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REVIEW ARTICLE

Opportunities for evaluating chemical exposures and child health in the United States: the Environmental influences on Child Health Outcomes (ECHO) Program

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Abstract

The Environmental Influences on Child Health Outcomes (ECHO) Program will evaluate environmental factors affecting children's health (perinatal, neurodevelopmental, obesity, respiratory, and positive health outcomes) by pooling cohorts composed of >50,000 children in the largest US study of its kind. Our objective was to identify opportunities for studying chemicals and child health using existing or future ECHO chemical exposure data. We described chemical-related information collected by ECHO cohorts and reviewed ECHO-relevant literature on exposure routes, sources, and environmental and human monitoring. Fifty-six ECHO cohorts have existing or planned chemical biomonitoring data for mothers or children. Environmental phenols/parabens, phthalates, metals/metalloids, and tobacco biomarkers are each being measured by ≥15 cohorts, predominantly during pregnancy and childhood, indicating ample opportunities to study child health outcomes. Cohorts are collecting questionnaire data on multiple exposure sources and conducting environmental monitoring including air, dust, and water sample collection that could be used for exposure assessment studies. To supplement existing chemical data, we recommend biomonitoring of emerging chemicals, nontargeted analysis to identify novel chemicals, and expanded measurement of chemicals in alternative biological matrices and dust samples. ECHO's rich data and samples represent an unprecedented opportunity to accelerate environmental chemical research to improve the health of US children.

Keywords Environmental exposures · Chemicals · Children's health · Environmental influences on child health outcomes

Introduction

Leading scientific and professional societies recognize that chemical exposures that occur via air, food, water, and dust can increase the risk of adverse child health outcomes—including adverse pregnancy outcomes, neurodevelopmental delays and deficits, asthma, obesity, diabetes, and cancer—some of which have been increasing over the last several decades [1–4]. Furthermore, chemicals can cross the placenta, and it is widely recognized that the in utero and child developmental periods are more susceptible to chemical perturbation and subsequent health effects compared with later life stages [5]. Simultaneous exposures to multiple chemicals can have additive or synergistic health effects [6, 7]. In addition, chemical manufacturing has grown dramatically over the past 60 years [8], with now nearly 8000 chemicals manufactured or imported in high amounts (>25,000 pounds per year), equaling about 9 trillion pounds per year in the United States [9].

Data from the US National Health and Nutrition Examination Survey (NHANES) show that ≥99% of US pregnant women are exposed to at least 43 different chemicals,

Members of the ECHO are listed in Appendix.

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including polybrominated diphenyl ethers (PBDEs), environmental phenols, phthalates, and pesticides, with some of these women exposed to at least 139 chemicals out of the 163 evaluated [10, 11]. Many of the chemicals were measured at levels shown to increase risks for adverse developmental outcomes in animal and human studies [12–16]. Biomonitoring studies have shown that population exposures to environmental chemicals can vary significantly by race/ethnicity, place of birth, and socioeconomic status [17–21], which can lead to disparities in health risks. For example, serum PBDE levels were higher among US-born participants compared with their foreign-born counterparts [17], certain perfluoroalkyl substance (PFAS) levels were higher among higher socioeconomic status groups, and bisphenol A levels were higher in low-income, emergency food assistance recipients [18].

Although recognition of the contribution of environmental chemical exposures to childhood disease has increased, there are many gaps in our understanding due to limitations of available data sources. The NHANES provides biomonitoring data on chemical exposures but does not routinely include a large sample of pregnant women or measure exposure among children under 3 years of age, a period during which exposures could be higher due to unique behavioral activities such as crawling on the ground, hand-to-mouth activity, and contact with baby products or toys [22]. While NHANES is useful for many purposes including exposure assessment and monitoring population-level exposure trends, it can only be used for cross-sectional studies linking exposures with health effects. Individual longitudinal cohort studies overcome some of these data gaps, but often do not have adequate sample sizes to detect small effect sizes, study rare outcomes, or identify susceptible subgroups. Thus, there is a need to understand chemical exposures across a broad range of developmental periods and their relationship to important childhood outcomes in a large study of US children.

In 2016, the National Institutes of Health (NIH) launched a 7-year initiative called the Environmental influences on Child Health Outcomes (ECHO) Program. The goal of ECHO is to understand the environmental influences on childhood disease with a focus on pre-, peri-, and postnatal outcomes, respiratory health, obesity, and neurodevelopment. ECHO consists of 71 linked cohorts with broad spatial coverage across the United States. With more than 50,000 children anticipated, it will capitalize on existing participant populations by supporting multiple synergistic, longitudinal studies to investigate environmental exposures —including chemicals—on child health and development. This rich resource will include key data collected by cohorts prior to their participation in ECHO as well as new data and biospecimens collected during ongoing ECHO-funded follow-up. The ECHO-wide data collection protocol describes information to be obtained during new follow-up visits spanning pregnancy through adolescence [23]. ECHO also has a Children's Health Exposure Analysis Resource (CHEAR) Program supplement to fund new biospecimen assays including chemical exposures [24]. In the future, the ECHO Program will provide a national research resource for use by the general scientific community via a public use anonymized dataset.

Our goal in this review is to identify opportunities for studies of chemical exposures in ECHO by leveraging existing cohort data and future assays of ECHO biospecimens. First, we describe chemical exposure data collected by ECHO cohorts, including biomonitoring, environmental monitoring, and questionnaires. Next, we review the literature on routes, sources, and environmental and human exposure monitoring to inform research opportunities using existing chemical data or new biomonitoring in ECHO. Finally, we discuss opportunities and challenges for chemical research in ECHO with the aim of spurring high-impact studies to inform interventions and policies to improve children's health. This review focuses on chemicals currently included in NHANES biomonitoring, which also have been measured by several ECHO cohorts; we previously published recommendations for novel chemicals with limited available biomonitoring data [25].

Methods

ECHO cohort data

At present, ECHO cohorts have not yet finalized participant consent and individual-level data transfer to the ECHO Program. Therefore, to facilitate study planning, the ECHO Data Analysis Center administered surveys to ascertain existing or planned data collection from each ECHO cohort at the start of the ECHO Program. We present results for 70 of 71 cohorts with completed data from three survey modules administered from 2017 to 2018: recruitment site locations (module 02: January 31, 2018); demographic and other data elements (module 03: October 3, 2018); and biospecimens and bioassays (module 04a: May 18, 2018). For module 04a, cohorts reported on: (1) assays that have already been run on biospecimens collected prior to ECHO, (2) stored biospecimens (i.e., extant specimens), (3) planned assays for stored biospecimens, and (4) future plans for assays and biospecimens. Respondents were instructed to include planned assays if they were already funded by either ECHO or other sources. To determine cohorts with substantial participant coverage for each chemical class, respondents were also instructed to exclude pilot studies with assays conducted for fewer than 100 participants. Cohorts specified whether data elements were ever collected

for mothers, fathers, and children. If data elements were collected, cohorts then provided the life stage(s) of data collection. For mothers, we include data collected during life stages defined as preconception, prenatal, and delivery/infancy (birth to <12 months). For the child, we include data collected during life stages defined as delivery and neonatal period (<1 month), infancy (1 to <12 months), early childhood (1 to <5 years), middle childhood (5 to <12 years), and adolescence (12 to <18 years).

The modules requested information on measurement of biomarkers of 16 broad chemical classes (i.e., groups of chemicals measured together in a panel) defined as disinfection byproducts (DBPs), perchlorate and related anions, environmental phenols and parabens, phthalates, metals/metalloids, PFASs, PBDEs, organophosphate ester flame retardants (OPFRs), fungicides or herbicides, organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), organophosphorus insecticides (OPs), pyrethroids, polycyclic aromatic hydrocarbons (PAHs), tobacco biomarkers, and volatile organic compounds (VOCs). Additional information was collected for selected chemicals within some of these classes. Three chemical classes measured by NHANES were not included in the survey (insect repellents and metabolites, carbamate pesticides, and heterocyclic amines). We excluded VOCs from the current paper because they were not measured by any ECHO cohorts, resulting in 15 chemical classes of interest.

As we did not have individual-level information or sample sizes of ECHO cohorts, all results summarize the number of cohorts with data, not the number of participants. We calculated descriptive statistics using Stata 15.1 (StataCorp, College Station, TX). We mapped the 333 recruitment site locations of the 70 ECHO cohorts to the centroid of the zip code using ArcGIS software version 10.5.1 (Esri, Redlands, CA). For this map, we summed the number of chemical classes with existing or planned assays in either the mother or the child (thus, the possible number of chemical classes ranged from 0 to 15).

Literature review

We conducted a narrative literature review of the 15 chemical classes biomonitored by at least one ECHO cohort. First, we reviewed government databases and the published literature to summarize information on exposure sources, routes, and biomonitoring considerations including half-lives and preferred biomonitoring matrices. Next, we searched government databases and the published literature for the detection prevalence and concentrations of chemicals measured in environmental media to characterize exposure sources and biological samples to assess concentrations and exposure trends.

To characterize chemicals in environmental media to understand sources of exposures, we extracted results from cohort or probability-based population studies that included children, were conducted primarily in the United States, and reported levels in ambient air [26–48], personal air [26, 27, 29–33, 36, 39, 41, 42, 45, 49–54], indoor air [26, 28–30, 32, 33, 36, 38, 40, 41, 44, 45, 48, 55–65], house dust [28, 40, 47, 60, 61, 63, 66–96], drinking water [96–107], or food [96, 103, 107–114]. For each chemical, we recorded the highest median, mean, or geometric mean values across multiple studies that were detectable in ≥20% of samples (for food, the highest detection frequency for a commodity was selected) [25]. For chemicals that were detected in ≥20% of samples of one medium and monitored but not detected in another medium, we also display the nondetects. For drinking water results reported by the US Department of Agriculture [104], we provide the frequency of detection because levels were given only as a range.

To characterize concentrations and temporal trends in chemicals measured in in biological samples, we used NHANES biomonitoring data during the years 1999–2016 [11]. We included biomonitoring data from adolescents aged 12–19 years, as data for younger children were not available for all reporting cycles. We indicate the parent compound as well as the relevant metabolite(s) where applicable. To describe concentrations, we recorded the highest 75th percentile value that was found at any of the NHANES reporting cycles [25]. To describe linear trends over time, we calculated cycle-to-cycle percentage changes in geometric mean concentrations of biomarkers detected in adolescents during at least three consecutive cycles. Because chemicals were monitored for different numbers of cycles, we calculated the average cycle-to-cycle percentage change and categorized trends as decreasing if the average percentage change was ≤−5%, increasing if the average percentage change was ≥5%, or stable if otherwise. We summarized data using a heat map to display the relative levels of chemicals found in ambient, personal, and indoor air; house dust; drinking water; food; and biospecimens (Supplementary Table S1).

Chemical exposure data collected by ECHO cohorts

Of the 70 ECHO cohorts with available information, 56 (80%) have existing or planned (i.e., funded) biomonitoring of at least one chemical class in mothers ($n = 39$ cohorts) or children ($n = 42$ cohorts). Figure 1 displays the availability of chemical biomonitoring data by ECHO recruitment site, illustrating the wide geographic distribution of ECHO participants with existing chemical assay data or the potential for future biomonitoring using stored samples. As shown in

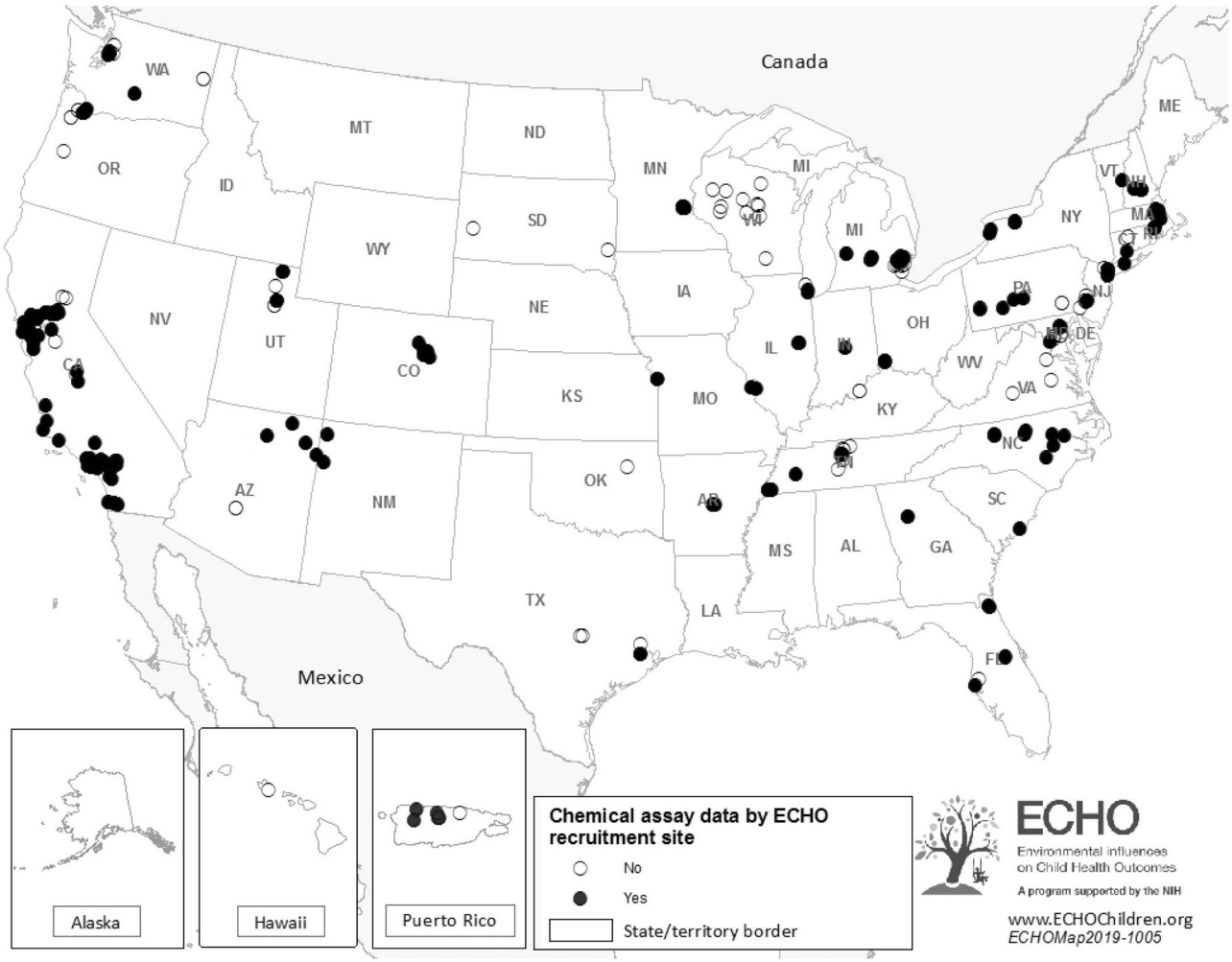

Fig. 1 Existing or planned chemical assay data available for mothers or children by ECHO recruitment site. Dark circles indicate available chemical assay data from mothers or children at that recruitment site; white circles indicate no existing or planned chemical assays. For mothers, we included any assay during preconception, prenatal, or delivery/infancy. For children, we included any assay during the delivery/neonatal period, infancy, childhood, middle childhood, or adolescence. We included existing assays already run by cohorts prior to the ECHO Program and planned assays funded by ECHO or other sources.

Table 1, the most common chemical classes with existing or planned biomonitoring in mothers are environmental phenols (24 cohorts), phthalates (20 cohorts), and tobacco biomarkers (18 cohorts). In children, metals/metalloids are by far the most common, with 31 cohorts measuring them in at least one life stage of the child (Table 1). Many cohorts have existing chemical biomonitoring data for mothers; in contrast, the majority of child biomonitoring data will be generated from planned assays (Fig. 2). To inform research that could be conducted using extant data, we provide information on existing chemical biomonitoring data (i.e., excluding planned assays) in the Supplementary Material (Table S2).

The vast majority of chemical biomonitoring for mothers is during the prenatal period, whereas chemical biomonitoring for children is being conducted over multiple life stages from delivery through middle childhood (Table 1). Several cohorts have chemical assays at delivery or during infancy, a time period not included in NHANES biomonitoring. Very few cohorts measured chemicals during adolescence, given that only 30 cohorts so far have collected data from children in that life stage; among these, four cohorts are measuring tobacco biomarkers and one cohort is measuring PAHs. There is substantial variability in the number of cohorts with measures of individual chemicals within classes (Supplementary Table S3). Paternal chemical biomonitoring is very limited, with no chemical classes measured in more than one cohort. In addition to targeted biomarker assays, four cohorts are conducting nontargeted or suspect screening approaches to assess chemical exposures in mothers and children.

While each class contains multiple chemicals, we also assessed the potential for multiclass analyses. Thirty cohorts are assessing more than one class of chemicals in mothers,

Table 1 Number of 70 ECHO cohorts with existing or planned chemical class assays by participant and life stage[a].

Chemical class	Mother				Child				
	Collected (any) ($n = 70$)	Preconception ($n = 50$)	Prenatal ($n = 69$)	Delivery/ Infancy ($n = 70$)	Collected (any) ($n = 70$)	Delivery/ neonatal ($n = 69$)	Infancy ($n = 70$)	Early childhood ($n = 68$)	Middle childhood ($n = 60$)
Environmental phenols and parabens	24	9	23	2	15	5	5	9	3
Phthalates	20	8	19	2	15	7	5	9	8
PFASs	13	1	12	1	7	4	1	2	1
PAHs	11	1	11	1	6	3	1	4	3
Organophosphorus insecticides	9	1	7	2	6	2	2	4	2
Organophosphate or other alternative flame retardants	3	0	2	1	0	0	0	0	0
Perchlorate and related anions	3	2	3	0	1	1	0	0	0
Pyrethroids	4	1	3	1	4	3	2	3	1
Metals/metalloids	14	2	12	7	31	16	11	17	13
Tobacco biomarkers	18	1	14	8	12	3	6	10	7
Disinfection byproducts	7	7	0	0	0	0	0	0	0
Fungicides or herbicides	2	0	2	1	1	0	1	1	0
Organochlorine pesticides	6	2	5	2	10	9	1	1	0
PBDEs	11	2	10	2	8	4	2	4	2
PCBs	8	2	7	2	10	9	1	2	1

n number of cohorts that collected any data at each life stage, *PFASs* perfluoroalkyl substances, *PBDEs* polybrominated diphenyl ethers, *PCBs* polychlorinated biphenyls, *PAHS* polycyclic aromatic hydrocarbons.

[a]Life stages defined as follows: delivery/infancy (birth to <12 months), delivery/neonatal (<1 month), infancy (1 to <12 months), early childhood (1 to <5 years), middle childhood (5 to <12 years).

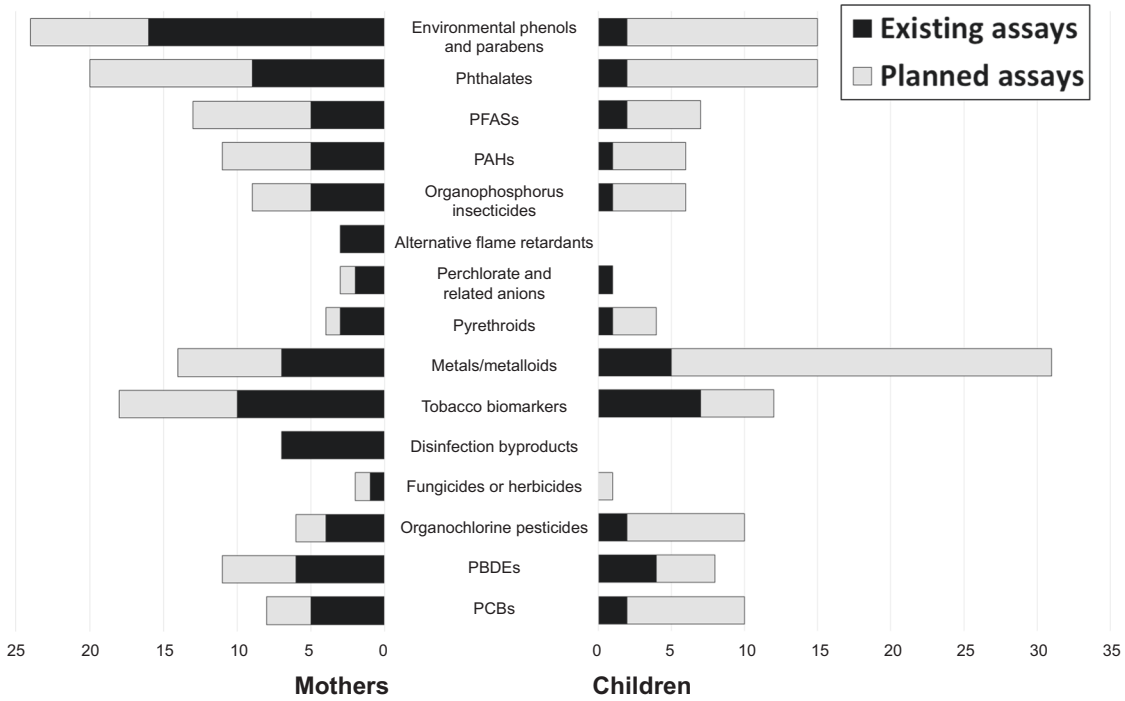

Fig. 2 Number of 70 ECHO cohorts with chemical classes biomonitored in mothers or children. For mothers, we included any assay during preconception, prenatal, or delivery/infancy. For children, we included any assay during the delivery/neonatal period, infancy, childhood, middle childhood, or adolescence. Existing assays are those already run by cohorts prior to the ECHO Program; planned assays are those funded by ECHO or other sources. Perfluoroalkyl substances (PFASs), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs).

and 22 are assessing more than one chemical class in children. Of these, eight cohorts will have more than five classes measured in mothers and in children. It is also notable that many chemical classes are being measured in multiple life stages. At least six ECHO cohorts are measuring tobacco biomarkers, environmental phenols, phthalates, or metals/metalloids in three or more life stages.

Many ECHO cohorts have banked biospecimens from mothers and children that could be used for future chemical assays (Table 2). Maternal prenatal and child neonatal and childhood blood samples have been biobanked by more than one-third of the ECHO cohorts. Few cohorts have collected biospecimens from fathers; only four cohorts collected paternal blood during the prenatal period, and seven cohorts collected urine and hair from fathers prior to conception.

In addition to biomonitoring data and specimens, several ECHO cohorts are conducting environmental monitoring including dust, air, and water sample collection (Table 3). Over one-third of ECHO cohorts are conducting home visits. ECHO cohorts have collected information on a wide range of variables that can be used in analyses of chemical exposures as predictors or key confounders (Table 4). Among these data elements, more than one-third of cohorts have information on pets, mold, or carpeting in the household, primary heating source, and type of residence. Most of the variables listed in Table 4 are either essential or recommended to be ascertained by questionnaire in the ECHO-wide data collection protocol, a common protocol being followed by all ECHO cohorts.

Opportunities for research and future biomonitoring in ECHO

We classified chemicals biomonitored by at least one ECHO cohort into five exposure-based groups to prioritize future research and biomonitoring opportunities within ECHO: ubiquitous, emerging, well-characterized, low detection, and legacy. Below, we describe these groups and the information we collected on chemicals within these groups.

Ubiquitous

This group includes five chemical classes with ubiquitous exposures in the general US population that warrant additional biomonitoring and children's health research: environmental phenols and parabens, phthalates, PFASs, PAHs, and OPs. Prenatal biomonitoring of these chemicals has already been conducted by many ECHO cohorts, and existing data offer sufficient opportunities for studies of

Table 2 Number of 70 ECHO cohorts with existing banked biospecimens by participant and life stage.

Life stage of the child	Number of cohorts[a]	Blood[b]	Urine	Hair	Toenails
Samples collected from the mother					
Preconception	50	2	9	7	0
Prenatal	69	27[c]	23[c]	10[d]	3[c]
Delivery/infancy (birth to <12 months)	70	11[d]	6	6	0
Early childhood (1 to <5 years)	63	16	3	2	0
Middle childhood (5 to <12 years)	39	2	0	0	0
Samples collected from the child					
Delivery/neonatal (<1 month)	69	35[d]	8	3[d]	0
Infancy (1 to <12 months)	70	10[d]	8[c]	5[d]	1[c]
Early childhood (1 to <5 years)	68	28[d]	12[c]	6[c]	1[c]
Middle childhood (5 to <12 years)	60	9[c]	5[c]	3[c]	1[c]
Adolescence (12 to <18 years)	30	5[c]	2[c]	2[c]	0[c]

[a]Number of cohorts that collected any data at each life stage.

[b]Cohorts are included if they banked serum, plasma, whole blood, or umbilical cord blood.

[c]Specimens in this life stage are essential data elements in the ECHO-wide data collection protocol.

[d]Specimens in this life stage are recommended data elements in the ECHO-wide data collection protocol.

exposure sources or health effects of gestational exposures or their mixtures. We recommend expanded postnatal biomonitoring of these chemical classes within the ECHO Program to provide data necessary to fill important gaps regarding childhood and adolescent exposures. For example, biomonitoring in early childhood is warranted given that young children may be particularly at risk of ingesting chemicals in dust through hand-to-mouth behaviors.

Environmental phenols and parabens

These nonpersistent chemicals are used in a wide range of consumer products including polycarbonate plastics, food packaging, and thermal transfer papers (bisphenols), as antiseptics in hygiene products (triclosan, triclocarban), as constituents of deodorizers (2,5-dichlorophenol), in the production of herbicides and chlorinated chemicals (2,4-dichlorophenol), as ultraviolet filters in lotions and plastics (benzophenone-3, also known as oxybenzone), and as preservatives in personal care products and foodstuffs (parabens) [115]. Their extensive use in consumer products leads to nearly ubiquitous, though episodic, exposure [116, 117] via diet, dermal absorption, and inhalation. Environmental phenols and parabens can be found in house dust and indoor air (Supplementary Table S1). These chemicals are metabolized and conjugated in the liver and excreted, with half-lives measured in hours [118]. Given their widespread uses, and potential for contamination by parent chemicals, analysis of conjugated urinary metabolites is preferred, although concentrations have been reported in serum and plasma [118, 119], and more recently in hair [120]. Several chemicals in this class have been the target of policy and regulatory activities, which can result in changing exposure profiles. For example, the FDA banned using triclosan in hand washes and skin formulations [121]. Still, with the exception of triclocarban and two parabens, all of these chemicals are detectable in over half the United States population [11]. Concentrations of BPA, triclosan, dichlorophenols, and *n*-propyl paraben declined in adolescents from 1996 to 2016, whereas benzophenone-3 concentrations increased (Supplementary Table S1). US biomonitoring data also suggest that bisphenol S and F exposures are increasing [122].

Phthalates

Phthalates are a class of chemicals widely used in consumer products. Major sources of exposure to high molecular weight phthalates include food, polyvinyl chloride products, and medical supplies, while low molecular weight phthalates are commonly found in personal care products and fragrances, paint, glue, detergents, and toys [115]. Human exposure can occur through ingestion, inhalation, or dermal contact [123]. Phthalates are widely detected in house dust (Supplementary Table S1). Humans rapidly metabolize phthalates, resulting in biological half-lives of less than 24 h [124]. At present, although phthalates have been detected in multiple human matrices (including blood and saliva), measurement of urinary phthalate metabolites is by far the most common method, and is currently the only well-accepted way to assess body burden [124]. Because phthalate exposures are widespread and continuous, studies typically find that 99–100% of people, including pregnant women and children, have measurable levels of one or more phthalate metabolites in their bodies [11]. Certain phthalates have been banned from use in children's toys and other

Table 3 Number of 70 ECHO cohorts with existing or planned environmental monitoring by participant and life stage[a].

Environmental monitoring	Mother				Child					
	Collected (any) ($n = 70$)	Preconception ($n = 50$)	Prenatal ($n = 69$)	Delivery/ Infancy ($n = 70$)	Collected (any) ($n = 70$)	Delivery/ Neonatal ($n = 69$)	Infancy ($n = 70$)	Early childhood ($n = 68$)	Middle childhood ($n = 60$)	Adolescence ($n = 30$)
Home visits	24	1	10	10	26	3	12	20	17	2
Silicone wristbands	3	0	2	0	1	0	0	1	0	0
Dust sample collection	17	1	8	7	21	2	9	16	11	5
Air sample collection	19	1	4	3	17	1	3	10	10	0
Water sample collection	8	0	1	1	7	0	1	1	2	0

n number of cohorts that collected any data at each life stage.

[a]Life stages defined as follows: delivery/infancy (birth to <12 months), delivery/neonatal (<1 month), infancy (1 to <12 months), early childhood (1 to <5 years), middle childhood (5 to <12 years), adolescence (12 to <18 years).

child care articles in the United States [125, 126]. NHANES biomonitoring suggests that adolescent exposure to certain phthalates (benzyl butyl, di-2-ethylhexyl, dibutyl, diethyl) is decreasing over time, while exposure to other phthalates (diisobutyl, diisononyl) is increasing (Supplementary Table S1).

PFASs

PFASs are widely used manmade organofluorine compounds with over 200 industrial and consumer product applications such as stain-resistant coatings in clothing and carpets, kitchenware, and food packaging [127]. They are resistant to metabolism and environmental degradation, leading to nearly ubiquitous human exposure from contamination in drinking water and food, indoor air, and dust (Supplementary Table S1) [128]. Drinking water, breast milk, and household dust are important sources of exposure for infants and toddlers [129]. Since 2000, perfluorooctanoic acid, perfluorooctanesulfonic acid, and several other PFASs were phased out through national voluntary initiatives, due to health and exposure concerns [130, 131] and have been gradually replaced with their shorter-chain homologs [132]. The long-chain PFASs biomonitored by NHANES have estimated half-lives ranging from 2 to 9 years [133]. PFASs have been measured in blood (serum or plasma) but recently hair and nails have been suggested as alternative noninvasive matrices in human biomonitoring for some PFASs [134, 135]. NHANES routinely measures 12 PFASs, a tiny fraction of the estimated >4000 PFASs in commerce [136]. Despite the decreasing levels of perfluorooctanoic acid and perfluorooctanesulfonic acid over time (Supplementary Table S1), some other long-chain PFASs are still widely detected [11].

PAHs

PAHs are produced by incomplete combustion of organic matter and are commonly found in cigarette smoke, vehicle exhausts, residential wood burning, wildfires, asphalt roads, coal, coal tar, and hazardous waste sites. Exposure to PAHs can occur through inhalation, ingestion, and dermal contact, since they occur in air, food, drinking water, house dust, soil, and hazardous waste sites (Supplementary Table S1) [137]. Occupational exposure occurs through inhalation, such as in coal tar production plants. PAHs or their metabolites can be measured in body tissues, blood, and in urine. Phenanthrene and metabolites are excreted mainly in the urine, while other PAHs and metabolites (e.g., chrysenes, benzofluoranthenes, benzo[*a*]pyrene) are excreted mainly in the feces. Urinary biomarkers of four PAHs have been routinely monitored by NHANES; fluorene and

Table 4 Number of 70 ECHO cohorts with existing or planned questionnaire data on chemical exposure sources by participant and life stage[a].

Variable	Mother			Child				
	Collected (any) ($n = 70$)	Preconception ($n = 50$)	Prenatal ($n = 69$)	Collected (any) ($n = 70$)	Infancy ($n = 70$)	Early childhood ($n = 68$)	Middle childhood ($n = 60$)	Adolescence ($n = 30$)
Pesticide application/use[b]	12	2	11	10	8	7	3	2
Farm animal contact	7	2	6	10	9	8	3	1
Pets in household[b]	21	4	19	48	39	42	21	7
Type of residence[b]	28	5	19	40	28	28	16	4
Attached garage[b]	2	0	2	3	3	2	1	0
Renovations[b]	17	8	16	16	14	14	5	2
Primary heating source[b]	24	3	22	30	18	20	7	5
Wood stove or fireplace[b]	11	1	10	22	11	19	7	5
Gas stove[b]	15	1	13	19	12	12	10	5
Cook stove type[b]	11	1	11	15	10	6	4	2
Burning candles or incense	5	1	5	2	2	2	1	1
Air fresheners[b]	13	0	13	2	2	2	2	1
Cleaning agents[b]	18	1	18	6	6	5	2	1
Personal care products[b]	12	2	12	9	8	7	2	1
Ventilation[b]	18	1	18	21	19	18	8	5
Mold in household[b]	24	3	22	29	19	21	6	6
Carpeting in household[b]	21	3	21	26	25	11	7	5
Furniture type/ condition	10	1	9	1	1	1	0	0
Primary source of water[b]	20	12	20	13	12	7	2	1
Fast food[b]	12	1	11	11	7	9	5	3
Time-activity data (e.g., time at home, outdoors, in transit)	8	0	7	7	5	5	5	1

n number of cohorts that collected any data at each life stage.

[a]Life stages defined as follows: infancy (1 to <12 months), early childhood (1 to <5 years), middle childhood (5 to <12 years), adolescence (12 to <18 years).

[b]Data collection by questionnaire is essential or recommended in the ECHO-wide data collection protocol.

phenanthrene metabolite concentrations are decreasing among adolescents over time, while naphthalene and pyrene metabolites have increased (Supplementary Table S1).

OPs

OPs are acetylcholine inhibitors that are primarily used for the control of insects in agriculture, buildings, and other public health applications (e.g., mosquito control) [138]. The US Environmental Protection Agency (EPA) banned many household uses of OPs in 2001, but agricultural use has increased, and more than 40 OPs are still registered for use in the United States [139]. Several OPs have been detected in environmental media, primarily food (Supplementary Table S1). Dermal, inhalation, and nondietary ingestion can occur following residential applications or from proximity to agricultural fields or other public health applications. Some pregnant women may be exposed occupationally, and some children may be exposed via lice treatments [139]. When ingested, OPs are rapidly metabolized and eliminated in urine [140]. However, some lipophilic OPs can bioaccumulate in adipose tissue, particularly from inhalation or dermal exposures, which may limit their rate of metabolism, detoxification, and excretion [140, 141].

While it is difficult to measure specific OP metabolites, cumulative OP exposure can be assessed via urinary concentrations of six nonspecific dialkyl phosphate metabolites that represent exposures to over 40 different OPs. Concentrations of chlorpyrifos and methyl chlorpyrifos are decreasing among NHANES adolescents (Supplementary Table S1).

Emerging

This group is composed of emerging chemicals of concern with biomonitoring available for fewer than five ECHO cohorts: alternative phthalates/plasticizers, OPFRs, perchlorate and related anions, and pyrethroids. These chemicals are not yet well-studied, with important gaps in understanding regarding pregnancy and childhood exposures and/or resultant health effects. Many of these chemicals are replacements for chemicals that have been phased out or banned due to concerns about toxicity. Thus, because they may be similar in structure and use, characterizing exposures is important for identifying potential health risks. We recommend biomonitoring of emerging chemicals in ECHO and other cohorts to provide necessary data to address these critical gaps.

Alternative phthalates/plasticizers

As the use of certain phthalates declines, chemicals such as di-2-ethylhexyl terephthalate and di(isononyl) cyclohexane-1,2-dicarboxylate are now being added as plasticizers to polyvinyl chloride products, children's toys, flooring, and food contact materials [142–144]. These alternative phthalates/plasticizers have similar sources and chemical properties as their predecessors and are also measured in urine. Recent biomonitoring suggests that exposure to these chemicals is increasing [142, 145] despite limited knowledge of potential toxicity or health effects.

Organophosphate ester flame retardants (OPFRs)

OPFRs are flame retardants introduced to replace PBDEs, legacy flame retardants that are described further below [146–148]. Indoor dust ingestion is considered to be a major route of OPFR exposure [149], particularly via hand-to-mouth activity in infants and children [150, 151]. Other exposure routes include inhalation of indoor air [152, 153], dermal absorption [67, 154], and dietary intake [155–157]. Chemicals in this class have been detected in indoor air, drinking water, and food, with high levels of some OPFRs in house dust (Supplementary Table S1). Most OPFRs are considered nonpersistent, and human exposure is quantified via metabolites measured in urine [158–160]. It is currently unknown whether adverse biological effects may result from exposure to metabolites as compared with the parent compounds [161, 162]. Several of the eight OPFRs included in NHANES were detected among adolescents (Supplementary Table S1). While these compounds have not been measured in a sufficient number of NHANES cycles to evaluate trends, human exposures appear to be increasing [163].

Perchlorate and related anions

Perchlorate salts are used in explosives, bullets, rocket propellants, fireworks, flares, and vehicle airbags, and lithium and magnesium perchlorates have been used in batteries. Agricultural use of Chilean nitrate fertilizer in the southwest US has contributed to perchlorate contamination of groundwater and farm products [164]. Perchlorate has been found in house dust, drinking water, and food (Supplementary Table S1), including beverages, leafy green vegetables, fish, and dairy milk [165–168]. Nitrate and nitrite are found in the diet, especially vegetables, fruits, cured or processed meats, fish, dairy products, beer, and cereals [169] and in drinking water (Supplementary Table S1). Thiocyanate exposure occurs via the diet and from active and passive smoking because cyanide in cigarette smoke is metabolized to thiocyanate [170]. The half-life of perchlorate in humans is ~8 h, and the majority of perchlorate is excreted in urine [171]. Besides urine, perchlorate can also be measured in saliva and serum [172, 173] as well as in breast milk [174]. Concentrations of perchlorate and nitrate among adolescents have been stable over time, while thiocyanate concentrations are decreasing (Supplementary Table S1).

Pyrethroids

Pyrethroids are included in over 3500 US EPA-registered pesticide products used in and around homes, on pets, in mosquito control, and in agriculture [175]. Indoor use has increased since 2001, when the US EPA banned the use of OPs in household products [176]. Exposure can occur from residues on food resulting from agricultural applications and as a result of indoor applications, with exposure primarily occurring through nondietary and dermal exposure pathways relevant to young children [177]. Several pyrethroids have been detected in house dust and food (Supplementary Table S1). Pyrethroid pesticides have a short half-life in the body, and metabolites are eliminated in the urine [115]. The most common measure of exposure for pyrethroids is 3-phenoxybenzoic acid, a common metabolite to six synthetic pyrethroids, and thus not compound specific. Three of four pyrethroid metabolites biomonitored by NHANES were commonly detected in adolescents (Supplementary Table S1).

Well-characterized

This group includes metals/metalloids and tobacco biomarkers. Exposure to these chemicals and their effects on child health are well-characterized in the literature, and ECHO cohorts have a significant amount of extant biomonitoring data offering rich opportunities to assess outstanding questions. Limited additional biomonitoring in ECHO may be warranted to address certain research questions, control for co-pollutant confounding, or study exposure mixtures.

Metals and metalloids

Many chemical elements, including copper (Cu), zinc (Zn), cobalt (Co), manganese (Mn), selenium (Se), and molybdenum (Mo), are considered essential at "trace" levels for normal healthy growth. Others such as lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As) play no biological role, and trace exposure levels may cause adverse health effects [178, 179]. Primary sources of exposure include ingestion through drinking water or diet, inhalation, and dermal contact. As and Hg have shorter biological half-lives compared with Pb and Cd, which bioaccumulate in bone and kidneys, respectively. Further, the toxicity of some elements depends on chemical speciation. Thus, speciation analysis may be crucial to accurately assess the risk of toxicity of certain elements (e.g., As and Hg) [179–181]. The estimated time window of exposure captured varies and depends on the biospecimen used and element of interest (e.g., As in urine is a short-term biomarker, whereas Cd in urine is a long-term biomarker) [182, 183]. Whole blood is typically used to measure many elements, including Co, Cd, Pb, Mn, and Hg, while serum is more commonly used for Cu, Se, and Zn [180, 181, 184–186]. The 29 biomarkers of metals or metalloids measured by NHANES suggest that concentrations among adolescents have remained stable or decreased over time (Supplementary Table S1). Nevertheless, exposures during susceptible periods of early life remain less well-characterized. Emerging methods such as analysis of metals in teeth [187] may help to inform remaining knowledge gaps regarding exposure histories.

Tobacco biomarkers

Exposure to secondhand tobacco smoke is the major source of involuntary tobacco smoke exposure in children. Thirdhand tobacco smoke (i.e., the material left on dust or surfaces) is another source, but levels are far lower [188]. The most extensively used biomarkers of children's exposure to tobacco smoke are cotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) [189, 190]. Cotinine is the major metabolite of nicotine, the primary addictive substance in tobacco products [191]. The half-life of cotinine is longer than that of nicotine, which makes it a more suitable biomarker of exposure than nicotine itself [191]. 3′-Hydroxycotinine, a metabolite of nicotine and cotinine, has also been used as a biomarker of secondhand smoke exposure, but less frequently [192]. NNAL is a major and persistent metabolite of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [190]. NNAL is a nearly ideal biomarker of tobacco smoke exposure because it is completely tobacco specific and has a relatively long half-life in humans. However, NNAL is not found in users of nicotine replacement products or e-cigarettes and should not be used as a biomarker of those exposures. Urine and serum are the most common matrices for measurement of NNAL and cotinine, although measures have also been taken in hair, nails, and saliva [193]. Studies demonstrate a strong correlation between levels of NNAL and cotinine in urine [194]. In NHANES, cotinine concentrations among adolescents have declined over time (Supplementary Table S1).

Low detection

This group includes DBPs, fungicides, and herbicides that are unlikely to have significant exposures among ECHO participants based on low prevalence of detection in NHANES. While ECHO-wide biomonitoring of these chemicals is not warranted, targeted measurement may be important for vulnerable or highly exposed subgroups within ECHO or in other studies.

DBPs

DBPs, or trihalomethanes, are formed by the interaction of chlorine or bromine with organic materials present in water during drinking water treatment [195]. General population exposure to DBPs occurs primarily through the ingestion of chlorinated water and inhalation of water vapor from chlorinated drinking water and swimming pools; dermal absorption can also occur during bathing and swimming [196–198]. DBPs are metabolized to carbon dioxide and exhaled within a few hours, and a small amount is eliminated unchanged in urine. The concentrations of blood DBPs reflect recent exposure, as elimination half-lives for these chemicals are less than 4 h [196, 198]. Owing to their high volatility, biomonitoring of DBPs is difficult, and water sampling is often used as a proxy for exposure. Measurement of DBPs in biological samples requires precautions during sample collection and analysis such as appropriate sample containers and rapid sample analysis. The geometric mean blood concentrations of all four DBPs measured in the 2015–2016 NHANES were below the limit of detection (LOD) among adolescents [11].

Fungicides and herbicides

Exposure to fungicides and herbicides can occur through contact with skin, inhalation, and ingestion. Various fungicides and herbicides are present in ambient, personal, or indoor air, as well as house dust, drinking water, and food (Supplementary Table S1). Urine has been the preferred matrix for monitoring, although other samples are feasible for determination of exposure during pregnancy, including amniotic fluid [199, 200]. These compounds are generally short-lived in vivo and are not persistent. NHANES has biomonitored four fungicides, three herbicides, and 17 sulfonyl urea herbicides (see Supplementary Table S1). With the exception of 2,4-dichlorophenoxyacetic acid (2,4-D), geometric mean urinary concentrations were below the LOD for all monitoring periods; these fungicides and herbicides are no longer measured in the ongoing NHANES survey [11]. The cross-sectional sampling strategy used by NHANES may not be optimal for detecting extensive seasonal exposures, which may occur in rural communities with agricultural exposures. In addition, other fungicides or herbicides not previously included in NHANES may be relevant for study in ECHO [25].

Legacy

We categorized OCPs, PBDEs, and PCBs as legacy chemicals for which exposures are on the decline, health impacts have already been demonstrated, and significant confounding is unlikely. For some of these chemicals, like PBDEs, additional children's health research is warranted and can be conducted using extant ECHO biomonitoring data. For other chemicals, additional biomonitoring in ECHO is not recommended given that assays are expensive and challenging, require a large sample volume, and typically have a low detection frequency.

OCPs

OCPs are a class of persistent pesticides historically used against a variety of pests. Use of certain OCPs, such as dichlorodiphenyltrichloroethane, was banned or restricted in the United States beginning in the 1970s, though use of other OCPs for agricultural purposes continued into the 1990s and early 2000s [115]. Relevant routes of exposure for pregnant women, infants, and children include ingestion of contaminated foods (particularly fatty fish given bioaccumulation and biomagnification in the food chain), breast milk, contaminated soil, and house dust [201]. OCPs have been found in environmental media, including ambient and indoor air, house dust, drinking water, and food (Supplementary Table S1). OCPs are lipophilic and have long half-lives ranging from 1 to 10 years [202]. OCPs and metabolites can be measured in a variety of biospecimens, including blood (preferred), urine, fat, semen, and breast milk [115]. Levels of most OCPs in the most recent NHANES biomonitoring cycles (including 20 individual chemicals) were below the LOD, with the exception of 4,4′-dichlorodiphenyldichloroethylene, gamma-hexachlorocyclohexane, and *trans*-nonachlor (Supplementary Table S1).

PBDEs

PBDEs are flame-retardant chemicals that were intentionally added to consumer products including plastics, foams, and textiles to slow ignition. PBDEs were until recently a dominant class of flame retardants, but were phased out of production in the United States in 2004 (pentaBDE, octaBDE) and 2012 (decaBDE) due to concerns about persistence and toxicity [203]. TetraBDE, pentaBDE, and decaBDE have been listed for global elimination by the Stockholm Convention on persistent organic pollutants, to which over 150 countries are signatories [204]. Blood concentrations of PBDEs have declined in the United States following the phaseout but exposure continues, potentially via the use of older consumer products and legacy contamination of the food supply [205]. Routes of exposure to PBDEs include inhalation from indoor air, ingestion of indoor dust, diet [203], and, for infants, breast milk [206]. Dermal absorption from treated furniture may also be a significant route of exposure [207]. PBDEs as a class are considered to be persistent and are typically measured in serum, adjusted for lipid content [208]. NHANES measures 11 PBDEs in pooled serum samples, including five majority detectable chemicals as well as six with medians below the LOD in the 2011–2016 surveys [11].

PCBs

PCBs are a class of chemicals once used in electrical and consumer products as plasticizers, lubricants, insulants, and coolants. The class includes 209 individual congeners that can be further subgrouped according to their chemical properties (e.g., dioxin-like, non-dioxin–like). Despite bans in the United States in 1979 and by the Stockholm Convention in 2001, these chemicals are still detectable in human specimens due to their lipophilic properties and bioaccumulation through the food chain [201]. The primary route of exposure is through ingestion of foods such as fatty fish; infants and young children may also be exposed through breast milk [201]. A large number of PCBs have been detected in ambient air, with a few also found at detectable levels in food and house dust (Supplementary Table S1). These chemicals may be measured in a variety of biological matrices [209], with the preferred biomonitoring

matrix being blood/serum, although concentrations may vary across matrices with higher concentrations noted in plasma than other blood-based matrices [210]. PCBs have long half-lives (between 3 and 9 years, depending on the congener) [211, 212]. A large number of non-dioxin–like PCBs, as well as three dioxin-like PCB congeners, have been measured at detectable levels in human biospecimens in recent NHANES biomonitoring cycles (Supplementary Table S1).

Discussion

ECHO cohorts are collecting a wide array of chemical exposure data through biomonitoring, questionnaires, and environmental monitoring. We identified several key opportunities for advancing the state of the science regarding effects of early life chemical exposures on child development and health. With more than 50,000 mother–child dyads, ECHO will have sufficient statistical power and participant diversity [213] to address many complex questions that cannot be adequately studied in smaller or more homogenous populations. Examples include analyses of exposure mixtures; interactions of chemicals with social, physical, and behavioral stressors; gene–environment interactions; and assessment of health effects in vulnerable populations.

Many of the chemicals discussed above co-occur in the environment or affect a common adverse children's health endpoint [7]. Researchers are increasingly interested in the impact of mixtures of chemicals on health [214, 215], with novel statistical tools being developed for this purpose [216, 217]. ECHO data provide an opportunity to better understand mixture effects from a robust pooled cohort. This is vital to improve our understanding of the determinants of children's health so that we may, ultimately, better inform public health policy and practice. ECHO provides a rare opportunity to better address this budding area in children's environmental health.

While gestation is a highly susceptible period to environmental exposures, preconception and postnatal exposures are also critically important [218]. ECHO's large biorepository with samples collected at key life stages will enable the repeated measurement of chemical exposures to facilitate well-powered analyses for assessing susceptible periods and effects of cumulative exposures from gestation through adolescence using state-of-the-art statistical approaches [219]. Characterizing chemical exposures in early childhood is a unique strength of the ECHO Program given that NHANES does not conduct biomonitoring of children under 3 years of age and has only recently begun measuring exposures among 3–5-year olds. This life stage is particularly relevant as many chemicals are present in house dust and previous studies have shown that early childhood exposures are higher than other age group, likely due to behavioral activities that include crawling and hand-to-mouth behaviors [22]. In the future, continued follow-up of ECHO participants may provide unique opportunities for investigating multigenerational effects of chemical exposures.

In addition to studies and new biomonitoring of the chemical classes discussed in this paper, we recommend expanded nontargeted analyses or suspect screening to identify high-priority chemicals for novel biomonitoring in ECHO cohorts. We previously evaluated chemicals not included in NHANES and recommended 12 pesticides, including glyphosate, and 24 other chemicals (four alternative flame retardants, two alternative plasticizers, three aromatic amines, six environmental phenols, five OPFRs, and four PFASs) as high priority for biomonitoring in ECHO and other studies [25]. We also encourage further validation and implementation of chemical biomarker measurement in alternative matrices. Hair, toenail, and tooth collection at multiple life stages is recommended for ECHO cohorts. These matrices are noninvasive, simple to collect from children, and may provide improved temporal information on exposures.

ECHO cohorts are administering questionnaires to collect exposure-related information that can be used for studies of exposure sources, particularly for emerging chemicals. Identifying contemporary exposure sources is important for identifying individual- and population-level interventions to reduce chemical exposures that impact children's health. Measurement of chemicals in environmental media is another potential opportunity to leverage ECHO data for exposure assessment. Although air, water, and dust sample collection are not part of the ECHO-wide data collection protocol, many cohorts are collecting these samples. Given that dust is a major contributor to child exposure for many of the chemical classes we assessed, we recommend future work leveraging dust samples for chemical exposure assessment in ECHO. For example, dust samples have been used to identify emerging chemicals of concern using nontargeted or suspect screening approaches [220].

ECHO faces several key challenges in studying chemical exposures. Existing data will need to be harmonized, which requires careful consideration of chemical assays performed by different laboratories at various time points. Some issues to be resolved include differences in the parent compounds or metabolites that were measured, matrices of measurement, analytical methods, and levels and frequencies of detection. Furthermore, archived biological samples may not have been collected, processed, or stored in a manner consistent with analysis for agents that were not initially of interest. For nonpersistent chemicals, a single urine sample

during pregnancy or a child developmental stage may not be representative of exposures over those time periods. For these chemicals, differences in number and timing of sample collection as well as measures of urinary dilution will need to be addressed. While there will be variability in exposure levels due to trends in exposure over time or regulatory policies, the ability to describe these temporal trends is a strength of the ECHO Program given that participant birth years span the early 1980s through present day. Overall, harmonization challenges can be overcome through thoughtful study design and statistical methods, as has been demonstrated in previous pooled studies of chemical exposures in US [221–223] and European [224–226] cohorts.

We note several limitations of the existing survey data used to ascertain data availability from ECHO cohorts presented here. We lacked information on whether ECHO cohorts measured several chemical classes biomonitored by NHANES (e.g., insect repellents, carbamate pesticides, and heterocyclic amines), which may be important to study or biomonitor in ECHO and other cohorts. Information was collected from cohorts during 2017–2018 and does not reflect any subsequent plans for biomonitoring using ECHO's CHEAR Program supplement or other funding opportunities. We were not able to include information on participant-level demographic characteristics or sample sizes of participating ECHO cohorts. Our survey data on chemical assays did not include biological matrix or number of assays within each life stage. Nevertheless, we provide a comprehensive and systematic description of current and planned chemical exposure data to inform future research efforts. Finally, we prioritized chemicals predominantly based on exposure considerations. Additional prioritization based on relevance to ECHO's child health focus areas is underway and will provide a more outcomes-centered approach.

Conclusions

With more than 50,000 children from diverse geographic and demographic populations, ECHO represents an unprecedented data resource for addressing complex environmental questions related to children's health in the United States. ECHO investigators are laying the groundwork to tackle such multifaceted problems such as co-pollutant mixtures; interactions of chemicals with social, physical, and behavioral stressors; gene–environment interactions; vulnerable populations; and effects of cumulative exposures throughout early life. To facilitate this research, we reviewed the literature and used an exposure-based grouping framework to summarize opportunities for future research and biomonitoring in ECHO. We recommend new biomonitoring of emerging chemicals including alternative phthalates/plasticizers, OPFRs, perchlorate and other anions, and pyrethroids. We also found that ECHO has rich data for studies of many chemical classes, though additional measurement of ubiquitous (environmental phenols, parabens, phthalates, PFASs, PAHs, and OPs), well-characterized (metals/metalloids and tobacco smoke), or low detection (DBPs, fungicides, and herbicides) chemicals may be necessary to address key knowledge gaps. We highlight the need for nontargeted or suspect screening approaches to identify novel chemicals of concern. Finally, we recommend future work leveraging dust samples for chemical exposure assessment in ECHO given that dust is a major contributor to child exposure for many of the chemical classes we assessed. By leveraging existing data and samples, conducting new biomonitoring, and implementing new approaches, ECHO will support high-impact research to inform programs, policies, and practices to enhance the health of children.

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Compliance with ethical standards

Conflict of interest WEF is a founding partner in EnMed Micro-Analytics, a company that provides heavy metal screening for newborns and children. MSB has worked for ICF International as a paid consultant on the US EPA "IRIS Draft Toxicological Review of PCBs: Effects Other Than Cancer." All other authors declare they have no actual or potential competing financial interests.

Appendix

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