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Review

Identifying and Prioritizing Chemicals with Uncertain Burden of Exposure: Opportunities for Biomonitoring and Health-Related Research

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BACKGROUND: The National Institutes of Health's Environmental influences on Child Health Outcomes (ECHO) initiative aims to understand the impact of environmental factors on childhood disease. Over 40,000 chemicals are approved for commercial use. The challenge is to prioritize chemicals for biomonitoring that may present health risk concerns.

OBJECTIVES: Our aim was to prioritize chemicals that may elicit child health effects of interest to ECHO but that have not been biomonitored nationwide and to identify gaps needing additional research.

METHODS: We searched databases and the literature for chemicals in environmental media and in consumer products that were potentially toxic. We selected chemicals that were not measured in the National Health and Nutrition Examination Survey. From over 700 chemicals, we chose 155 chemicals and created eight chemical panels. For each chemical, we compiled biomonitoring and toxicity data, U.S. Environmental Protection Agency exposure predictions, and annual production usage. We also applied predictive modeling to estimate toxicity. Using these data, we recommended chemicals either for biomonitoring, to be deferred pending additional data, or as low priority for biomonitoring.

RESULTS: For the 155 chemicals, 97 were measured in food or water, 67 in air or house dust, and 52 in biospecimens. We found *in vivo* endocrine, developmental, reproductive, and neurotoxic effects for 61, 74, 47, and 32 chemicals, respectively. Eighty-six had data from high-throughput *in vitro* assays. Positive results for endocrine, developmental, neurotoxicity, and obesity were observed for 32, 11, 35, and 60 chemicals, respectively. Predictive modeling results suggested 90% are toxicants. Biomarkers were reported for 76 chemicals. Thirty-six were recommended for biomonitoring, 108 deferred pending additional research, and 11 as low priority for biomonitoring.

DISCUSSION: The 108 deferred chemicals included those lacking biomonitoring methods or toxicity data, representing an opportunity for future research. Our evaluation was, in general, limited by the large number of unmeasured or untested chemicals. https://doi.org/10.1289/EHP5133

Introduction

Environmental chemical exposures can adversely impact children's health (Bellinger 2013; Bose-O'Reilly et al. 2010; Grandjean and Landrigan 2006; Grandjean et al. 2008; Jurewicz and Hanke 2011; Lanphear et al. 2005; Selevan et al. 2000; Sharpe and Irvine 2004; Weiss 2000; WHO 2010). Children are susceptible to environmental influences during developmental periods, including *in utero* exposures, due to rapidly and uniquely changing physiology, behaviors, and exposures, including hand-to-mouth behaviors and increased contact with the ground. Environmental exposures can interact with other physiological and external stressors to modify risks of adverse child health outcomes (Holmstrup et al. 2010). Despite advances in children's environmental health science, there is still a paucity of data to inform intervention and prevention

activities. This is of particular concern given that the prevalence of certain child diseases has increased over the last 10–30 y, including adverse birth outcomes, neurodevelopmental delays and deficits, respiratory effects, obesity, diabetes, and cancer (American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women et al. 2013; Diamanti-Kandarakis et al. 2009; Reuben 2010). This is an underlying driver for the National Institutes of Health (NIH)'s Environmental influences on Child Health Outcomes (ECHO) initiative launched in 2016, whose goal is to understand the environmental influences on childhood disease with a focus on pre-, peri-, and postnatal factors for respiratory, endocrine, neurodevelopmental, and other outcomes. ECHO consists of multiple cohorts of participating children, with broad spatial coverage across the United States. Comprising >50,000 children, it will capitalize on existing participant populations by supporting multiple, synergistic, and longitudinal studies to investigate environmental exposures—including chemicals—on child health and development.

One of the challenges in ECHO (https://echochildren.org/) is to identify and evaluate health effects resulting from chemical exposures. Although many of the ECHO cohorts plan to evaluate exposures to about 200 chemicals—the same chemicals measured in the National Health and Nutrition Examination Survey (NHANES) (CDC 2018a, 2019b)—via biomonitoring, exposure questionnaires, and geospatial mapping. A few examples of chemical panels currently being studied in ECHO include alternative plasticizers (APs), environmental phenols (EPs), organophosphate flame retardants (OPFRs), perfluoroalkyl substances (PFASs), and pesticides (PEs). This still leaves thousands of chemical exposures

unconsidered. Tens of thousands of chemicals have been approved for use in the United States (Board on Population Health and Public Health Practice 2014). Further, nearly 8,000 chemicals are manufactured or imported in high amounts (>11,000 kg/y) (U.S. EPA 2016a), indicating that humans are likely exposed to many more chemicals than are routinely measured via biomonitoring (Wang et al. 2016). There is a paucity of information on biomonitoring of exposures in pregnant women, infants, and children that limits our ability to evaluate the potential health impact of these chemicals.

Exposure to chemicals primarily occurs through one or a combination of three routes—inhalation, ingestion, and dermal absorption—and by secondary mechanisms such as maternal transfer *in utero*, breastfeeding, or intravenous injections (e.g., phthalates as contaminants from medical devices and in drugs). Further, exposures occur to mixtures of many chemicals, creating opportunities for additive, synergistic, or antagonistic interactions (NRC 2007; Rider et al. 2013). The large number of chemicals that are not currently evaluated for prenatal or childhood exposures creates a challenge for determining the best approach to prioritize chemicals for biomonitoring and evaluation in ECHO.

In this paper, we collect and evaluate quantitative extant data for chemicals that are not currently measured by ECHO or NHANES (CDC 2019c). Our specific objectives were to *a*) identify chemicals to which mothers and children are likely exposed based on environmental and biomonitoring data and chemicals associated with commercial/consumer products, *b*) compile and use information on the health effects/toxicity relevant to ECHO to prioritize the chemicals for study, and *c*) identify knowledge gaps needing further research. We limited our scope to a segment of the universe of chemicals that have been measured in environmental media from industrial processes or have been identified as being in consumer products and have the potential for health effects in pregnant women and in children. Chemicals reported only as occupational exposures were not considered.

Methods

Overview of Approach

The goal of ECHO is to study pre-, peri-, and postnatal factors affecting upper and lower airway, respiratory, endocrine, neurodevelopmental, and other outcomes. Our overall screening framework integrated exposure- and toxicity-related data to identify and prioritize chemicals (Figure 1) with this goal in mind. Chemicals of interest were identified using a two-prong approach. First, we sought chemicals in environmental media reported in government databases (drinking water and food) and the literature (air, drinking water, house dust, and food) that occurred at a quantifiable frequency of ≥20% in samples [Figure 1 (environmental media list); Excel Table S1]. We recorded the mean or median value for each chemical by sample type that was published in an environmental study or the highest value from multiple studies. For biospecimens, we recorded the highest value at the 75th percentile from one or more yearly reporting cycles in NHANES.

Second, we selected chemicals in the U.S. Environmental Protection Agency (EPA) consumer product database (CPCat) that had a potentially toxic structural moiety to construct the consumer products list (Figure 1). After removing duplicates and inorganic chemicals, metalloids, radionuclides, and particulate matter from the environmental media and consumer products lists, the two lists were combined [Figure 1 (C list)]. Inorganic chemicals and metalloids were excluded, given that they are currently being studied in ECHO and have been measured in NHANES (CDC 2019c).

Subsequently, we sorted the chemicals on the C list (see Excel Table S2) into five groups, setting aside from further consideration those measured in NHANES [Figure 1 (Group I)], and those considered as legacy chemicals (Group II). Legacy chemicals—such as, heptachlor, *p,p′*-dichlorodiphenyltrichloroethane (*p,p′*-DDT), and polychlorinated biphenyls—have been extensively studied and have a clear health impact but with dramatically decreasing exposure over the last four to five decades. From the remaining three groups (see Excel Tables S3–S5), we selected a subset of chemicals to create the eight panels—alternative flame retardants (AFRs), APs, aromatic amines (AAs), EPs, OPFRs, PFASs, PEs, and quaternary ammonium compounds (QACs) (Figure 1). Chemicals in the panels were then prioritized. Chemicals recommended for biomonitoring supplement those currently being measured in ECHO.

### Search Strategy for Prevalent Chemicals

Government databases. We reviewed the chemicals reported in several government databases for prevalence and levels of chemicals in environmental media and human biospecimens. Specifically, we examined the U.S. EPA Six-Year Review 1, 2, and 3 Compliance Monitoring Data (1993–1997, 1998–2005, and 2006–2011) for water (U.S. EPA 2016b, 2016c, 2016d); the U.S. Department of Agriculture (USDA) Pesticide Data Program, 2010–2011 Pilot Study data containing PE residues occurring in food commodities and drinking water (USDA 2017), and the U.S. Food and Drug Administration (FDA) files containing results for PEs reported for the periods 2004–2005 and 2006–2011 (FDA 2011).

We recorded chemicals found in environmental media with the highest reported median or mean results from across multiple studies and occurring at least at a detection frequency of 20% in the sample type. The purpose for applying this threshold was to find chemicals that were more likely to be detected in biospecimens than if no detection threshold was used. We normalized the data to a common set of concentration units by medium (e.g., food) and class of compounds (e.g., pesticides) when the reported units (means or medians) differed in multiple studies. USDA data for PEs in drinking water were only reported in ranges; thus, chemicals with a detection frequency of ≥20% to 40% and >40% were recorded. (A description of the search of the literature for the levels found in human biospecimens for chemicals in panels slated for prioritization is presented below, in the "Searching for environmental and biomonitoring data" section.)

For chemicals measured in human serum and urine, we reviewed the *Updated Tables*, March 2018 and January 2019, Volumes 1 and 2, published in the *Fourth National Report on Human Exposure to Environmental Chemicals*, a Centers for Disease Control and Prevention NHANES study (CDC 2018b, 2019a, 2019b). This report contains nationally representative biomonitoring data for survey periods 1999–2000 through 2015–2016, including pooled samples.

We recorded the highest value for each chemical found across the yearly reporting cycles at the 75th percentile in the age group of 12–19 y from the NHANES database. In addition, we noted nonmeasurable values at the 75th percentile interval.

We used the U.S. EPA's CPCat Database and its search algorithms to find chemicals that may lead to human exposure and health-related consequences (U.S. EPA 2014a, 2014b). This search ended in June 2017. We limited our search to a segment of the universe of chemicals in commerce by focusing on a subset of consumer products. We chose product categories in the CPCat database that included products that may expose expectant mothers, infants, or children to chemicals. There were 372 consumer product categories, and we chose 45 to include in our search (see Table S1). Twenty-seven were categories that
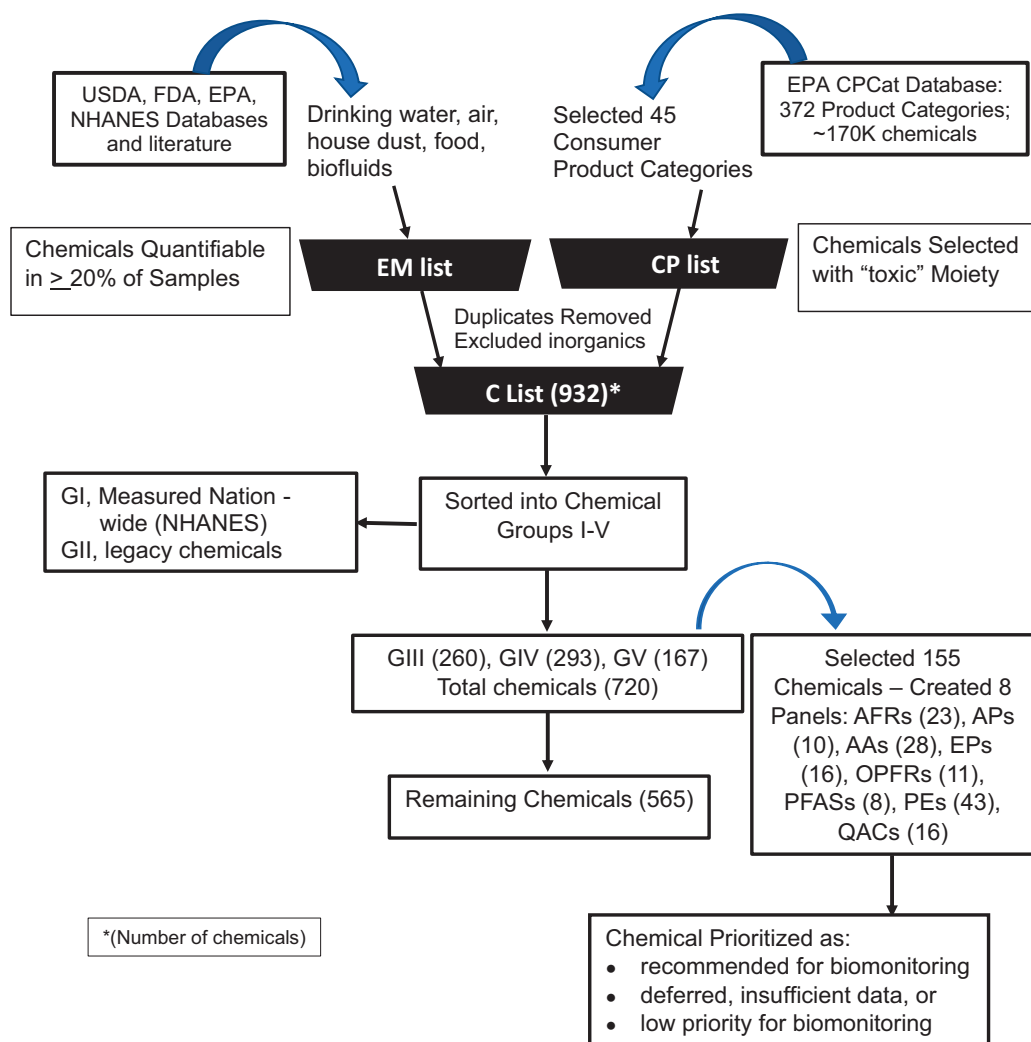
Figure 1. Overview for identifying chemicals of interest in environmental media and consumer products. C list, combined list (EM plus CP lists); CP list, consumer product list; CPCat, Consumer Product Categories; EM list, environmental list; EPA, U.S. Environmental Protection Agency; FDA, Food and Drug Administration; GI, Group I chemicals with NHANES exposure data; GII, Group II Legacy chemicals with extensive environmental, exposure and health data; GIII, Group III, chemicals with extensive environmental and no NHANES exposure data; GIV, Group IV chemicals with U.S. EPA exposure predictions and limited environmental and exposure data; GV, Group V chemicals with no U.S. EPA exposure predictions and limited environmental and exposure data; AFRs, alternative flame retardants, APs, alternative plasticizers, AAs, aromatic amines, EPs, environmental phenols, OPFRs, organophosphorus flame retardants, PFASs, perfluoroalkyl substances, PEs, pesticides; NHANES, National Health and Nutrition Examination Survey; QACS, quaternary ammonium compounds; USDA, U.S. Department of Agriculture. *, number of chemicals.

contained formulated personal products, and the remaining 18 categories contained chemicals used as biocides or to control pests or are constituents in household items. We screened chemicals in these product categories to identify those that qualified as potentially toxic. For the chemicals with structures in the 45 categories, we visually inspected each chemical structure for functional moieties that have been empirically determined to elicit toxic effects. These moieties generally follow the principle of Chemical Structure—Toxicological Activity Relationships (Cronin et al. 2003). The moieties were acyl halide, aldehyde, aliphatic or aromatic *N*-nitroso, alkyl nitrite, aromatic mono- or dialkylamine, aziridine, carbamate, epoxide, halogenated aliphatic or aromatic, halogenated polycyclic aromatic hydrocarbon, heterocyclic aromatic hydrocarbon, hydroxyl amine, isocyanate, isothiocyanate, lactone, phosphonic or sulfonic acid, polycyclic aromatic hydrocarbon (PAH), sultone, triazene, primary aromatic amine, thiocarbamate, thiocarbonyl, and α and β unsaturated carbonyl (Chen et al. 2013). We regard this approach as a screening method because it only broadly differentiates the categories of toxicity. Furthermore,

it does not account for absorption, distribution, metabolism, and excretion of the chemical in a living organism or for the minimal dosage to affect toxicity—all factors that play a role in determining toxic potency.

We only inspected chemicals with displayed structures in CPCat (U.S. EPA 2014a, 2014b). Chemicals listed by name and Chemical Abstracts Service Registry Number (CASRN) with no accompanying structures were excluded because creating their chemical structures would have been overly burdensome. The resulting group of chemicals constituted the consumer products list (Figure 1).

Published literature. Besides government reports, we searched the literature for chemicals in environmental media with at least a 20% detection frequency and recorded the highest median or mean concentration for chemicals reported in one or more studies in an electronic database. We focused our search on environmental media such as drinking water, food, indoor dust, and air that are closely associated with a route of exposure—inhalation, ingestion, and dermal. Papers that represented U.S. nationwide, probability-based, or

cohort studies that quantified hundreds to thousands of samples were included while small studies with fewer than 25 observations were excluded. Additional study criteria included papers published (in English) in or after 1995.

We conducted an extensive search ending in December 2018 using Science and Technology Collection (advanced search mode), Google Scholar, Scopus, and Web of Science. We used the search terms listed in Table S2. Studies met eligibility criteria if the reporting nationwide data were from the United States, Canada, the European Union, Japan, or Australia. We excluded *a*) countries with no, few, or unknown regulatory standards on chemical releases to the environment; *b*) media from occupational environments; and *c*) publications not in English.

For the chemicals selected for prioritization (discussed below), we will elaborate on additional literature searches in sections on measured levels in human biospecimens, toxicity, and biomarkers.

Acquiring Exposure Predictions

We obtained the U.S. EPA exposure predictions and NHANES-reported measured values for the youngest age group, 6–11 y (no data were available for younger age groups), that were available for each chemical on the C list (see Excel Table S2). U.S. EPA exposure predictions were provided by the U.S. EPA as an ExpoCast™ Excel file or retrieved from U.S. EPA's Chemistry Dashboard (U.S. EPA 2017; Wambaugh et al. 2014) during the period from June to October 2017. The chemicals on the C list were sorted into those with and without exposure predictions.

Grouping Chemicals by Data Availability

We assigned each chemical on the C list to one of five groups based on available information and according to the following characteristics: *a*) Group I—chemicals with NHANES exposure data and measured in environmental media; *b*) Group II—legacy chemicals with extensive environmental, exposure and health data; *c*) Group III—chemicals with extensive environmental and no NHANES exposure data; *d*) Group IV—chemicals with U.S. EPA exposure predictions and limited environmental and exposure data; and *e*) Group V—chemicals with no U.S. EPA-predicted exposures and limited environmental and exposure data (Figure 1). A purpose of this grouping was to identify chemicals reported in the NHANES and legacy chemicals (Groups I and II, respectively) and, given that many of these chemicals were already being studied in ECHO, they were excluded from this paper. Instead, we focused on the chemicals found in Groups III–V (see Excel Tables S3–S5).

Creating Chemical Panels

To fulfill our primary goal of recommending priority chemicals for biomonitoring in ECHO, we evaluated chemicals that have been understudied with respect to human health effects. Because Groups III–V contain a total of 719 chemicals, we limited our prioritization to a manageable subset of potential candidates for study in ECHO (Figure 1; Table 1).

Alternative flame retardants. Polybrominated diphenyl ethers were used for decades as flame retardants but are gradually being phased out of commerce and replaced by AFRs. AFRs consist of a diverse array of bromine-, chlorine-, and nitrogen-containing compounds. They are found in environmental media, and with continual use, their levels in the environment will likely increase.

Alternative plasticizers. Developed as substitutes for phthalates, APs (e.g., terephthalate esters) have been introduced into commerce (Nayebare et al. 2018). Phthalates, depending on their structure, have been identified as reproductive and developmental toxicants (Wu et al. 2013), whereas APs are not well studied regarding their potential effects on human health. Like phthalates, APs are not chemically bound to the polymer (Kastner et al. 2012) and can leach out of children's and other consumer products, leading to exposure.

Aromatic amines. Predominantly used in dyes (e.g., Acid Red, Red 9 and 22, and D&C Red 21, 21L, and 22) (Abe et al. 2016; Fautz et al. 2002) and pigments (including hair dyes, mascara, tattoo ink, toners, paints) (Anezaki et al. 2015; Clarke and Anliker 1980), polyurethane production, polymeric resins, corrosion inhibitors, rubber vulcanization accelerators, PEs, and pharmaceuticals (Ahlström et al. 2005; Anezaki et al. 2015; Trier et al. 2010; Weisz et al. 2004; Yavuz et al. 2016). AAs have been reported in tobacco smoke; however, the AAs listed in this panel were also found in consumer products that are used by children and mothers. Thus, dermal contact from the use of consumer products is an important route of exposure for many AAs.

Environmental phenols. Depending on their structures, EPs are used in consumer and household products and serve as plasticizers, detergents, and preservatives (Cadogan and Howick, 2000; U.S. EPA 2010). 3,3′,5,5′ Tetrabromobisphenol A is used both as a plasticizer and flame retardant (Alaee et al. 2003). Research on EPs that have been in the environment for decades—such as bisphenol A, triclosan, parabens, and triclocarban—has shown the potential for endocrine disruption (Cullinan et al. 2012; Koeppe et al. 2013; Meeker 2012; Witorsch and Thomas 2010). We found several EPs that have structures similar to bisphenol A and may have similar endocrine toxicity.

Organophosphorus-based flame retardants. OPFRs are one of several classes of AFRs and comprise at least two groups (alkyl- and aryl-). The alkyl group has been in commerce for several decades, whereas the aryl group is an emerging group (Christia et al. 2018). Patent activity in the flame-retardant field has proliferated (Weil 2005), and OPFRs are produced in high volumes. In addition to serving as flame retardants, they are applied to consumer products as plasticizers, stabilizers, lubricants,

Table 1. Number of chemicals evaluated in each panel.

Panel name	Chemicals (*n*)	Recommended for biomonitoring	Deferred pending additional data	Low priority for biomonitoring
Alternative flame retardants (AFRs)	23	4	16	3
Alternative plasticizers (APs)	10	2	5	3
Aromatic amines (AAs)	28	3	25	0
Environmental phenols (EPs)	16	6	9	1
Organophosphorus-based flame retardants (OPFRs)	11	5	5	1
Perfluoroalkyl substances (PFASs)	8	4	4	0
Pesticides (PEs)	43	12	28	3
Quaternary ammonium compounds (QACs)	16	0	16	0
Total	155	36	108	11

and antifoaming agents (Brandsma et al. 2014; Levchik and Weil 2006). They are incorporated after polymerization, and as a result are not chemically bonded to the material, permitting their release from products into the environment. They are used in electronic equipment, furniture, and textiles (van der Veen and de Boer 2012).

Perfluoroalkyl substances. Comprising perfluoroalkyl and polyfluoroalkyl substances, PFASs are widely used in the production of Teflon® and related fluorinated polymers (Wang et al. 2013). They have been used to confer hydrophobicity, stain-resistance to fabrics, and as fire-fighting foams. In addition, they are designed with properties to reduce surface tension. They concentrate at the aqueous–lipid interface due to the lipophobicity of fluorocarbons and the hydrophilicity of carboxyl and sulfonic acid moieties (Ritscher et al. 2018). As such, PFASs are extremely stable. Some tend to bioaccumulate and are stored in tissues. After reviewing the environmental monitoring literature and consumer products, we selected PFASs as panel category because they are chemically related to perfluorooctane sulfonate and perfluorooctanoic acid and have been shown to exhibit health effects (DeWitt 2015).

Pesticides. PEs are extensively used to control fungal disease and pests and for growth stimulation and vector disease control such as lice treatment (Casida 2009). To account for infections by numerous fungi, multiple applications of a spectrum of fungicides are needed (Casida 2009). Thus, numerous chemicals are applied to food commodities to cover the array of diseases. For example, in 2015, the USDA monitored >470 PEs (USDA 2018). Similarly, the FDA monitors >700 PEs in a broad range of food samples (FDA 2018).

Quaternary ammonium compounds. Used in fabric softeners, antistatics, disinfectants, biocides, detergents, phase transfer agents, and numerous personal care products such as hair care products (Tsai and Ding 2004; Zhang et al. 2015), QACs are released into the environment in effluents and sludge from sewage treatment plants (Zhang et al. 2015). Other sources contaminating the environment are effluents from hospitals, laundry wastewater, and roof runoff (Zhang et al. 2015) and consumer products. The sorption of QACs to media is faster than degradation. Therefore, QACs accumulate in the environment, especially in anoxic/anaerobic compartments (Zhang et al. 2015). The presence of QACs in the environment is toxic to both aquatic and terrestrial organisms (Zhang et al. 2015). However, human exposure and health effects remain mostly unknown.

Chemicals were selected for prioritization based on their potential occurrence in media that may lead to human exposure and health effects. A total of 155 chemicals were selected from Groups III–V and assigned to the eight panels (Table 1). Even though the AFR, AP, EP, OPFR, PFAS, and PE panels are the same as those currently being evaluated in ECHO, the new chemicals selected are supplementary. The AAs and QACs are new panels and have not been widely measured in environmental media and human biospecimens.

Last, our strategy was to group chemicals in panels with similar chemical properties, permitting the development of multi-chemical analysis methods. This approach allows for an economies-of-scale cost savings as compared with a method that analyzes a single compound. Except for PEs, we assigned all chemicals on the C list with common functional properties to a chemical panel.

Because the environmental media list (see Excel Table S1) had many PEs, we reduced the number to a manageable list for this paper. Our selected PEs came primarily from the USDA's database of reported PE residues (see Excel Table S6) because this database emphasizes food commodities highly consumed by infants and children (USDA 2017). Of the 180 PEs measured in food and drinking water, we found 156 had not been biomonitored in the NHANES (see Excel Table S6). Of the 156 PEs, we selected 40 that represented those with higher prevalence and median concentrations in food (>50 ng/g) or drinking water (see Excel Table S6). This selection included 12 PEs that exhibited overlapping toxicity (U.S. EPA ToxCast™ Program results) and U.S. EPA exposure predictions (Wetmore et al. 2012). Furthermore, we added three PEs to this panel (acifluorfen, fluroxypr-meptyl, and isoxaben) that were also reported with overlapping toxic activity and predicted exposures (Wetmore et al. 2012), yielding a total of 43 pesticides for prioritization.

Because PE exposure is episodic (i.e., primarily by ingestion), we chose PEs that occur on several food commodities (FDA 2018; USDA 2018), thus likely increasing the frequency of exposure episodes. In addition, children can have greater exposures because of their smaller body size and select eating of certain food groups (Bruckner 2000). Even though PEs associated with fruits and vegetables grown domestically are seasonal, they also occur on imported foods (USDA 2018). In addition, we chose PEs that were found on domestic and on imported foods, increasing the likelihood that exposure occurs year-round.

Prioritizing Candidate Chemicals for Biomonitoring

Figure 2 depicts the overall approach used for prioritizing candidate chemicals for biomonitoring in ECHO. We conducted literature searches (described below) to gather information that answered three questions. If all three questions (exposure, toxicity, biomarker) were answered affirmatively for a chemical, then it was recommended for biomonitoring in ECHO. For cases lacking enough information, we recommended deferring biomonitoring pending additional data. Chemicals in the deferred group were divided into four categories based on data available for
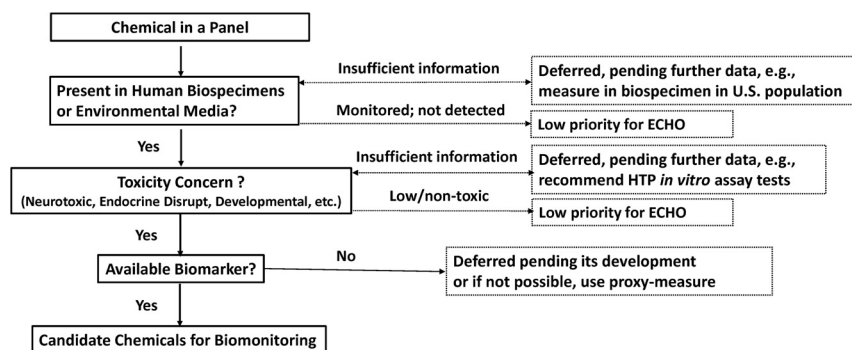
Figure 2. Overview for identifying candidate chemicals for biomonitoring. ECHO, Environmental Influences on Child Health Outcomes; HTP, high throughput.

Table 2. Categories of additional data needed for deferred chemicals.

Category	Detected in biospecimens?	Detected in environmental media?	Toxicity concern?	Biomarker exists?	Additional research needed
A	Insufficient information	Insufficient information	Yes	Yes	Chemicals should be measured in biospecimens of a nonoccupationally exposed population to determine if there is exposure.
B	Insufficient information	Yes	Yes	No	No biomarker exists; develop one and test it in nonoccupationally exposed human biospecimens to confirm anticipated exposure.
C	Insufficient information	Insufficient information	Yes	No	Needs data on exposure levels for nonoccupationally exposed population and develop a biomarker.
D	Insufficient information	Insufficient information	Insufficient information	Yes/no	Needs information on exposure, toxicity and perhaps biomarker development.

exposure, toxicity, and availability of a biomarker (Table 2). These categories were created to elucidate research needed to fill existing knowledge gaps concerning exposure, chemical toxicity, or development of a biomarker.

The literature searches yielded a spectrum of information types within and across chemicals. As such, we grouped each type of information into categories to indicate their relative importance as either high, moderate, or low to help guide answering the three questions and prioritizing the chemicals (Table 3). The intention of this classification approach was to denote the relative certainty that *a*) a chemical found in a human biofluid signifies exposure or in an environmental medium can lead to human exposure, *b*) health effects occur in humans or are suggested by *in vivo* or *in vitro* results, and *c*) a biomarker is available to assess chemical exposure. We used expert judgement guided by the following decision criteria for each question:

1. Was the chemical (or its metabolite) found in quantifiable levels in biospecimens (Figure 2)?
   a. If a chemical was detected at >10% detection frequency in human biospecimens, then it was further considered for biomonitoring, pending Question 2 being satisfied.
   b. If only measured in environmental media at ≥20% detection frequency, which suggested a potential for exposure, and the U.S. EPA exposure predictions were in the 1.0×10^{-7} mg/kg body weight (BW) per day range or higher, then the chemical was further considered for biomonitoring, pending Questions 2 and 3 being satisfied. If a U.S. EPA exposure prediction was not available, then biomonitoring was recommended in samples from

nonoccupationally exposed U.S. subjects to establish the frequency of detection in biospecimens, and Steps 1a or 1c should be applied, based on the detection frequency found.
   c. If there was limited chemical occurrence in biospecimens (<10% detection frequency) or environmental media (<20% detection frequency), then it was assigned a low priority for biomonitoring at this time.
   d. If there were no publications on biomonitoring or environmental data, and U.S. production volume (PV) data were available, then for PVs ≥450,000 kg/y it was further considered for biomonitoring, pending Question 2 being satisfied and additional information on its prevalence in biospecimens for a nonoccupationally exposed U.S. population becoming available.
2. Was there evidence that the chemical may cause health effects of interest to ECHO?
   a. Nonoccupational exposure to a chemical that yielded positive endocrine disruption or reproductive, developmental, or neurotoxicity results in an epidemiological study was adequate evidence for considering biomonitoring (also satisfies Questions 1 and 3).
   b. In the absence of human data, *in vivo* animal (rat, mouse, rabbit, dog) data were used to prioritize. When available, if risk-based assessments using animal study data exhibited observable effects at doses <100 mg/kg BW per day (or <30 μg/kg BW per day when applying a 3,000-uncertainty factor), then the chemicals were considered potentially toxic and further considered for biomonitoring, pending Questions 1 and 3 being satisfied. For example, for doses

Table 3. Information used for prioritizing chemicals for biomonitoring: grouped by subject and relative importance.

Subject	Highly important	Moderately important	Low importance
Environmental media/ biomonitoring measurements	• Biomonitoring or environmental media (air, house dust, food, and drinking water) data; with ≥20% detection frequency in environmental media and ≥10% in biospecimens reported by cohort or epidemiological studies conducted in the United States, Canada, European Union, Japan, and Australia • Qualitative screening studies for chemical in biofluids	• Qualitative screening data for chemical in dust. U.S. EPA exposure predictions (ExpoCast)	• Production and usage statistics for chemical in the United States • Presence of chemical in consumer products
Health effects/toxicity	• Federal review of pesticide's toxicity, risk assessments, state priority lists, or human health studies	• *In vivo* animal toxicological studies • U.S. EPA-reported overlapping bioassay activity and predicted exposure	• *In vitro* studies • HTP *in vitro* assay data • Predictive modeling
Biomarkers	• Specific parent or metabolite has been quantified in a biospecimen in cohort or epidemiological study	• Chemical measured in limited, small scale; method demonstration study in humans or animals • Favorable toxicokinetic parameters of parent or metabolite support potential marker; however, needs validation • Chemical quantified in occupational studies where exposure levels are higher than under environmental conditions	• Biomarker available; however, it may not be specific (i.e., metabolite formed from multiple compounds). In such cases, proxy exposure methods may be recommended

of up to 1,000 mg/kg BW per day developmental effects were not observed for metolachlor ethane sulfonic acid (MESA; MDH 2018a) and metolachlor oxanilic acid (MOXA; MDH 2018b). Thus, MESA and MOXA were assigned a low priority for biomonitoring even though they were detected at a frequency of >20% in groundwater samples (Sutherland-Ashley et al. 2017).

   c. In the absence of *in vivo* data, *in vitro* assay and *in silico* predictive data were used to prioritize chemicals for biomonitoring. If chemicals showed positive high-throughput (HTP) *in vitro* assay and predictive modeling results for the same end point of toxicity, then they were further considered for biomonitoring, pending Questions 1 and 3 being satisfied. Predictive modeling data alone were insufficient evidence, and the chemical was deferred pending additional data.

   d. If no data were available for *in vivo* studies, HTP *in vitro* assays, and predictive modeling, then we deferred the inclusion of a chemical in ECHO pending additional toxicity data.

3. Was there a biomarker that may assess body burden of the chemical?

   a. If the chemical or its metabolite was measured in biospecimens, then this criterion was satisfied.

   b. If the first two questions were affirmatively answered and the use of a biomarker was not reported, we recommended one be developed, if possible.

   c. If a biomarker(s) was not specific or could not be developed, then we recommended the use of proxy measures to estimate exposure.

If chemicals had <10% detection frequency in human biospecimens, <20% environmental levels, or low reported toxicity, they were assigned a low priority for ECHO.

Next, we searched the literature for data to answer the three questions: *a*) Was the chemical (or its metabolite) found in quantifiable levels in biospecimens? *b*) Was there evidence that the chemical may cause health effects of interest to ECHO? *c*) Was there a biomarker that may assess body burden to the chemical (Figure 2)? We performed literature searches on measurement levels in human biospecimens, levels in environmental media, toxicity, and biomarkers of exposure for the 155 chemicals.

Searching for Environmental and Biomonitoring Data

Because chemicals in Groups IV and V were from the consumer product search, we sought biomonitoring and environmental media data. We conducted literature searches ending in December 2018 for studies reporting chemical levels in environmental media and human biomonitoring data and using Science and Technology Collection (advanced search mode), Google Scholar, Scopus, Web of Science, and PubMed for all document types. We limited our search to studies published in or after 2000. We used a combination of the strings of terms listed in Table S2. There were instances where expert judgement was used, due to the complexity of chemical nomenclature and environmental media characteristics. Studies met eligibility criteria if the reporting data were from the United States, Canada, the European Union, Japan, or Australia. We excluded countries with no, few, or unknown regulatory standards on chemical releases to the environment. Publications not in English were excluded.

Searching for Health Effects and Toxicity Data

For the 155 chemicals we searched for data on health effects in humans and *in vivo* toxicity studies in animals using ToxNet

(International Toxicity Estimates for Risk; Developmental and Reproductive Toxicology Database, https://toxnet.nlm.nih.gov/), PubMed, Scopus, and Google Scholar for all document types. We did not limit the period of years searched. We used a combination of the strings of terms listed in Table S2. *In vivo* studies met the criteria if they were conducted in humans, rats, mice, rabbits, or dogs, and *in vitro* studies met the criteria if they were conducted using tissues from those species.

In addition, we examined the following databases: the State of California's *Chemicals Known to the State to Cause Cancer or Reproductive Toxicity* (OEHHA 2018); the State of Minnesota's *Chemicals of High Concern List* (Bell 2016); and the State of Washington's *Chemicals of High Concern to Children Reporting List* (WADEC 2018). These databases list chemicals in alphabetical order, and the information of interest was obtained manually.

Searching for Biomarkers for Chemicals on Panels

We used PubChem and the literature search approach and key words (see Table S2) for human biomonitoring of chemicals or their metabolites as described above except that we included papers from any country that reported on biomarkers of exposure. Furthermore, we searched for papers that reported metabolism of chemicals and excretion of metabolites in humans or animals.

Acquiring HTP in Vitro Assay Data

The goal of ECHO is to study pre-, peri-, and postnatal factors affecting upper and lower airway and neurodevelopment outcomes. For chemicals in Groups III–V (see Excel Tables S3–S5), we utilized additional HTP *in vitro* assay results from ToxCast™, and where possible, from scientific papers that merged results from several assays, producing an overall score (Judson et al. 2015; Karmaus et al. 2016; Kleinstreuer et al. 2017). We focused on results related to all neurological, endocrine, and obesity processes.

Neurological assays. There were three calcium, one ligand, three potassium, and one sodium ion-channel assays, all in the ToxCast™ database and reported as NVS_IC (Sipes et al. 2013). These assays were included directly and were evaluated based on the hit call value being equal to 1. We also utilized an integrated assay that measures neural network activity *in vitro* using microelectrode arrays (mwMEA). This assay has performed well when run on known neuroactive compounds (Strickland et al. 2018; Valdivia et al. 2014) and has been used to screen 1,055 chemicals from the U.S. EPA's Phase II ToxCast™ library with data from the paper presented as binary MEA-Hits (Strickland et al. 2018).

Endocrine processes. The four main endocrine processes evaluated were estrogen, androgen, thyroid, and steroidogenic. Eighteen *in vitro* HTP assays were developed measuring estrogen receptor binding, dimerization, chromatin binding, transcriptional activation, and estrogen receptor-dependent cell proliferation. We used the results from an algorithm that combined the assays into a single interaction score [area under the curve (AUC) score], providing a more robust measure of the potential for estrogenic activity (Judson et al. 2015). Compounds with an AUC score as either antagonist or agonist of >0.1 were considered. We used the published results from an integrated model of 11 HTP *in vitro* androgen receptor assays (Kleinstreuer et al. 2017). Ideally, four thyroid processes should be considered, specifically: receptor activity, thyroperoxidase inhibition, deiodinase inhibition, and sodium iodide symporter inhibition. We used results from the Amplex UltraRed-thyroperoxidase (AUR-TPO) assay that captures multiple molecular-initiating events that converge on perturbed thyroid hormone homeostasis for those resulting in >20% thyroperoxidase inhibition (Friedman et al. 2016). The results

from the thyroid receptor activity measured by a specific HTP assay were used (Rotroff et al. 2013). We incorporated results from a method that considered 10 steroid hormones—including progestogens, glucocorticoids, androgens, and estrogens—using an HTP assay with H295R human adrenocortical carcinoma cells (Karmaus et al. 2016).

Obesity. Several biological processes have been associated with diabetes and obesity (insulin sensitivity in peripheral tissue, pancreatic islet and β-cell function, adipocyte differentiation, and feeding behavior). HTP assay results relative to these processes were used (Auerbach et al. 2016).

In Silico *Predictive Modeling of Chemicals for Toxicity*

To supplement gaps in our knowledge about potentially toxic chemicals, we applied *in silico* models to predict toxicity for chemicals in Groups III–V. We used quantitative structure–activity relationship (QSAR) models on all chemicals in these groups to predict developmental and reproductive toxicity and carcinogenicity. Even though carcinogenicity is not being studied in ECHO, it was included because a risk for carcinogenicity is likely to also affect child health in other ways. We applied an *in silico* docking model to predict endocrine disruption for only chemicals in the eight panels.

Bioaccumulation factors were determined using the Toxicity estimator Software (TEST) model (see below). These data were used as a proxy for chemical persistence in tissues of organisms. The Canonical Simplified Molecular Input Line Entry Specification (SMILES) code for each chemical was submitted to the models.

Endocrine disruption. We used the Endocrine Disruptome® model, an open source, web-based prediction tool that uses molecular docking to predict the binding of compounds to 16 different human nuclear receptors (Kolšek et al. 2014). The nuclear receptors were two androgen receptors [AR and AR antagonist (an)]; four estrogen receptors (α and α an; β and β an); two glucocorticoid receptors (GR and GR an); two liver X receptors (α and β); four peroxisome proliferator-activated receptors (α, β, γ, and δ); and two thyroid receptors (α and β). We applied only the Endocrine Disruptome® model to the chemicals selected for prioritization, given that the model interface did not permit submitting SMILES in batch form, making the process burdensome.

TEST model. We used TEST (version 4.2), a U.S. EPA-developed model that estimates the toxicity of chemicals using QSAR methodologies (U.S. EPA 2016e). TEST has several modules; we used the Developmental Toxicity and Bioconcentration Factor modules.

Virtual models for property evaluation of chemicals within a global architecture. We used virtual models for property evaluation of chemicals within a global architecture (VEGA), a consortium of models based on QSAR methodologies (Benfenati et al. 2013). Specifically, we employed the Developmental, Developmental/Reproductive, Estrogen-binding, and Carcinogenicity modules to assess the toxicity of each chemical.

CarcinoPred-EL. We used CarcinoPred-EL to predict carcinogenicity. This model consisted of three individual classification models—Ensembles SVM, RF, and XGBoost—that use seven types of molecular fingerprints and three machine-learning methods (Zhang et al. 2017). A score of 0–3 was recorded based on the number of ensembles that gave positive predictions.

Output information from the QSAR models also provided the level of reliability for its prediction, and this qualifier was depicted in a heat map format. The Endocrine Disruptome® model provided the binding intensity to each of 16 nuclear receptors; this affinity measure was also displayed in a heat map form.

Results

Compiled List of Chemicals

We found >560 chemicals with a quantifiable frequency ≥20% in samples of environmental media that were reported in government databases and published literature (Figure 1; Excel Table S1). A total of 180 PEs from the U.S. EPA, USDA, and FDA databases met the quantifiable criteria frequency. Of the 180, 156 had not been measured in the NHANES biomonitoring program (see Excel Table S6). Forty were selected for prioritization in this paper, which leaves another 116 pesticides that can be evaluated for future biomonitoring.

To qualify a chemical for inclusion in our environmental media data set, we set our detection frequency cut point at ≥20%. We evaluated this cut point with data we initially collected for chemicals in environmental media that were also measured in biospecimens by the NHANES (see Excel Table S1). There were 129 chemicals that were detected in environmental media (ambient air, personal air, indoor air, house dust, drinking water, or food). Of these 129 chemicals 67% also had quantifiable levels in biospecimens. Grouping these 129 chemicals as APs, EPs, OPFRs, PFASs, and PEs, we found that PEs had the lowest percentage of quantifiable levels in both environmental and biospecimens (38%). For other chemical panels, these proportions were 66%, 83%, and 91% for PFASs, EPs, and APs, respectively. Based on these observations, we believe that a cut point of ≥20% was adequate for identifying chemicals with a likelihood of ≥10% prevalence in biospecimens, the criterion we used to include a chemical for biomonitoring.

For the 45 consumer product categories we selected, approximately 36% of the entries depicted chemical structures (see Table S1). Chemicals with and without structures in CPCat contained considerable redundancy (i.e., the same chemical appeared in multiple consumer products). In addition, consumer products contained inorganics and water. Thus, the tallies in Table S1 include this redundancy.

We found >500 chemicals in the consumer product survey that met the potentially "toxic" chemical moiety criterion (consumer products list). After combining this group with the >560 chemicals found in environmental media and removing duplicates and only including organic chemicals, the result yielded 932 chemicals (Figure 1; Excel Table S2). There were 568 and 364 chemicals with and without U.S. EPA exposure predictions, respectively (see Excel Table S2) (U.S. EPA 2017).

Chemical Groups and Panels

From the 932 chemicals that we started with, we were left with 720 chemicals in Groups III–V after removing legacy chemicals and those biomonitored in NHANES (Figure 1). The number of chemicals in Groups III, IV, and V was 260, 293 and 167, respectively. Chemicals in Groups IV and V were from the consumer products list.

The amount of published data decreased from Groups III to V (see Excel Tables S3–S5) for human biomonitoring, environmental media levels, and U.S. EPA exposure predictions. Sixty-five percent of the chemicals in Group III had U.S. EPA exposure predictions (see Excel Table S3). All chemicals in Group IV (see Excel Table S4) had U.S. EPA exposure predictions. Group V chemicals (see Excel Table S5) had no U.S. EPA exposure predictions.

The number of the chemicals prioritized in each panel is given in Table 1. Except for AAs and QACs, all remaining panels contain chemicals that would supplement the panels currently being studied in ECHO. The AAs and QACs represent a new class of chemicals that have not been previously included in children health-related studies such as ECHO. The individual chemicals are listed in Tables 4–6.

Table 4. Chemicals recommended for biomonitoring.

Chemical panel	Chemical name	Chemical name
Alternative flame retardants (AFRs)	Bis(2-ethylhexyl) tetrabromophthalate (BEH-TEBP)	Hexabromobenzene (HBBz)
	Hexabromocyclododecane (HBCD)	Melamine
Alternative plasticizers (APs)	Bis(2-ethylhexyl) adipate (DEHA)	Bis(2-ethylhexyl)-1,4-benzenedicarboxylate
Aromatic amines (AAs)	2-Methoxyaniline (anisidine)	2-Methylaniline (also known as *o*-toluidine)
	3,4-Dichloroaniline	
Environmental phenols (EPs)	Bisphenol A diglycidyl ether (BADGE)	Bisphenol AF (BPAF)
	Bisphenol B	3,3′,5,5′-Tetrabromobisphenol A (TBBP-A)
	2,2′,6,6′-Tetrachlorobisphenol A (TraTBA)	4-*n*-Nonylphenol
Organophosphorus-based flame retardants (OPFRs)	2,2-Bis(chloromethyl) propane-1,3-diyltetrakis(2-chloroethyl) bisphosphate (V6)	2-Ethylhexyl diphenyl phosphate (EHDPP)
	Bis(2-ethylhexyl) phosphate (BEHP)	Tris(2-butoxyethyl) phosphate (TBOEP)
	Tris(2-ethylhexyl) phosphate (TEHP)	
Perfluoroalkyl substances (PFASs)	Perfluorobutanoic acid (PFBA)	Perfluorohexanoic acid (PFHxA)
	Perfluoropentanoic acid (PFPeA)	Perfluorotridecanoic acid (PFTrDA)
Pesticides (PEs)	Azoxystrobin	Benomyl
	Captan	Chlorpropham
	Cyprodinil	Dicloran
	Glyphosate	Iprodione
	Metalaxyl	Propiconazole
	Pyrimethanil	Tebuconazole

HTP *in Vitro Assay Results*

Of the chemicals not assigned to one of the eight panels, there were 80, 180, and 120 chemicals in Groups III, IV, V, respectively, that were not tested in HTP *in vitro* assays (see Excel Table S7). Testing results were available for 98, 33, and 0 compounds in Groups III, IV, and V, respectively (see Excel Table S8).

A full complement of HTP *in vitro* assay results were not available for 45% of the 155 chemicals selected for prioritization. One or more HTP *in vitro* assay results were reported for 5 of 23 AFRs, 8 of 10 APs, 9 of 28 AAs, 9 of 16 EPs, 7 of 11 OPFRs, 1 of 8 PFASs, 39 of 43 PEs, and 8 of 16 QACs (see Excel Table S9). Of the chemicals tested, 1 of 2 AFRs, 6 of 9 APs, 5 of 9 AAs, 8 of 9 EPs, 6 of 9 OPFRs, 30 of 35 PEs, and 3 of 4 QACs were active in the obesity *in vitro* assays. Except for tris-(2-ethyl-hexyl) trimellitate, which was active in the estrogen agonist, thyroperoxidase thyroid, and endocrine assays, the remaining APs were not positive in the assays (see Excel Table S9). Of those tested, 4 OPFRs and 10 PEs were active in the calcium ion-channel assays, a test for neurotoxicity (see Excel Table S9). One of 8 APs, 9 of 9 AAs, 6 of 7 EPs, 9 of 39 PEs, and 1 of 2 QACs tested positive in the thyroperoxidase assay (see Excel Table S9). Eighteen AFRs, 2 APs, 19 AAs, 7 EPs, 4 OPFRs, 7 PFAs, 7 PEs and 8 QACs lacked HTP *in vitro* assaying and are candidates for future testing (see Excel Table S9).

In Silico *Predictive Toxicity Modeling Results*

Approximately 96% of the nearly 700 chemicals in Groups III, IV, and V exhibited positive results for developmental, reproductive, or estrogen toxicities, or carcinogenicity (see Excel Table S10). Fifty-eight percent of the chemicals were positive for multiple end points of toxicity. The endocrine disruption prediction results were observed for 97% of the chemicals in the panels (see Excel Table S11). Strong binding affinities were observed for 4 AAs, 2 EPs, 1 OPFR, 6 PFASs, 11 PEs, and 1 QAC (see Excel Table S11).

For some chemicals, the QSAR *in silico* and docking models did not converge to predict toxicity (see Excel Tables S10 and S11). For 15 chemicals, the QSAR models predicted that the chemical was inactive. However, the absence of predicted toxicity does not necessarily indicate an absence of toxicity, given that a model may not have enough reference compounds for making a comparison. In addition, we are cognizant that models may yield false-positive and false-negative predictions.

Literature Search Results

The literature searches yielded a broad spectrum of information types within and across chemicals in our eight panels (see Excel Table S12). We found variable amounts of information across the parameters considered, with some chemicals having ample information to prioritize them for biomonitoring, whereas published data were sparse for others (see Excel Table S12). For example, we did not find information on biomonitoring or environmental media levels for 7 AFRs, 2 APs, 10 AAs, 1 OPFR, 2 PEs, and 8 QACs. Twelve AFRs, 2 APs, 10 AAs, 4 OPFRs, 3 PFASs, 2 PE, and 12 QACs had no *in vivo* or *in vitro* toxicity data. Twenty-one AFRs, 2 APs, 18 AAs, 6 EPs, 4 OPFRs, 7 PFASs, 5 PEs, and 7 QACs lacked HTP *in vitro* assay data. No published biomarkers were found for 14 AFRs, 6 APs, 11 AAs, 5 EPs, 3 OPFRs, 21 PEs, and 16 QACs. This lack of information resulted in many chemicals being deferred pending more data.

Prioritized Chemicals for Biomonitoring

We prioritized 155 compounds based on exposure, toxicity, and biomarker(s) (see Tables S3–S5). Although we reviewed published data available for exposure, toxicity, and biomarkers, we did not review or comment on the quality of the studies.

Alternative flame retardants. We evaluated 23 AFRs for biomonitoring in ECHO (see Tables S3–S5). Biomonitoring measurements were reported for 9 AFRs, and 19 have been measured in environmental media (see Excel Table S12). *In vivo* and *in vitro* endocrine disruption, developmental, reproductive, and neurotoxicity studies have been reported for 14, 6, 2, and 2 AFRs, respectively (see Excel Table S12). Our modeling results suggested that some may be endocrine disruptors and developmental toxicants (see Excel Table S12). Moreover, some of these chemicals are persistent in the body—that is, they have a propensity to bioaccumulate in tissues (see Excel Table S10). In adults, their clearance rates vary from a few days to months (Covaci et al. 2011; Geyer et al. 2004; Trudel et al. 2011). Biomarkers for 11 AFRs were used in studies (see Excel Table S12).

We recommended 4 AFRs for biomonitoring in ECHO (Table 4); 16 as deferred pending more research on exposure, toxicity, or biomarker development (Table 5); and 3 as low priority for biomonitoring (Table 6). Of the 16 AFRs deferred pending additional data, all were in Category D (Table 5).

Table 5. Chemicals deferred pending additional data.

Category	Chemical Panel	Chemical Name	Chemical Name
A: Enough concern for toxicity; a biomarker exists; need to measure chemicals in human biospecimens of a non-occupationally exposed population to determine if there is exposure.	Aromatic amines (AAs)	2,4-Diaminotoluene	4,4′-Diaminodiphenylmethane
	Environmental phenols (EPs)	3,3′,5-Trichlorobisphenol A (TrCBA)	
	Perfluoroalkyl Substances (PFASs)	Perfluorooctadecanoic acid (PFODA)	
	Pesticides (PEs)	Difenocoazole	Metribuzin
		Pyraclostrobin	Tetraconazole
		Triclopyr	
B: Enough concern for toxicity; exposure is likely prevalent based on measured levels in food; no biomarker, develop one and test it in non-occupationally exposed human biospecimens to confirm exposure.	Alternative plasticizers (APs)	2,2,4-Trimethyl 1,3-pentanediol monoisobutyrate (TXIB)	Acetyl tributyl citrate (ATBC)
		Tri-2-ethylhexyl trimellitate (TETM)	
	Aromatic amines (AAs)	2-Methoxy-5-methylaniline	4,4′-Methylenebis(2-methylaniline)
		4,4′-Oxydianiline (ODA)	
	Environmental phenols (EPs)	2,6-Di-Tert-butylphenol	Dibutylated hydroxytoluene (BHT)
		4-Nonylphenol diethoxylate	4-Nonylphenol monoethoxylate
		Phenol	
	Organo-phosphorus flame retardants (OPFRs)	Triethyl phosphate (TEP)	Tris(2,3-dichloropropyl) phosphate (TDCnPP)
	Pesticides (PEs)	Boscalid	Carbendazim (MBC)
		Dimethomorph	Diphenylamine
		Fenbuconazole	Fludioxonil
		Thiabendazole (TBZ)	Triflumizole
	Quaternary ammonium compounds (QACs)	Benzylhexadecyldimethylammonium chloride (BAC C16)	Didecyldimethylammonium chloride (DDMAC)
		N, N-Dimethyl-N-benzyl-N-octadecy-lammonium chloride (BAC C18)	
C: Enough concern for toxicity; insufficient environmental measures to determine if exposure is likely; no biomarker, develop one and test it in non-occupationally exposed population to determine if there is exposure.	Alternative plasticizers (APs)	o-Toluene sulfonamide (OTSA)	
	Aromatic amines (AAs)	2-Amino-5-azotoluene	2,3-Dichloroaniline
		2,5-Dichloroaniline	2-Nitro-1,4-phenylenediamine (2NPPD)
	Pesticides (PEs)	Acetochlor ethane sulfonic acid (ESA)	Acifluorfen
		Alachlor ethane sulfonic acid	Alachlor oxanilic acid (OA)
		Piperonyl butoxide	Quinclorac
		Spiroxamine	
	Quaternary ammonium compounds (QACs)	1-(Benzyl)quinolinium chloride	
D: Need more information on toxicity, may or may not have enough information on exposure and biomarkers	Alternative flame retardants (AFRs)	1,2-Bis(2,4,6-tribromophenoxy) ethane (TBE)	2-Bromoallyl 2,4,6-tribromophenyl ether (BATE)
		alpha-Tetrabromoethylcyclohexane (α-DBE-DBCH)	beta-Tetrabromoethylcyclohexane (β-DBE-DBCH)
		Dibromostyrene (DBS)	Decabromobiphenyl ethane (DBDPE)
		Dimethyl hydrogen phosphite (DHP)	Dimethyl propyl phosphonate (DMPP)
		Dimethyl N-methylolphosphonopro-pionamide (DNMPP)	Ethylene bis(tetrabromo) phthalmide (ETBP)
		Pentabromobenzene (PBBz)	Pentabromoethylbenzene (PBEB)
		Pentabromotoluene (PBT)	Tetrabromo-o-chlorotoluene (TBCT)
		Tetrabromophthalic anhydride (TBPA)	Tetrabromophthalate diol (TBPD)
	Alternative plasticizers	Dioctyl terephthalate (DOTP)	
	Aromatic amines (AAs)	1,2,4-Benzenetriamine, N′-phenyl	1,3-Benzodioxol-5-amine
		2,4,6-Tribromoaniline (TBA)	2,6-Toluenediamine
		2-Aminotoluene-5-methylbenzenesulphonic acid (PTMS/PTMSA)	2-Biphenylamine (2-aminobiphenyl)
		2-Bromo-4,6-dinitroaniline	2-Chloro-1,4-diaminobenzene sulfate
		2-Chloro-4,6-dinitroaniline	2-Naphthylamine
		3-Nitroaniline	4,4′-Methylenebis(2-chloroaniline) (MOCA)
		4-Chloro-2-nitroaniline	Aniline
		N,N,4-Trimethylaniline	p-Chloroaniline
	Environmental phenols (EPs)	4-Nonylphenol ethoxycarboxylate	4-Octylphenol diethoxylate
		4-Octylphenol monoethoxylate	
	Organophosphorus-based flame retardants (OPFRs)	Diquanidine hydrogen phosphate (DHP)	Tris(2-chloro-iso-propyl) phosphate (TCIPP)
		Tris-(tribromoneopentyl) phosphate (TTBNPP)	
	Perfluoroalkyl substances (PFASs)	Perfluoroheptane sulfonic acid (PFHpS)	Perfluorohexadecanoic acid (PFHxDA)
		Perfluoropentane sulfonic acid (PFPeS)	
	Pesticides (PEs)	2-Hydroxyatrazine	Fenamidone
		Fenhexamid	Fluroxypyr-meptyl
		Isoxaben	Metolachlor
		Prometon	Tetrahydrophthalimide (THPI)

Table 5. (*Continued.*)

Category	Chemical Panel	Chemical Name	Chemical Name
	Quaternary ammonium compounds (QACs)	3-Methylbenzethonium chloride	Behentrimonium methosulfate
		Benzyldimethyldodecylammonium chloride (BAC C12)	Benzyldimethyl[2-[2-[[4-(1, 1, 3, 3-tetramethylbutyl)-m-tolyl]oxy] ethoxy]ethyl]ammonium chloride
		Dimethyldiallylammonium chloride (DADMAC)	Dodecyldimethyl(4-ethylbenzyl) ammonium chloride
		N,N-Trimethyloctadecan-1-aminium chloride (ATMAC C18)	Octyl decyl dimethyl aminium chloride
		Quaternium-15	Quaternium-24
		Quaternium-52	Tetradonium bromide

Alternative plasticizers. Ten APs were evaluated as candidates for biomonitoring in ECHO (see Tables S3–S5). Biomonitoring measurements for 3 APs were reported, whereas 8 were measured in environmental media (see Excel Table S12). *In vivo* and *in vitro* endocrine disruption, developmental, reproductive and neurotoxicity was reported for 1, 4, 4, and 1 APs, respectively (see Excel Table S12). None of those tested activated *in vitro* neurotoxicity assays (see Excel Table S12). Six compounds were active in HTP *in vitro* assays for obesity (see Excel Table S12). The QSAR modeling results for each AP suggested 5 were developmental and 3 reproductive toxicants (see Excel Table S12). They have a low bioaccumulation factor (see Excel Table S10) and adult urinary elimination rates of hours to a few days. Biomarkers for 4 APs were used in biomonitoring studies (see Excel Table S12). Biomarkers for 4 APs were used in studies (see Excel Table S12).

We recommended two APs for biomonitoring in ECHO (Table 4), five as deferred pending more research (Table 5), and three as low priorities (Table 6). Of the 5 APs deferred pending additional data, 3, 1, and 1 APs were in Categories B, C, and D, respectively (Table 5).

Aromatic amines. Of the 28 AAs we evaluated, environmental or biomonitoring information was available for 16 compounds (see Excel Table S12 and Tables S3–S5). Biomonitoring results for AAs were reported for 7 chemicals, whereas 15 were measured in environmental media (see Excel Table S12). *In vivo* and *in vitro* effects for endocrine disruption, developmental, reproductive, neurotoxicity, and carcinogenicity were reported for 1, 6, 1, and 14 AAs, respectively (see Excel Table S12). A major toxic effect of AAs was carcinogenicity (see Excel Table S12). We found occupational exposure studies for several AAs that linked to cancer (mostly bladder and methemoglobinemia) in highly exposed workers. For compounds that had undergone HTP *in vitro* assay testing, 2 were neurotoxic, 2 were endocrine disruptors, and 5 affected obesity processes (see Excel Table S12). The predictive QSAR modeling results for AAs also suggested that 4 were endocrine disruptors, 13 developmental toxicants, and 1 a reproductive toxicant (see Excel Table S12). Most of them are high-PV chemicals (U.S. EPA 2016a). They vary in bioaccumulation factors from 10 to 1,000s (see Excel Table S10), with urinary elimination rates on the order of hours to a few

days. Biomarkers for 15 AAs were reported (see Excel Table S12). Biomarkers for 18 APs were used in studies (see Excel Table S12).

We recommended 3 AAs for biomonitoring in ECHO (Table 4), 25 deferred pending more research (Table 5), and none as low priority for biomonitoring. Of the 25 AAs deferred pending additional data, 2, 3, 4, and 16 AAs were in Categories A, B, C, and D, respectively (Table 5).

Environmental phenols. We evaluated 16 EPs as candidates for biomonitoring in ECHO (see Tables S3–S5). Biomonitoring measurements for 11 EPs were reported, whereas 15 were measured in environmental media (see Excel Table S12). We identified EPs occurring in environmental media that have limited research on early life exposure and health effects. *In vivo* and *in vitro* toxicity studies for endocrine disruption, developmental, reproductive, and neurotoxicity were published for 13, 9, 5, and 6 EPs, respectively (see Excel Table S12). Predictive modeling results for each EP also suggested that 2 were endocrine disruptors (see Excel Table S11), 13 were developmental toxicants, and 6 were reproductive toxicants (see Excel Table S12). Their bioaccumulation factors vary from 100 to 1,000s (see Excel Table S10), and urine elimination rates range from days to weeks. Biomarkers for 11 EPs were measured in biospecimens (see Excel Table S12).

We recommended six EPs for biomonitoring in ECHO (Table 4), nine as deferred pending more research (Table 5), and one as low priority for biomonitoring (Table 6). Of the 9 EPs deferred pending additional data, 1, 5, and 3 EPs were in Categories A, B, and D, respectively (Table 5).

Organophosphorus flame retardants. Eleven OPFRs were evaluated as candidates for biomonitoring in ECHO (see Tables S3–S5). Biomonitoring measurements for 8 OPFRs were reported, whereas 9 were measured in environmental media (see Excel Table S12). *In vivo* and HTP *in vitro* endocrine disruption, developmental, reproductive, and neurotoxicity studies were reported for 2, 6, 5, and 3 OPFRs, respectively (see Excel Table S12). Predictive modeling results for OPFRs also suggested that some were endocrine disruptors (see Excel Table S11) and developmental toxicants (see Excel Table S12). Relative to brominated AFRs, OPFRs have lower bioaccumulation factors of 10 to 100 (see Excel Table S10) and urinary elimination rates of hours to a few days

Table 6. Chemicals with low priority for biomonitoring in ECHO.

Chemical panel	Chemical name	Chemical name
Alternative flame retardant (AFRs)	2,3,5,6-Tetrabromo-*p*-xylene (pTBX)	1,2-Bis(2,4,6-tribromophenoxy) ethane (BTBPE)
	2,3-Dibromopropyl 2,4,6-tribromophenyl ether (TBP-DBPE)	
Alternative plasticizers (APs)	Di-butyl adipate (DBA)	Di-butyl sebacate (DBS)
	Dioctytl succinate (DOS)	
Environmental phenols (EPs)	4-Methyl phenol (*p*-cresol)	
Organophosphorus-based flame retardants (OPFRs)	Tris (2,3-dibromopropyl) phosphate	
Pesticides (PEs)	Imazapyr	Metolachlor ethane sulfonic acid (MESA)
	Metolachlor oxanilic acid (MOXA)	

([Lynn et al. 1981](); [Nomeir et al. 1981]()). Biomarkers for 8 OPFRs were applied in biomonitoring studies (see Excel Table S12).

We recommended five OPFRs for biomonitoring in ECHO ([Table 4]()), five as deferred pending more research ([Table 5]()), and one as a low priority for biomonitoring ([Table 6]()). Of the 9 OPFRs deferred pending additional data, 2 and 3 OPFRs were in Categories B and D, respectively ([Table 5]()).

Perfluoroalkyl substances. We evaluated eight PFASs as candidates for biomonitoring (see Tables S3–S5). Biomonitoring measurements for seven PFASs was reported, whereas nine were measured in environmental media (see Excel Table S12). Health effects for several PFASs were reported; however, we identified a few additional PFASs occurring in environmental media that have been understudied regarding exposure and health effects in children. In fact, >4,000 perfluoroalkyl and polyfluoroalkyl substances were reported to be in commerce, and only a small fraction of them were studied for their occurrence, toxicity, and exposures ([Ritscher et al. 2018]()).

In vivo and HTP *in vitro* toxicity studies for endocrine disruption, developmental, reproductive, and neurotoxicity were reported for four, four, one, and one PFASs, respectively (see Excel Table S12). Predictive modeling results for PFASs also suggested that six were endocrine disruptors (see Excel Table S11) and one was a reproductive toxicant (see Excel Table S12). The bioaccumulation factors for PFASs are chain-length dependent (see Excel Table S10). Likewise, their urine elimination rates are lower (days to months) for the short-chain lengths as compared with long-chain (years) PFASs ([Olsen et al. 2007]()). Biomarkers for eight PFASs were measured in biospecimens.

We recommended four PFASs for biomonitoring in ECHO ([Table 4]()) and four as deferred pending more research ([Table 5]()). Of the 4 PFASs deferred pending additional data, 1 and 3 PFASs were in Categories A and D, respectively ([Table 5]()).

Pesticides. Forty-three PEs (24 fungicides, 3 insecticides, and 16 herbicides) were evaluated for biomonitoring in ECHO (see Tables S3–S5). The same PE was often detected on different food commodities ([USDA 2018]()). For example, azoxystrobin was detected in 16 different food commodities and tebuconazole in 11 different foods. Biomonitoring measurements for 10 PEs were reported, whereas 38 and 14 were measured in foods and air/house dust, respectively (see Excel Table S12). Results for *in vivo* developmental and reproductive toxicity were reported for 41 PEs. Thirty and 20 PEs exhibited activity in HTP *in vitro* obesity and neurotoxicity assays, respectively (see Excel Table S12). Predictive modeling results for PEs also suggested that 11, 22, and 11 exhibited strong binding to endocrine nuclear receptors and developmental and reproductive toxicity, respectively (see Excel Tables S11 and S12). The fungicides and herbicides have a low propensity to accumulate in biological tissues (see Excel Table S10), and their estimated biological half-lives are <24 h. Biomarkers for 21 PEs were measured in biospecimens (see Excel Table S12).

We recommended 12 PEs (10 fungicides and 2 herbicides) for biomonitoring in ECHO ([Table 4]()), 28 deferred pending more research ([Table 5]()), and 3 as low priority for biomonitoring ([Table 6]()). Of the 28 PEs deferred pending additional data, 5, 8, 7, and 8 PEs were in Categories A, B, C, and D, respectively ([Table 5]()).

Quaternary ammonium compounds. We evaluated 16 QACs (see Tables S3–S5). The 3 most frequently detected QACs in natural environments were alkyltrimethyl ammonium compounds (ATMACs) (C12–C18), benzylalkyldimethyl ammonium compounds (BACs) (C12–C18), and dialkyldimethyl ammonium compounds (DADMACs) (C8–C18) ([Zhang et al. 2015]()). We did not include all the individual ATMACs, BACs, and DADMACs in the current study because they were not present in consumer product categories that were surveyed.

Six QACs were measured in food or drinking water, and dermal exposure was reported for 2. We deferred 16 QACs pending additional data on biological concentrations in biospecimens, environmental media, toxicity, and biomarkers ([Table 5]()).

Deferred and Low-Priority Chemicals

For 108 chemicals, there was insufficient information regarding exposure, toxicity, or availability of a biomarker to recommend for biomonitoring ([Table 5]()). The data gaps for each of these 108 chemicals (see Tables S4 and S5 for more detail) serve as opportunities for future research. Forty-five chemicals in Categories A–C lack exposure data ([Table 5]()). Thirty-eight compounds lack a developed biomarker. Sixty-three chemicals in Category D have insufficient toxicity data and, in some cases, insufficient exposure prevalence and/or biomarker information ([Table 5]()).

We recommended 11 chemicals as a low priority for biomonitoring ([Table 6]()). These chemicals either have been measured but not detected in environmental media or have low toxicity effects as tested in animals or in HTP *in vitro* tests.

Discussion

Data Gaps, Opportunities for Research, and Limitations

There are about 8,000 chemicals that are manufactured or imported in high volumes in the United States ([U.S. EPA 2016a]()). In this effort, we identified 720 chemicals as candidates for inclusion in ECHO. We selected 155 for prioritization based on inclusion in one of eight chemical panels, and then found that only 36 had enough data for consideration. Thus, for chemicals that did not make our prioritization due to lack of data, there is a large opportunity to expand our ability to measure and evaluate chemicals to which the public is likely exposed. These opportunities include performing exposure measurements, developing methods for biomonitoring, and toxicity testing of chemicals.

Our selection approach was limited to evaluating chemicals that had structures displayed in the CPCat database (see Table S1) and possessed a toxic moiety, an empirically determined characteristic that is subject to false negatives. In addition, because only chemicals with displayed structures were visually inspected, approximately 64% of the chemicals (see Table S1) were excluded from the selection process. Thus, our approach addressed only a small segment of the universe of chemicals in consumer products that may have some type of childhood toxicity. In addition, there were additional product categories in the U.S. EPA CPCat database that we did not select for screening. These product categories may also contain chemicals that have end points of toxicity important to ECHO. Finally, CPCat is far from comprehensive due to the lack of federal laws and regulations requiring full disclosure of chemicals used in consumer products.

Our strategy was to group chemicals into panels based on their similar chemical properties and uses in commerce. The composition of these panels will likely be dynamic over time because exposure to some may decrease, chemical toxicity may be discovered for others, and some may be deleted from the lists and new ones added. Nevertheless, a common factor is the methodology used for their analyses. Because single-chemical analysis methods are prohibitively expensive to implement, biomonitoring methods are developed to provide analysis for a suite of chemicals to achieve scales of economy while conserving human biospecimens. Thus, we selected chemicals from the 720 candidates with common analytical properties to create chemical panels amenable to a single extraction step to yield multi-chemical analysis.

We confined the ranking of chemicals to eight panels: AFRs, APs, AAs, EPs, OPFRs, PFASs, PEs, and QACs for biomonitoring

in ECHO. Many chemicals that we have prioritized for biomonitoring add to the AFRs, EPs, OPFRs, PFASs, and PEs panels currently being studied by ECHO. The AAs and QACS are new classes of chemicals that have not been previously examined in a nationwide study. Over a dozen additional chemical panels remain for future prioritization.

Six of the eight panel categories are currently being studied in ECHO. The analytical methodology for current chemicals in a panel is likely applicable to new supplemental chemicals (Table 4), thus reducing costs for method development and for performing measurements in large populations Because the chemicals selected have available methods for measuring biomarkers, analytical standards are available for quantitative analysis, which are required for measurement.

We followed an evidence-driven approach for prioritizing chemicals using published data on exposure, health effects, and availability of biomarkers. Our evaluation was conservative, given that we required a fairly high level of data to be recommended for analysis in ECHO. For most of the chemicals we evaluated, there were insufficient data. This resulted in a relatively small portion of the chemicals evaluated being recommended as our highest priority for study in ECHO. For example, several compounds we evaluated were known or possible human carcinogens (e.g., AAs such as 2-naphthylamine, 4,4′-methylene-bis(2-chloroaniline), aniline, and *p*-chloroaniline), but they have not been recommended based on the lack of *in vivo* or HTP *in vitro* data for endocrine, reproductive, developmental, or neurotoxicity effects. Future use of our methodology could consider a wider range of toxicity end points to qualify for high priority.

Humans are often more sensitive than not at lower chemical doses compared with animals (NRC 2000; National Academies of Sciences, Engineering, and Medicine 2017) and children are more sensitive than adults (Bruckner 2000). Thus, our prioritization may be conservative when relying on risk assessments derived from animal toxicity data and studies based on adults. Given the high number of chemicals and the modest resources of ECHO, we used rigorous prioritization criteria to select a reasonable number of chemicals that could be studied with available resources.

Taking into consideration that environmental contamination and exposure as well as knowledge about toxicity likely will change over time, intermittent reassessment of a chemical's priority for biomonitoring is recommended. Chemical exposure and usage should be periodically assessed to determine whether exposure levels or uses have increased. For this reason, prioritization should be considered a dynamic process.

For chemicals in the deferred categories B–D, to our knowledge, there are no known biomarkers or they have not yet been developed (Table 5). We recommend developing biomarkers and obtaining additional toxicity data for the deferred chemicals, which

includes most of the QACs and APs, AAs, EPs, OPFRs, and PEs, given that there was some suggestion for both toxicity and exposure (Table 5). To develop methods for their analysis, we recommend toxicokinetic research to determine whether the parent compound or its metabolite, if any, is best suited for biomonitoring. If standards do not exist for the parent compound or metabolite, then they need to be developed and may involve custom synthesis. Once a method is developed, then round-robin interlaboratory studies should be performed to establish method and laboratory performance. Because there can be a substantial cost associated with method development, combining chemicals with similar properties to produce a multi-chemical analysis method is preferred.

We used QSAR *in silico* predictions only to screen for toxicity because it can be prone to false-positive and false-negative predictions. To substantiate positive *in silico* prediction results, we sought corresponding positive results from HTP *in vitro* assays (Table 7) for all compounds that had HTP assay results. The results for 11 chemicals agreed between the two methods. However, the results for 16 compounds differed between the two methods. False-negative results can occur, given that their predictions depend on the availability of model reference compounds in the database with similar chemical features. For *in vitro* assays, parameters such as temperature control, pH, osmotic pressure, solubility, and volatility properties can cause errors in the results obtained (Saeidnia et al. 2013).

The *in silico* prediction models, including the Chen model (Chen et al. 2013), do not discern toxic potency. An absence of toxicokinetic factors in *in silico* and *in vitro* procedures may lead to misclassification of the results because they do not incorporate absorption, distribution, metabolism, and excretion by a living organism or the minimum dosing level needed to elicit an effect in their predictions. These models may underpredict toxicity because they do not account for genetic variation or susceptibility. Thus, caution was exercised when making interpretations based on these approaches. We recommend that *in vivo*, HTP *in vitro*, and *in silico* modeling results be compared to assess the frequency of false-positive and false-negative results. Thus, for prioritization we relied on additional evidence of toxicity, such as *in vivo* animal toxicity data and HTP *in vitro* assay results.

We found many of the remaining 565 chemicals (Figure 1; Table 8) were positive in the *in silico* prediction models (see Excel Table S8) but have not been tested in HTP *in vitro* assays. We recommend HTP testing (Table 8) to fill in knowledge gaps for these chemicals. We note that some chemicals in Table 8 have been studied *in vivo*, whereas others are in queue to be tested in the National Toxicology Program (NTP 2019) or by HTP *in vitro* assays. Additional HTP *in vitro* assay results coupled with *in vivo* data would permit verification of the predictive modeling results. These added toxicity data would allow prioritization of additional chemicals for biomonitoring in ECHO.

Table 7. Comparison of results for *in vitro* HTP assays and prediction models.

Comparison of *in vitro* and model results	Chemical panel	Chemical name
Positive in *in vitro* assays and in prediction models	Phthalate, alternative plasticizers, and metabolites	4-*n*-Octylphenol; di-*n*-butyl phthalate (DBP); di-*n*-hexyl phthalate (DnHP)
	Polyaromatic hydrocarbons	Benzo[*b*]fluoranthene
	Amines	3,3′-Dimethylbenzidine; 4,4′-methylenebis(*N,N*-dimethyaniline); 4-aminoazobenzene; benzidine
	Miscellaneous	Benzophenone-2; C.I. Solvent Yellow 14; phenolphthalein
Positive in *in vitro* assays and negative in prediction model	Miscellaneous	1-Naphthol (carbaryl MTB); biphenyl; ethoxyquin; benz(a)anthracene; 2-ethyl-1-hexanol
Positive in *in vitro* assays and in prediction models	Environmental haloacids	Dichloroacetic acid; trichloroacetic acid
	Phthalate, alternative plasticizers, and metabolites	Di-*n*-pentyl phthalate; di-*n*-propyl phthalate
	Volatile organic compounds	1,2,3-Trichloropropane; 1,2,4-trimethylbenzene; 1-butanol; 2-methyl-1-butanol; 3-methyl-1-butanol; alpha-pinene; isobutanol

Table 8. Chemicals positive in prediction models and not tested in HTP *in vitro* assays.

Chemical class	Chemical name
Aldehydes	3-(4-*tert*-Butylphenyl)-2-methyl propanal; acrolein; formaldehyde; piperonal
Dyes	HC Yellow no. 10; C.I. Pigment Red 122; C.I. Pigment Red 2; C.I. Pigment Yellow 74; C.I. Solvent Yellow 6
Environmental haloacids	Dibromoacetic acid, monobromoacetic acid; monochloroacetic acid
Isocyanates	4,4′-Diphenylmethane diisocyanate; 4-chlorophenyl isocyanate; allyl isothiocyanate; methylene bis(thiocyanate); toluene 2,6-diisocyanate; toluene-2,4-diisocyanate
Pesticides	Benoxacor; bromoxynil; dichlorophen; trichlorfon; voriconazole; etidronic acid; flucytoxine; fluridone; folpet; leptophos; lythidathion; metronidazole; nitroxoline; parthenolide; piperazine; 1,4-dimethylpiperazine
Phenolic compounds	1,2,4-Benzenetriol; 1,2-benzenediol, 4-(phenylazo)-; 2,4-dihydroxybenzophenone; 2,4-dinitrophenol; 2-amino-5-nitrophenol; 2-methyl-1,3-benzenediol; 2,3,4,5-tetrabromo-6-methylphenol; 3-hydroxycarbofuran; 3,4,5-tri-chlorophenol; 4-amino-3-fluoro-phenol; 4-aminophenol; 5-aminno-2-methylphenol; 2-methoxy-4-nitro-; phenol, octylphenol diethoxylate
Polyaromatic hydrocarbons	Benzo[*ghi*]perylene; coronene; cyclopenta(*c,d*)pyrene; perylene
Polybrominated diphenyl ethers	2,2′,4,5′-Tetrabromodiphenyl ether (PBDE 49); 2,2′,3,3′,4,4′,5,6′-Octa-bromodiphenyl ether (PBDE 196); 2,2′,3,4,4′,5,5′,6-Octa-bromodiphenyl ether (PBDE 203); heptabromodiphenyl ether
Pyrrolidone and hydantoin compounds	1-(Hydroxymethyl)-5,5-dimethylhydantoin; 1,2-dichloro-5-ethyl-5-methylhydantoin; 1,3-dibromo-5,5-dimethyl-hydantoin; 1,3-dichloro-5,5-dimethylhydantoin; 1,3-dimethylol-5,5-dimethylhydantoin; 1-bromo-3-chloro-5,5-dimethylhydantoin; 1-vinyl-2-pyrrolidone, 2-pyrrolidinone; 3-bromo-1-chloro-5,5-dimethylhydantoin; 5,5-dimethylhydantoin
Volatile organic compounds	1,2-Epoxybutane; 1,4-dioxane; 2-hexanone; 3-buten-2-one; 3-methylfuran; alpha-methyl styrene; beta-pinene; diisopropyl ether; hexane; isopropyl benzene; styrene oxide; *tert*-amyl methyl ether; vinyl chloride
Halogenated containing compounds	1,1,3,3-Tetrachloropropanone; 3,3-dichloropropenoic acid; allyl pentabromophenyl ether; chlorobenzophenone; chlorendic acid; chloroprene; chlorophene; hexachlorophene
Nitrogen-containing compounds	1,3,5-Triazine-1,3,5(2*h*,4*h*,6*h*)-triethanol; 1*h*-1,2,4-triazole; 1*h*-benzo[*de*]isoquinoline-1,3(2*h*)-dione; 1-(2,4-dia-mino-5-methylphenoxy)ethan-1-ol; 1,4-bis(butylamino)anthracene-9,10-dione; 2-butanone oxime; 2,6-diamino-3-((pyridine-3-yl)azo)pyridine; 2-amino-2-methylpropanol; 2-amino-5-; 3,5-dinitrotoluene; *cis*-4-cyclohexene-1,2-dicarboxamide; diethanol amine; indole-3-butyric acid; *n*-(2-hydroxyethyl)acetamide; niacinamide
Other compounds	1,4-Benzodioxin; 1′-acetonaphthone; 2-ethylhexyl acrylate; 3-methyl-4-phenyl-; 5,6,7,8-tetrahydroquinoxaline; 6-methylcoumarin; beta-propiolactone; butyl glycidyl ether; clioquinol; coumarin; coumatetralyl; furan; glycolic acid; methyl *trans*-styryl ketone; octyl methoxycinnamate; oxalic acid; phenyl glycidyl ether; saccharin; sesa-mol; tris(4-methylphenyl) phosphate

Toxicokinetic Considerations That Modulate Chemical Levels and Health Effects

There is a growing body of animal and *in vitro* data that suggest exogenous chemical exposures, endogenous physiological changes, and genetic regulation may together heighten susceptibility to some chemicals and increase pregnant women's health risks (Varshavsky et al. 2019). Furthermore, the susceptibility of infants and children to chemicals may vary considerably, depending on factors such as the age of the child because changes occur in organ size, structure, and function from infancy through puberty (Bruckner 2000), all affecting the toxicokinetics and toxicodynamics of chemicals. Thus, there may be windows of vulnerability from infancy to adulthood that were not accounted for in the animal toxicity data that we used for prioritizing chemicals.

Toxicokinetics and elimination rates discussed earlier for chemicals in the panels generally pertain to adults. However, toxicokinetics can differ between children and adults due to physiological differences, immaturity of enzyme systems, and clearance mechanisms (Ginsberg et al. 2002). Ginsberg et al. (2002) estimated clearance rates of chemicals for six age groupings by comparing toxicokinetics parameters between children and adults using published data. Their results suggest that from premature to 2 years of age, a child has lower clearance rates for certain structures than an adult, comparable clearance rates at 2 years of age, and then a higher clearance rate up to 12 years of age. Finally, there are some toxicant elimination rate data for animal (Hurst et al. 1998; Lin et al. 2013; Loccisano et al. 2012) and human (Burd et al. 2012) fetuses that suggest their rates are slower than infants.

Young infants and toddlers also have less lipophilic proteins in their blood, and could have less likelihood of protein binding, leaving more lipophilic chemicals free in the blood and able to diffuse and accumulate in adipose tissue (Beamer et al. 2012). This phenomenon may partly account for the differences in clearance rates of chemicals between infants, children and adults.

Detection of chemicals in children may be enhanced by the slower clearance rate and the reduced protein binding that occurs up to 2 years of age; however, their detection frequency and levels thereafter may be diminished because of higher clearance rates and if exposure is episodic. We have recommended biomonitoring for chemicals measured in urine (those that are generally rapidly metabolized) and blood (those with slower clearance); however, newer methods, such as hair analysis, which represent a less invasive method that can also reflect temporal exposures (LeBeau et al. 2011) may not be viable for all populations of interest because of cultural beliefs (e.g., Native Americans).

The predicted bioaccumulation factors were based on lipophilicity of chemicals. We used these factors to approximate the accumulation of chemicals in tissues, thus the chemical's retention. In general, a chemical that persists in the body for a week to years is suitable for measuring in serum, plasma, or tissues. However, nonpersistent chemicals with short half-lives (e.g., hours) are generally measured in urine if the route of exposure is primarily episodic and infrequent (e.g., ingestion of a contaminated food commodity). Measurement of chemicals with short half-lives in serum may be suitable if continuous or near-continuous exposure occurs that results in a steady-state or near steady-state serum level.

This work is intended to encourage the scientific community to study the chemicals identified here, specifically to improve our understanding of the potential health consequences for pregnant women, infants, and young children from exposures to chemicals found in environmental media. Five hundred and sixty-five chemicals remain as candidates for prioritization and are opportunities for future research.

Acknowledgments

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