Photopolymerization initiator used in preparation of photosensitive resin needed to form a black matrix for use in display liquid crystal and plasma displays.[77]	N, Y, Y
24329	157229453	5-chloro-2-methyl-3-nitrobenzotrifluoride		Based on information for its analogue without the methyl group (chloronitrobenzotrifluoride),[78] may be used as an intermediate for pharmaceuticals and agrochemicals	Y, N, Y
7739	28736427	1,4-Difluoroanthraquinone		Used for synthesizing functional compounds such as hair dyes.[79]	Y, N, N
32713	690562	1,1,3,3-tetramethyl-1,3-bis(3,3,3-trifluoropropyl)-disiloxane		Uses include dispersant for copier toners and inkjet printers, in silicone products to provide water repellency, oil resistance, solvent resistance, and heat resistance.[80]	N, Y, Y
29411	7126047	1,1,2-trichloro-1,2-difluoro-propane		Similar structure to refrigerants such as HCFC-222 (pentachlorodifluoropropane) and HCFC-224 (trichlorotetrafluoropropane). Long atmospheric lifetimes (> 6 mo)	N, N, Y
30701	374776	1,1,2,2,3,4,4,5,5,6-decafluoro-3,6-bis(trifluoromethyl)-cyclohexane		Used as heat transfer fluid, cleaning agent for electronic components, including light-sensitive materials, plasticizers, surfactants, fluorocarbon polymers.[81] Previous measurements by Simmons et al.[82]	N, N, Y
33103	3194578	1,2,5,6-tetrabromocyclooctane		Flame retardant used in polystyrene (EPS), extruded polystyrene (XPS), high impact polystyrene (HIPS) and in textiles.[83]; Detected in the Arctic[53]	Y, Y, N
36253	76092290	1-bromo-4-(tribromomethyl)benzene		Chemical intermediate. Flame retardant used in styrenic polymers.[84]	Y, N, Y
23911	77169187	2,4-dichloro-N-(1,2-dichloroethylidene)aniline		Chemical intermediate for preparation of Imidazolo-N-(phenyl)-azomethine based pesticides [85]	Y, N, N
32824	14047097	3,3',4,4'-tetrachloro-azobenzene		No uses found. Extensive literature on this compound. Known carcinogen. Metabolite of 3,4-dichloroaniline and its herbicidal derivatives such as Propanil, Linuron, and Diuron.[54, 55]	N, Y, Y
23981	4430211	4,4'-(1,1-Dioxido-3H-2,1-benzoxathiole-3,3-diyl)bis(2,6-dichlorophenol)		Applications in lithography and opto-chemical sensors;[86] chlorophenol blue dye (chemical reagent)	N, Y, N
31629	21232473	bis(3,4-dichlorophenyl)-diazene-1-oxide		No uses found. Metabolite of 3,4-dichloroaniline and Propanil[55]	N, Y, N
9664	5181102	4,4'-dichlorophenyl sulfide		Used as high-temperature lubricants, flame-retardants, pesticides and pharmaceuticals[87] and have been detected in surface water and sediment in China.[56] and Germany[57]	N, N, Y
23368	6558301	1,2,3,4,7,7-hexachloro-5-phenyl-bicyclo[2.2.1]hepta-2,5-diene		No uses found. Substructure of hexachlorocyclopentadiene, which is the key intermediate in the synthesis of many stable (now banned) chlorinated cyclodiene insecticides[58]	N, N, Y

[a]The chemicals of greater concern have at least one of the following properties: (I) logK_{AW} and logK_{OA} in the ACBAP region and $HL_a \geq 2$ d; (II) $HL_a \geq 2$, $HL_w \geq 37.5$, BAF or BCF ≥ 2000; (III) P−B-LRT score and Arctic POP score similar or higher than that of PCBs.[73−87] [b]CASRN not available. The SMILES was obtained by parsing the IUPAC names using OPSIN.[31]

tests, $p < 1 \times 10^{-5}$). In contrast, the two groups have no significant difference in long-range transport potential ($p = 0.10$). These differences can be partially attributed to the higher percent of fluorine and silicon containing organics that are unique in the IECSC (Figure 1d). The unique fluorine containing organics had significantly higher values of logBAF and TE ($p = < 1 \times 10^{-6}$, and 6.0×10^{-6}) than those for organofluorines also in the North American and European chemical inventories but no significant difference in P_{ov} ($p = 0.94$). In contrast, organosilicons unique to the IECSC had no

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difference in P_{ov}, BAF, or TE from those also present in the North American and European chemical inventories (p = 0.15, 0.81, and 0.20).

The estimated P_{ov}, logBAF, and TE of chemicals in the IECSC were compared with that of PCBs (mono- to deca-chloro), a group of well-known POPs that are often used as a benchmark for comparison of P and B.[44] Of all the 14 938 chemicals in the IECSC, 598 (4%), 2428 (16%), and 5267 (35%) have P_{ov}, logBAF, and TE within the range (7,273, 245 d, 3.3−6.6, 0.15−52%) of PCBs; 72 (0.4%), 12 (0.08%), and 126 (0.8%) have higherP_{ov}, logBAF, and TE than PCBs. Altogether 153 chemicals have three fate and exposure indicators that fall within the range of those for PCBs. Of these, 132 are halogenated compounds and 20 have the CASRN unique to the IECSC (SI Table S3).

Chemicals with elevated ACBAP fall within the boundary of dash lines in the K_{OA}−K_{AW} chemical space (Figure 2d). The mono- to octa-PCBs, are also included in Figure 2d as benchmark compounds for POPs.[44] A total of 2281 chemicals in the IECSC are included within the region of concern. P−B−LRT scores of chemicals range from −2.0 to 6.3, with a median of 0.49. For all the chemicals within the K_{OA}−K_{AW} screening region, 109 (including 19 unique to IECSC, SI Table S4) have P−B−LRT scores higher than the minimum value of the PCB congeners (3.25). Chemicals with low P−B−LRT scores mostly have short predicted atmospheric half-lives due to rapid oxidation. For those with P−B−LRT scores less than 0, atmospheric reaction half-lives are <0.01−2.1 d (median: 0.14 d). These chemicals are unlikely to undergo long-range atmospheric transport and thus will not likely contaminate regions like the Arctic and other remote areas. The boundary set up for elevated ACBAP in the K_{OA}−K_{AW} chemical space is based on hypothetical persistent chemicals, that is, environmental degradation is not considered.

POP-Like Neutral Organics Unique to the IECSC. We identified 18 organohalogens and nine nonhalogenated compounds (including organosiloxanes and aromatics) that were high priority for additional screening and not found in the European or North American chemical inventories (Table 1, SI Table S5).

Due to their POP-like properties and uniqueness to the IECSC, these 27 chemicals warrant additional detailed assessments of their sources and environmental risks. The structures and uses of the 18 halogenated compounds are briefly summarized in Table 1 and their environmental fate, and bioaccumulation potential as described by previously defined Criteria I (logK_{AW} and logK_{OA} in the ACBAP region), II ($HL_a \geq 2$ d; $HL_w \geq 40$ d, BAF or BCF ≥ 2000), III (P−B−LRT and Arctic POP scores similar to PCBs) are discussed below. Information on the nine nonhalogenated compounds is provided in the SI.

We identified a polyhalogenated biphenyl (4-bromo-2,3′,4′,5′-tetrafluoro-1,1′-biphenyl, CASRN: 187804−77−9) as POP-like according to Criteria I, II, and III,. Structurally, this chemical is similar to PCBs (Table 1). This polyhalogenated biphenyl is an intermediate for synthesizing poly substituted biphenyl and cyclohexyl biphenyl liquid crystal monomers (LCMs).[45,46] Four other priority compounds were also related to liquid crystal and electro-photosensitive materials. CASRN 107392−35−8 (5-propyl-2-(3,4-difluorophenyl)-pyrimidine) met Criteria I and II. 4”-bromo-2′,3,4,5-tetrafluoro[1,1′:4′,1”-terphenyl] (CASRN not available) was flagged by Criteria I. CASRN 17078−76−1 (4-ethyl-4′-iodo-1,1′-biphenyl) met by Criteria II and III, and CASRN 172600−80−5 (2-(3-bromo-4-methoxyphenyl)-4,6-bis-(trichloromethyl)-1,3,5-triazine) met Criteria II and III. Direct emissions of these polyhalogenated compounds to the environment may not occur because they appear to be used as intermediates in liquid crystal manufacturing, however, residuals of the hazardous incomplete reactant could be present as an impurity together with the LCMs and emitted during use. Thus, four of five of this group of chemicals met criteria for persistence and bioaccumulation, and/or ACBAP. Considering potential uncertainties with the estimated K_{OA} and K_{AW}[47] all five have potential for transport to the Arctic.

Environmental concerns with chemicals used in liquid crystal display (LCD) manufacturing have been raised.[48,49] Su et al.[49] evaluated the persistence, bioaccumulation, and toxicity of 362 commercial LCMs based on a list developed from products used by Chinese LCD panel manufacturers. Of the 296 LCMs with CASRNs, 189 were in the IECSC. Su et al.[49] identified 10 as very persistent (Half-life in soil >180 days) and/or very bioaccumulative (log BCF ≥ 3.7). Five of these were in the IECSC (CASRNs 157248−24−3, 167306−96−9, 174350−05−1, 205806−87−7, 326894−55−7). However, these five substances (SI Table S6) were not among the top 25 chemicals with combined high ACBAP and P−B−LRT scores because their predicted P_{OV} was lower than some other chemicals. Nevertheless, the first three were in the top 10% of ACBAP scores. However, little information is available on the quantities of these chemicals used and emitted to the environment during the LCD life-cycle. This is essential for characterizing the environmental risks associated with use of these chemicals. Global demand for LCD panels has doubled over the past decade and reached 190 million square meters in 2018.[50] Asia has the largest number of LCD manufacturers (14 in China) and is producing more than half of the global LCD panels.[50] Further assessment of potential environmental impacts of the diverse organic compounds[51] used in the liquid crystal industry is needed.

Our priority list derived from the IECSC includes five other neutral organofluorines with diverse uses as intermediates or commercial products (Table 1). CASRN 157229−45−3 (5-chloro-2-methyl-3-nitrobenzotrifluoride) was flagged by Criteria I and III but has a BAF < 2000 and does not meet Criteria II. CASRN: 28736−42−7 (1,4-difluoroanthraquinone) had elevated ACBAP but its BAF was <2000 and thus did not meet Criteria II. CASRN 690−56−2 (1,1,3,3-tetramethyl-1,3-bis-(3,3,3-trifluoropropyl)-disiloxane) is a organosiloxane containing 3,3,3-trifluoropropyl groups. This compound met Criteria II and III but was not predicted to have elevated ACBAP due to its high volatility (K_{AW}) which makes it unlikely to undergo deposition in remote environments.

Two additional compounds on the priority list containing fluorine, 1,1,2-trichloro-1,2-difluoro-propane (CASRN 7126−04−7) and 1,1,2,2,3,4,4,5,5,6-decafluoro-3,6-bis-(trifluoromethyl)-cyclohexane (CASRN 374−77−6) are also volatile and have commercial uses (Table 1). These two compounds were identified based on Criterion III due to high predicted P_{OV}. Due to high volatility they are mostly present in the air and therefore unlikely to deposit to the earth surface and accumulate in the food web. However, these two compounds have predicted atmospheric lifetimes longer than half a year and are likely associated with other environmental impacts such as stratosphere ozone depletion and global warming potential.[52]

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There are eight other halogenated compounds (Table 1) included on our priority list. 1,2,5,6-tetrabromocyclooctane (CASRN 3194−57−8; TBCO) and 1-bromo-4-(tribromomethyl)benzene (CASRN 76092−29−0) are brominated compounds that can be used as flame retardants. TBCO is an alternative to hexabromocyclododecane, which was widely used as a brominated flame retardant and currently listed in the Annex A of the Stockholm Convention. TBCO was predicted to have elevated ACBAP and was also flagged by Criterion II. It was detected in passive water samplers deployed in the Arctic with concentrations higher than all the other brominated flame retardants measured.[53] 1-bromo-4-(tribromomethyl) was flagged by Criteria I and III. Its predicted BAFs for the lower and midtrophic organisms (1260 and 1860) are slightly lower than cutoff value of 2000 but there is some uncertainty in these BAFs and the value for higher level trophic level organisms exceeds 2000. Based on this, we posit that compound may also be bioaccumulative.

CASRN 77169−18−7 (2,4-dichloro-*N*-(1,2-dichloroethylidene) aniline) was predicted to have elevated ACBAP (Criterion I). CASRN 14047−09−7 (3,3′,4,4′-tetrachloroazobenzene; TCAB) and its oxidized product bis(3,4-dichlorophenyl)diazene-1-oxide (CASRN 21232−47−3) are relatively well studied compounds because TCAB is a known carcinogen. These two compounds both meet Criterion II. Given the known toxicity, their listing on the IECSC is surprising but possibly they also have uses as chemical intermediates, as TCAB is a byproduct during manufacturing of 3,4-dichloroaniline and its herbicidal derivatives such as Propanil, Linuron, and Diuron.[54,55] CASRN 4430−21−1 (4,4′-(1,1-dioxido-3H-2,1-benzoxathiole-3,3-diyl)bis(2,6-dichlorophenol) is flagged as persistent and bioaccumulative (Criterion II) but its K_{AW} is too low and K_{OA} is too high for it to reach the identified range of ACBAP. CASRN 5181−10−2 (4,4′-dichlorophenyl sulfide), a polychlorinated diphenyl sulfide (PCDS), is more widely used in commercial products and structurally similar to polybrominated or polychlorinated diphenyl ethers. PCDSs have been detected in surface water and sediment in China.[56] and in sediment from the Elbe River in Germany.[57] 4,4′-CDS was identified by Criterion III but it did not meet Criteria I and II due to a predicted half-life in air <2 d and an ACBAP outside of the optimum range. CASRN 6558−30−1 (1,2,3,4,7,7-hexachloro-5-phenyl-bicyclo[2.2.1]-hepta-2,5-diene) was also flagged by Criterion III. This compound has a substructure of hexachlorocyclopentadiene, and resembles cyclodiene insecticides such as aldrin, dieldrin, endosulfan, heptachlor, chlordane, etc.[58]

Poly- and Per-Fluoroalkyl Substances (PFAS) Unique to the IECSC. Well-known PFAS such as PFOS and PFOA that were produced and released to the environment have caused great concerns due to their ecological and health impacts. Other PFAS with similar structures have also been produced for their hydrophobic and oleophobic properties and deserve further assessment for their environmental releases, fate, and impact. SI Table S7 lists the names and structures of 69 chemicals that contain more than three perfluorinated moieties and have CASRNs unique to the IECSC. We identified 39 organofluorine chemicals with similar structures (Figure 3) that contain a perfluoroalkyloxyphenyl or a perfluoroalkenyloxyphenyl subunit. Lengths of the fluorocarbon chain range from three to nine carbons. Those chemicals contain nonpolar fluoroalkenyl chains with length of six to nine carbons and polar terminal units such as carboxylic acid,

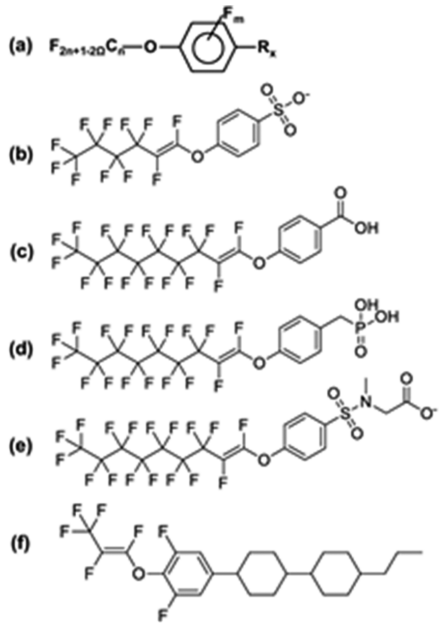

Figure 3. General structures and examples of a group of 39 organofluorines (see SI Table S7 for more information) that are included in the Inventory of Existing Chemical Substances Produced or Imported in China (IECSC)[6] but not in the North American and European chemical inventories.[17−19]

sulfonic acid, and sulfonyl amino groups. The different fluoroalkenyl chain lengths tend to affect their bioaccumulation potentials, which need to be evaluated with environmental monitoring and laboratory experiments. Little information is available on the production, uses, and environmental releases of these lesser-known PFAS. However, as chemicals listed in the IECSC, at least 1 tonne per year of these PFAS have been produced in China and used in parallel with or as alternatives to the well-known PFAS. Further information and detailed assessment on the production, uses, and environmental impact of these new fluorinated surfactants are needed.[59,60]

The other organofluorines containing perfluoroalkyl-oxyphenyl or perfluoroalkenyl-oxyphenyl subunits are featured with a shorter fluorinated carbon chain (carbon number 3−5) and a neutral and rod-like (e.g., *n*-alkylbicyclohexanyl) subunit on the para position. Some of these compounds also contain one or two fluorine atoms on the phenyl group. This group of compounds match the typical structural template of calamitic liquid crystal. The fluorocarbon unit acts as a rod-shaped rigid core to facilitate molecules to organize into liquid crystal phases.[61]

Besides the important group of organofluorines mentioned above, there are 10 perfluoroalkylsulfonyl compounds, eight fluorotelomer based compounds and two perfluoroalkylcarbonyl compounds unique to the IECSC (SI Table S7). These perfluoroalkylsulfonyl compounds have perfluorinated carbon chain lengths of 3, 4, 6, 7, and 8. Some of these compounds only have slightly differences from the well-known PFAS measured in environmental media. For example, *N*-butyl-heptadecafluoro-1-octanesulfonamide (BuFOSA) is only different from the well-known EtFOSA by two CH_2 unit, we can infer BuFOSA would share similar environmental fate and partitioning with EtFOSA. As EtFOSA has higher bioaccumulation potential than PFOS, with increased *N*-alkyl chain length, bioaccumulation potential of BuFOSA could be even

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higher than PFOS, making it a PFAS deserving further assessment. It is worth noting the IECSC listed substances analyzed in this study were in commerce between 2003 and 2013 and other possible replacements for C8 based perfluoroalkanesulfonic acid (PFSA) related compounds restricted by the Stockholm Convention could now be in commerce in China. For example, Ruan et al.[62] identified novel polyfluorinated ether sulfonates (e.g., 6:2, 8:2:, and 10:2 chlorinated polyfluorinated ethers as well as the nonchlorinated analogues), as PFOS alternatives in municipal sewage sludge that are not in the IECSC. Of the fluorotelomer based compounds, we noticed two interesting compounds: 6:2 fluorotelomer thioether propanoic acid (6:2 FtTP) and 8:2 fluorotelomer thioether isobutyric acid. 6:2 FtTP was found as a degradation product of 6:2 fluorotelomer thioether amido sulfonate (6:2 FtTAoS) which was found in aqueous film forming foam in the United States.[63] The thioether group is stable making 6:2 FtTP resistant to biotransformation under sulfate reducing conditions. But under aerobic conditions, fluorotelomer thioether carboxylic acid can be transformed into stable perfluoroalkyl carboxylates and fluorotelomer sulfonates and carboxylates. The presence of fluorotelomer thioether carboxylic acids in the IECSC suggests these compounds can come not only from degradation of other PFAS, but also from intentionally produced products. This case of degradation also underlines the importance of understanding degradation pathways when screening and assessing new PFAS and their analogues.

Implications and Outlook. By analyzing substances in the IECSC and conducting in silico screening of their persistence, bioaccumulation, and long-range transport, we identified POP-like chemicals unique to the Chinese inventory (not in the current North American and European inventories). While the uses of these POP-like chemicals (Table 1, Refs. 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87) is mostly gained from patents, little information on their presence in commercial products and releases to the environment is available. Detection of such chemicals in products and characterization of their releases would facilitate their environmental impact assessment. To our knowledge, none of the 69 organofluorine compounds, and only 4 of the 27 neutral organics have been previously assessed or measured in environmental media. Our results can be used to guide further assessment of global fate processes and potential environmental impacts of these chemicals using integrated modeling and monitoring approaches. Some of the priority chemicals identified here, such as those used in the manufacturing of LCDs, are mostly used and produced in China as the predominant global manufacturer. Therefore, the migration of these POP-like chemicals in consumer products via global commerce, or in materials destined for recycling,[64] could be substantial and should also be characterized when assessing the risks of such chemicals in the global environment. While the initial screening conducted in this study is based on generic models for environmental distribution and fate, a more specific model targeted for the Chinese environment and nested in a global environmental model would be necessary to compare global environmental risk from chemicals produced and emitted in China and emitted via uses and disposal of products in other parts of the globe. Besides prioritizing the chemicals for further modeling assessment, the in silico screening results also provide a useful guide for measurements of the chemical in environmental samples.

Similar to other studies,[9,65] different in silico tools may lead to different screening results (chemical ranking or classification based on their environmental impact). This discrepancy originates from uncertainties in predicted physicochemical properties and model simplifications or assumptions[37,47,66] The modules in EPI Suite have been developed using training sets of chemicals that cover different domain ranges,[67−69] and thus the estimated parameters tend to have different levels of uncertainty. While evaluations of EPI Suite modules KOWWIN,[88] HENRYWIN,[89] and AOPWIN[69] with experimental data suggest mean errors of 0.31, 0.43, and a factor of 2 for predictions of logK_{OW}, logK_{AW}, and OH radical reaction rate constants, the uncertainty in this study may be higher due to the diverse structures of the screened chemicals even when those (SI Table S8) clearly outside of the applicability domains were excluded. Nevertheless, screening based on predicted physicochemical properties has assisted in the identification of new chemicals of environmental concern.[8−13] Uncertainty involved with in silico screening can only be resolved with additional experimental data. Our approach in this study was to integrate different approaches (e.g., P−B−LRT scores and location in chemical space), which have their own strengths and weaknesses. Integrating the different screening results may help reduce false negatives that might lead to overlooking potentially hazardous chemicals.

The in silico screening in this study could only be applied to 56% of the substances in the IECSC that had well-defined chemical structures (i.e., with SMILES strings) due to the need to be within the applicability domain of the physicochemical property prediction tools and the environmental fate models. Over half of the IECSC substances are UVCBs (e.g., chlorinated paraffins, resins, and oil products). Such complex mixtures are challenging to assess using the existing in silico approaches unless information on components of the complex mixtures can be retrieved[70] and thus new frameworks for screening assessment of UVCBs are needed. Some compounds such as peroxides, disulfides, epoxides, sulfonic acids, carboxylic acids, carbonyl halides, and sulfonyl halides (SI Table S8) were excluded for the screening because these groups of compounds fall out of the applicability domains of the in silico tools. However, it is worth noting some of these compounds can be associated with potential environmental risk given evidence that suggests half-lives of some organoperoxides can be hundreds of hours[71] and some epoxides can be highly stable in organisms.[72]

Some new PFAS with similar structures to the well-known PFOS and PFOA are in the IECSC. To our knowledge these new PFAS have not been detected in the environment but the information from this study can serve as a screening library and assist analytical chemists to detect these compounds. In order to assess the environmental risk of these unique PFASs, information on the sources, environmental fate, bioaccumulation, and biological effects will be needed. .

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.0c01898.

Code for an algorithm to determine chemical classes, additional text, and Figures S1 and S2 (PDF)

Tables S1 to S8 (XLSX)

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AUTHOR INFORMATION

Corresponding Authors

Xianming Zhang − *Department of Physical and Environmental Sciences, University of Toronto, Toronto, Ontario M1C 1A4, Canada; Harvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts 02138, United States*; Phone: 857-600-0969; Email: xianming.zhang@utoronto.ca

Derek C. G. Muir − *Department of Physical and Environmental Sciences, University of Toronto, Toronto, Ontario M1C 1A4, Canada; Guangdong Key Laboratory of Environmental Pollution and Health, School of Environment, Jinan University, Guangzhou 511443, China; Environment and Climate Change Canada, Aquatic Contaminants Research Division, Burlington, Ontario L7S 1A1, Canada*; orcid.org/0000-0001-6631-9776; Phone: 905-319-6921; Email: derek.muir@canada.ca

Authors

Xiangfei Sun − *Guangdong Key Laboratory of Environmental Pollution and Health, School of Environment, Jinan University, Guangzhou 511443, China*

Ruifen Jiang − *Guangdong Key Laboratory of Environmental Pollution and Health, School of Environment, Jinan University, Guangzhou 511443, China*; orcid.org/0000-0002-0506-2775

Eddy Y. Zeng − *Guangdong Key Laboratory of Environmental Pollution and Health, School of Environment, Jinan University, Guangzhou 511443, China*; orcid.org/0000-0002-0859-7572

Elsie M. Sunderland − *Harvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts 02138, United States*; orcid.org/0000-0003-0386-9548

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.0c01898

Notes

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