



HHS Public Access

Author manuscript

J Expo Sci Environ Epidemiol. Author manuscript; available in PMC 2020 August 17.

Published in final edited form as:

J Expo Sci Environ Epidemiol. 2020 May ; 30(3): 397–419. doi:10.1038/s41370-020-0211-9.

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

Jessie P. Buckley, PhD^{1,2}, Emily S. Barrett, PhD², Paloma I. Beamer, PhD³, Deborah H. Bennett, PhD⁴, Michael S. Bloom, PhD⁵, Timothy R. Fennell, PhD⁶, Rebecca C. Fry, PhD⁷, William E. Funk, PhD⁸, Ghassan B. Hamra, PhD⁹, Stephen S. Hecht, PhD¹⁰, Kurunthachalam Kannan, PhD^{11,12}, Ramsunder Iyer, PhD⁸, Margaret R. Karagas, PhD¹³, Kristen Lyall, ScD¹⁴, Patrick J. Parsons, PhD^{11,12}, Edo D. Pellizzari, PhD¹⁵, Antonio J. Signes-Pastor, PhD¹³, Anne P. Starling, PhD¹⁶, Aolin Wang, PhD¹⁷, Deborah J. Watkins, PhD¹⁸, Mingyu Zhang, MHS⁹, Tracey J. Woodruff, PhD¹⁷ program collaborators for ECHO

¹Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

²Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, NJ

³Department of Community, Environment and Policy, Zuckerman College of Public Health, University of Arizona, Tucson, AZ

⁴Department of Public Health Sciences, University of California, Davis, CA

⁵Departments of Environmental Health Sciences and Epidemiology & Biostatistics, University at Albany, State University of New York, Albany, NY

⁶Discovery Sciences, RTI International, Research Triangle Park, NC

⁷Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC

⁸Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

⁹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

¹⁰Masonic Cancer Center, University of Minnesota, Minneapolis, MN

¹¹Division of Environmental Health Sciences, Wadsworth Center, New York State Department of Health, Albany, NY

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use:http://www.nature.com/authors/editorial_policies/license.html#terms

Correspondence Jessie P. Buckley, Departments of Environmental Health & Engineering and Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Room W7513A, Baltimore, MD 21205. (410) 502-6150. jessie.buckley@jhu.edu.

Conflicts of interest. WEF is a founding partner in EnMed MicroAnalytics, 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 Polychlorinated Biphenyls (PCBs): Effects Other Than Cancer'. All other authors declare they have no actual or potential competing financial interests.

Supplementary information is available at the *Journal of Exposure Science & Environmental Epidemiology* website.

¹²Department of Environmental Health Sciences, University at Albany, State University of New York, Albany, NY

¹³Department of Epidemiology, Geisel School of Medicine, Dartmouth College, Hanover, NH

¹⁴A.J. Drexel Autism Institute, Drexel University, Philadelphia, PA

¹⁵Fellows Program, RTI International, Research Triangle Park, NC

¹⁶Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO

¹⁷Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, CA

¹⁸Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI

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, non-targeted 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 which 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]. Additionally, chemical manufacturing has grown dramatically over the past 60 years [8], with now nearly 8,000 chemicals manufactured or imported in high amounts (>25,000 pounds per year), equaling about 9 trillion pounds per year in the US [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, 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 to 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 US. 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 [26].

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 2017–2018: recruitment site locations (module 02: Jan. 31, 2018); demographic and other data elements (module 03: Oct. 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 flame retardants (OPFRs), fungicides or herbicides, organochlorine pesticides, 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.

All results summarize the number and proportion of cohorts, not participants, with data as we did not have individual-level information or sample sizes of ECHO cohorts. 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 biomonitoring 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 US, and reported levels in ambient air [27–49], personal air [27, 28, 30–34, 37, 42, 43, 46, 50–55], indoor air [27, 29–31, 33, 34, 37, 39, 41, 42, 45, 46, 49, 56–66], house dust [29, 41, 61, 62, 64, 67–97], drinking water [97–108], or food [97, 104, 108–115]. 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) [26]. For chemicals that were detected in 20% of samples of one medium and monitored but not detected in another medium, we also display the non-detects. For drinking water results reported by the US Department of Agriculture [105], we provide the frequency of detection because levels were given only as a range.

To characterize concentrations and temporal trends in chemicals measured 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 [26]. 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 (Supplemental 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 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 (Figure 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 Supplemental 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 (Supplemental 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 non-targeted or suspect screening approaches to assess chemical exposures in mothers and children.

While each class contains multiple chemicals, we also assessed the potential for multi-class analyses. Thirty cohorts are assessing more than one class of chemicals in mothers, 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 biomonitoring 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 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 non-persistent 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) [116]. Their extensive use in consumer products leads to nearly ubiquitous, though episodic, exposure [117, 118] via diet, dermal absorption, and inhalation. Environmental phenols and parabens can be found in house dust and indoor air (Supplemental Table S1). These chemicals are metabolized and conjugated in the liver

and excreted, with half-lives measured in hours [122]. 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 [122, 123], and more recently in hair [124]. 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 US population [11]. Concentrations of BPA, triclosan, dichlorophenols, and n-propyl paraben declined in adolescents from 1996–2016, whereas benzophenone-3 concentrations increased (Supplemental Table S1). US biomonitoring data also suggest that bisphenol S and F exposures are increasing [125].

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 [116]. Human exposure can occur through ingestion, inhalation, or dermal contact [126]. Phthalates are widely detected in house dust (Supplemental Table S1). Humans rapidly metabolize phthalates, resulting in biological half-lives of less than 24 hours [130]. 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 [130]. 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 child care articles in the US [128, 129]. NHANES biomonitoring suggests that adolescent exposure to certain phthalates (benzyl butyl, di-2-ethyl hexyl, dibutyl, diethyl) is decreasing over time, while exposure to other phthalates (diisobutyl, diisononyl) is increasing (Supplemental Table S1).

Perfluoroalkyl substances (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 [131]. 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 [132] (Supplemental Table S1). Drinking water, breast milk, and household dust are important sources of exposure for infants and toddlers [135]. Since 2000, perfluorooctanoic acid, perfluorooctanesulfonic acid, and several other PFASs were phased out through national voluntary initiatives, due to health and exposure concerns [136, 137] and have been gradually replaced with their shorter-chain homologues [138]. The long-chain PFASs biomonitored by NHANES have estimated half-lives ranging from 2 to 9 years [139]. PFASs have been measured in blood (serum or plasma) but recently hair and nails have been suggested as alternative non-invasive matrices in human biomonitoring for some PFASs [140, 141]. NHANES routinely measures 12 PFASs, a tiny fraction of the estimated >4000 PFASs in commerce [142]. Despite the decreasing levels of perfluorooctanoic acid and

perfluorooctanesulfonic acid over time (Supplemental Table S1), some other long-chain PFASs are still widely detected [11].

Polycyclic aromatic hydrocarbons (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 [143] (Supplemental Table S1). 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 phenanthrene metabolite concentrations are decreasing among adolescents over time, while naphthalene and pyrene metabolites have increased (Supplemental Table S1).

Organophosphorus insecticides (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) [144]. 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 US [145]. Several OPs have been detected in environmental media, primarily food (Supplemental Table S1). Dermal, inhalation, and non-dietary 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 [145]. When ingested, OPs are rapidly metabolized and eliminated in urine [146]. 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 [146, 147]. 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 (Supplemental 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 [148–150]. 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 [148, 151] 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 [152–154]. Indoor dust ingestion is considered to be a major route of OPFR exposure [155], particularly via hand-to-mouth activity in infants and children [156, 157]. Other exposure routes include inhalation of indoor air [158, 159], dermal absorption [68, 160], and dietary intake [161, 162]. Chemicals in this class have been detected in indoor air, drinking water, and food, with high levels of some OPFRs in house dust (Supplemental Table S1). Most OPFRs are considered non-persistent, and human exposure is quantified via metabolites measured in urine [164–166]. It is currently unknown whether adverse biological effects may result from exposure to metabolites as compared to the parent compounds [167, 168]. Several of the eight OPFRs included in NHANES were detected among adolescents (Supplemental 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 [169].

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 [170]. Perchlorate has been found in house dust, drinking water, and food (Supplemental Table S1), including beverages, leafy green vegetables, fish, and dairy milk [171–174]. Nitrate and nitrite are found in the diet, especially vegetables, fruits, cured or processed meats, fish, dairy products, beer, and cereals [175] and in drinking water (Supplemental Table S1). Thiocyanate exposure occurs via the diet and from active and passive smoking because cyanide in cigarette smoke is metabolized to thiocyanate [176]. The half-life of perchlorate in humans is approximately eight hours, and the majority of perchlorate is excreted in urine [177]. Besides urine, perchlorate can also be measured in saliva and serum [178, 179] as well as in breast milk [180]. Concentrations of perchlorate and nitrate among adolescents have been stable over time, while thiocyanate concentrations are decreasing (Supplemental Table S1).

Pyrethroids.—Pyrethroids are included in over 3,500 US EPA-registered pesticide products used in and around homes, on pets, in mosquito control, and in agriculture [181]. Indoor use has increased since 2001, when the US EPA banned the use of OPs in household products [182]. Exposure can occur from residues on food resulting from agricultural applications and as a result of indoor applications, with exposure primarily occurring through non-dietary and dermal exposure pathways relevant to young children [183]. Several

pyrethroids have been detected in house dust and food (Supplemental Table S1). Pyrethroid pesticides have a short half-life in the body, and metabolites are eliminated in the urine [116]. 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 biomonitoring by NHANES were commonly detected in adolescents (Supplemental 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 [184, 185]. Primary sources of exposure include ingestion through drinking water or diet, inhalation, and dermal contact. As and Hg have shorter biological half-lives compared to 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) [185–187]. 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) [188, 189]. 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 [186, 187, 190–192]. The 29 biomarkers of metals or metalloids measured by NHANES suggest that concentrations among adolescents have remained stable or decreased over time (Supplemental Table S1). Nevertheless, exposures during susceptible periods of early life remain less well-characterized. Emerging methods such as analysis of metals in teeth [193] 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. Third-hand tobacco smoke (i.e., the material left on dust or surfaces) is another source, but levels are far lower [194]. The most extensively used biomarkers of children’s exposure to tobacco smoke are cotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) [196, 197]. Cotinine is the major metabolite of nicotine, the primary addictive substance in tobacco products [198]. The half-life of cotinine is longer than that of nicotine, which makes it a more suitable biomarker of exposure than nicotine itself [198]. 3’-Hydroxycotinine, a metabolite of nicotine and cotinine, has also been used as a biomarker of secondhand smoke exposure, but less frequently [199]. NNAL is a major and persistent metabolite of the tobacco-specific lung

carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [197]. 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 [200]. Studies demonstrate a strong correlation between levels of NNAL and cotinine in urine [202]. In NHANES, cotinine concentrations among adolescents have declined over time (Supplemental 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.

Disinfection byproducts (DBPs).—DBPs, or trihalomethanes, are formed by the interaction of chlorine or bromine with organic materials present in water during drinking water treatment [203]. 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 [204–206]. 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 hours [204, 206]. 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 (Supplemental Table S1). Urine has been the preferred matrix for monitoring, although other samples are feasible for determination of exposure during pregnancy, including amniotic fluid [209, 210]. 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 Supplemental 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 [26].

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.

Organochlorine pesticides (OCPs).—OCPs are a class of persistent pesticides historically used against a variety of pests. Use of certain OCPs, such as dichlorodiphenyltrichloroethane (DDT), was banned or restricted in the US beginning in the 1970s, though use of other OCPs for agricultural purposes continued into the 1990s and early 2000s [116]. 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), breastmilk, contaminated soil, and house dust [211]. OCPs have been found in environmental media, including ambient and indoor air, house dust, drinking water, and food (Supplemental Table S1). OCPs are lipophilic and have long half-lives ranging from 1–10 years [212]. OCPs and metabolites can be measured in a variety of biospecimens, including blood (preferred), urine, fat, semen, and breastmilk [116]. 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 (Supplemental Table S1).

Polybrominated diphenyl ethers (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 US in 2004 (pentaBDE, octaBDE) and 2012 (decaBDE) due to concerns about persistence and toxicity [213]. 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 [214]. Blood concentrations of PBDEs have declined in the US following the phase-out but exposure continues, potentially via the use of older consumer products and legacy contamination of the food supply [215]. Routes of exposure to PBDEs include inhalation from indoor air, ingestion of indoor dust, diet [213], and, for infants, breast milk [217]. Dermal absorption from treated furniture may also be a significant route of exposure [218]. PBDEs as a class are considered to be persistent and are typically measured in serum, adjusted for lipid content [219]. 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].

Polychlorinated biphenyls (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 sub-grouped according to their chemical properties (e.g., dioxin-like, non-dioxin-like). Despite bans in the US 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 [211]. The primary route of exposure is through ingestion of foods such as fatty fish; infants and young children may also be exposed through breastmilk [211]. A large number of PCBs have been detected in ambient air, with a few also found at detectable levels in food and house dust (Supplemental Table S1). These chemicals may be measured in a variety of biological matrices [220], 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 [221]. PCBs have long half-lives (between 3–9 years, depending on the congener) [222, 223]. 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 (Supplemental 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 [224] 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 [225, 226], with novel statistical tools being developed for this purpose [227, 228]. 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, pre-conception and postnatal exposures are also critically important [229]. 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 [230]. 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 non-targeted 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 (4 alternative flame retardants, 2 alternative plasticizers, 3 aromatic amines, 6 environmental phenols, 5 OPFRs, and 4 PFASs) as high priority for biomonitoring in ECHO and other studies [26]. 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 non-targeted or suspect screening approaches [231].

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 non-persistent 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 [232–234] and European [235–237] 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 biomonitoring 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 US. ECHO investigators are laying the groundwork to tackle such multifaceted problems 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 (disinfection byproducts, fungicides, and herbicides) chemicals may be necessary to address key knowledge gaps. We highlight the need for non-targeted 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank David Balshaw (National Institute of Environmental Health Sciences) for insightful contributions and Emma Alquist and Timothy Shields (ECHO Data Analysis Center, Johns Hopkins Bloomberg School of Public Health) for technical assistance.

Funding

Research reported in this publication was supported by the Environmental influences on Child Health Outcomes (ECHO) program, Office of The Director, National Institutes of Health, under Award Numbers U2COD023375 (Coordinating Center), U24OD023382 (Data Analysis Center, Buckley, Hamra, Pellizzari, Zhang), UG3OD023305, UH3OD023305, UG3OD023271, UH3OD023271, and UG3OD023349, UH3OD023349 (Barrett), UG3OD023282 (Beamer), UG3OD023365, UH3OD023365 (Bennett), UG3OD023316 (Bloom), U2CES026544 (Fennell), UG3OD023348, UH3OD023348 (Fry), U24OD023319-01 (Person-Reported Outcomes Core, Funk, Iyer), 3U2CES026533-01S1-3 (Hecht), U2CES026542-01 (Kannan, Parsons), UG3OD023275, UH3OD023275 (Karagas, Signes-Pastor), UG3OD023342, UH3OD023342 and 1U2COD023375-02 (Lyll), UG3OD023248, UH3OD023248 (Starling), UG3OD023251, UH3OD023251 (Watkins), UG3OD023272, UH3OD023272 (Wang, Woodruff). This research was also supported by NIEHS P01ES022841 (Woodruff), NIEHS R01ES027051 (Woodruff), USEPA RD 83543301 (Woodruff), U2CES026542-01 (Kannan, Parsons), P30 ES006694 (Beamer), NIEHS P30 ES005022 (Barrett), NIDDK R01DK076648 (Starling), NIEHS R00ES025817 (Starling), NIEHS P01ES022832 (Karagas), and USEPA RD-83544201 (Karagas). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix

The authors wish to thank our ECHO colleagues, the medical, nursing and program staff, as well as the children and families participating in the ECHO cohorts. We also acknowledge the contributions of the ECHO program collaborators.

ECHO Components

Coordinating Center: Duke Clinical Research Institute, Durham, North Carolina: Smith PB, Newby KL, Benjamin DK

Data Analysis Center: Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland: Jacobson LP; Research Triangle Institute, Durham, North Carolina: Parker CB
 Person-Reported Outcomes Core: Northwestern University, Evanston, Illinois: Gershon R, Cella D
 Children's Health and Exposure Analysis Resource: Icahn School of Medicine at Mount Sinai, New York City, New York: Teitelbaum SL; Wright RO; Wadsworth Center, Albany, New York: Aldous, KM, RTI International, Research Triangle Park, North Carolina: Fennell T; University of Minnesota, Minneapolis, Minnesota: Hecht SS, Peterson L; Westat, Inc., Rockville, Maryland: O'Brien B

Idea States Pediatric Clinical Trials Network (ISPCTN): *University of Arkansas for Medical Sciences, Little Rock*: Lee JY, Snowden J

ISPCTN Data Coordinating and Operations Center: University of Arkansas for Medical Sciences, Little Rock

Pediatric Cohorts: See below under ECHO cohort awardees and cohort sites

ECHO Cohort Awardees

- Albert Einstein College of Medicine, Bronx, New York: Aschner JL

- Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio: Poindexter B
- Icahn School of Medicine at Mount Sinai, New York, NY: Teitelbaum SL; Stroustrup A; Grennings C; Andra S; Arora M
- University of Buffalo, Buffalo, NY: Reynolds AM
- University of Florida, Gainesville, FL: Hudak M
- University of Rochester, Rochester, NY: Pryhuber G
- Vanderbilt University Medical Center: Nashville, Tennessee: Moore P
- Wake Forest University Health Sciences, Winston Salem, NC: Washburn L; Helderman J
- Avera McKennan Hospital and University Health Center, Sioux Falls, South Dakota: Elliott AJ
 - The Trustees of Columbia University in the City of New York: Fifer W; Isler J; Myers M; Perzanowski M; Rauh V
- Brigham & Women’s Hospital, Boston, Massachusetts: Litonjua AA, Weiss ST
- Columbia University, New York, New York: Perera FP, Herbstman JB
- Dartmouth College, Hanover, New Hampshire: Karagas MR
- Pennsylvania State University, State College, Pennsylvania: Newschaffer CJ
 - Children’s Hospital of Philadelphia, Pennsylvania: Schultz RT
 - Johns Hopkins University, Baltimore, Maryland: Volk HE
 - Kaiser Permanente, Oakland, California: Croen LA
 - Kennedy Krieger Institute, Baltimore, Maryland: Landa RJ
 - University of California, Davis: Schmidt RJ, Ozonoff S
 - University of North Carolina, Chapel Hill: Piven J
 - University of Washington, Seattle: Dager SR; Mayock D
- Emory University, Atlanta, Georgia: Dunlop AL, Brennan PA, Corwin EJ
- Harvard Pilgrim Health Care, Boston, Massachusetts: Oken E, Kleinman KP
- Icahn School of Medicine at Mount Sinai, Boston, Massachusetts: Wright RJ, Wright RO
 - Boston Children’s Hospital: Enlow MB
- Kaiser Permanente, Oakland, California: Ferrara A, Croen LA
- Massachusetts General Hospital, Boston: Camargo CA
- Michigan State University, East Lansing, Michigan: Paneth N, Elliott MR, McKane P, Kerver JM, Ruden DM

- Henry Ford Health System, Detroit, MI: Barone C
- Wayne State University, Detroit, MI: Douglas, RM
- Memorial Hospital of Rhode Island, Pawtucket: Deoni S, D’Sa VA
 - Brown University, Providence, RI: Braun J
 - Johns Hopkins University School of Medicine, Baltimore, MD: Carnell S
 - The Translational Genomics Research Institute, Phoenix AZ: Huentelman, M
 - University of California, Davis: Mueller HG; Wang JL
 - University of Colorado Boulder: LeBourgeois M
 - Wellesley College, Wellesley, MA: Klepac-Ceraj, V
 - Women & Infants Hospital, Providence RI: Matteson K
- New York State Psychiatric Institute at Columbia University, New York: Duarte CS, Canino GJ, Monk CE, Posner JE
- New York University, New York, New York: Blair CB
- New York University School of Medicine, New York, New York: Trasande L
- Northeastern University, Boston, Massachusetts: Alshawabkeh AN
- Oregon Health & Science University, Portland, Oregon: McEvoy CT, Spindel ER
- University of California, Davis: Hertz-Picciotto I, Bennett DH, Schweitzer JB
- University of Colorado Anschutz Medical Campus, Aurora, Colorado: Dabelea D
- University of Illinois, Urbana: Schantz SL
 - University of California, San Francisco: Woodruff T
- University of New Mexico, Albuquerque: Lewis JL
- University of North Carolina, Chapel Hill: O’Shea M, Fry R
- University of Oregon, Eugene: Leve LD
 - George Washington University, Washington D.C.: Ganiban JM
 - Penn State, University Park, Pennsylvania: Neiderhiser JM
- University of Pittsburgh, Pennsylvania: Hipwell AE, Keenan KE
- University of Rochester, New York: O’Connor TG, Buss C, Miller RK, Wadhwa PD
 - University of Pittsburgh. Magee-Women’s Hospital, Pennsylvania: Simhan HN

- University of Southern California, Los Angeles: Gilliland FD, Breton CV
- University of Utah, Salt Lake City: Stanford JB, Clark EB, Porucznik C
- University of Washington, Seattle: Karr C, Sathyanarayana S
 - University of California, San Francisco: Lewinn KZ; Bush NR
 - University of Tennessee Health Sciences Center: Tylavsky FA
- University of Wisconsin-Madison: Gern J
 - Boston University: O'Connor G
 - Brigham & Women's Hospital, Boston, Massachusetts: Gold D
 - Columbia University, New York, NY: Miller R
 - Henry Ford Health System, Detroit, Michigan: Johnson C; Ownby D.; Zoratti E.
 - John's Hopkins University: Wood R
 - Marshfield Clinic Research Foundation, Marshfield, WI: Bendixsen C
 - University of Cincinnati: Hershey GK
 - Vanderbilt University Medical Center, Nashville, Tennessee: Hartert T
 - Washington University, St. Louis, MO: Bacharier L
- Women & Infants Hospital of Rhode Island, Providence: Lester B
 - Emory University, Atlanta, Georgia: Marsit CJ

References

1. American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women, American Society for Reproductive Medicine Practice Committee, The University of California San Francisco Program on Reproductive Health and the Environment Exposure to toxic environmental agents. No. 575. The American College of Obstetricians and Gynecologists: Washington, D.C., 2013.
2. Diamanti-Kandarakis E, Bourguignon J-P, Giudice LC, Hauser R, Prins GS, Soto AM et al. Endocrine-disrupting chemicals: an Endocrine Society Scientific Statement. *Endocr Rev* 2009; 30: 293–342. [PubMed: 19502515]
3. President's Cancer Panel. Reducing Environmental Cancer Risk: What We Can Do Now. U.S. Department of Health and Human Services Bethesda, MD, 2010.
4. American Academy of Pediatrics. Pediatric Environmental Health. American Academy of Pediatrics Council on Environmental Health: Itasca, IL, 2018.
5. ACOG Committee Opinion No. 575. Exposure to toxic environmental agents. *Obstet Gynecol* 2013; 122: 931–935. [PubMed: 24084567]
6. National Research Council. Science and Decisions: Advancing Risk Assessment. National Academies Press: Washington, D.C, 2009.
7. National Research Council. Phthalates and Cumulative Risk Assessment: The Task Ahead. National Academies Press: Washington, D.C, 2008.
8. OECD (Organisation for Economic Co-operation and Development). 40 Years of Chemical Safety at OECD: Quality and Efficiency, 2011.

9. EPA (US Environmental Protection Agency). 2016 Chemical Data Reporting Results. 2016 <https://www.epa.gov/chemical-data-reporting/2016-chemical-data-reporting-results>.
10. Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. *Environ Health Perspect* 2011; 119: 878–885. [PubMed: 21233055]
11. CDC (U.S. Centers for Disease Control and Prevention). Fourth National Report on Human Exposure to Environmental Chemicals-Updated Tables, January 2019. U.S Centers for Disease Control and Prevention: Atlanta, GA, 2019.
12. Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect* 2005; 113:1056–1061. [PubMed: 16079079]
13. Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S et al. The Navigation Guide - evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. *Environ Health Perspect* 2014; 122: 1040–1051. [PubMed: 24968389]
14. Lederman SA, Jones RL, Caldwell KL, Rauh V, Sheets SE, Tang D et al. Relation between cord blood mercury levels and early child development in a World Trade Center cohort. *Environ Health Perspect* 2008; 116: 1085–1091. [PubMed: 18709170]
15. Herbstman JB, Sjödin A, Kurzon M, Lederman SA, Jones RS, Rauh V et al. Prenatal exposure to PBDEs and neurodevelopment. *Environ Health Perspect* 2010; 118: 712–719. [PubMed: 20056561]
16. Chevrier J, Eskenazi B, Holland N, Bradman A, Barr DB. Effects of exposure to polychlorinated biphenyls and organochlorine pesticides on thyroid function during pregnancy. *Am J Epidemiol* 2008; 168: 298–310. [PubMed: 18550560]
17. Zota AR, Rudel RA, Morello-Frosch RA, Brody JG. Elevated house dust and serum concentrations of PBDEs in California: unintended consequences of furniture flammability standards? *Environ Sci Technol* 2008; 42: 8158–8164. [PubMed: 19031918]
18. Nelson JW, Scammell MK, Hatch EE, Webster TF. Social disparities in exposures to bisphenol A and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003–2006. *Environ Health* 2012; 11: 10. [PubMed: 22394520]
19. Calafat AM, Wong LY, Kuklennyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. *Environ Health Perspect* 2007; 115: 1596–1602. [PubMed: 18007991]
20. Calafat AM, Ye X, Wong L-Y, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. *Environ Health Perspect* 2008; 116: 39–44. [PubMed: 18197297]
21. Sjödin A, Wong LY, Jones RS, Park A, Zhang Y, Hodge C et al. Serum concentrations of polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyl (PBB) in the United States population: 2003–2004. *Environ Sci Technol* 2008; 42: 1377–1384. [PubMed: 18351120]
22. EPA (US Environmental Protection Agency). Child-Specific Exposure Factors Handbook. National Center for Environmental Assessment Washington, DC, 2002.
23. National Institutes of Health (NIH). Environmental influences on Child Health Outcomes (ECHO)-wide Cohort Data Collection Protocol, Version 1.2. 2018 <https://echochildren.org/wp-content/uploads/2019/06/ECHO-Wide-Cohort-Data-Collection-Protocol-Approved-v01.201.pdf>.
24. Wright RO, Teitelbaum S, Thompson C, Balshaw D, Network C. The child health exposure analysis resource as a vehicle to measure environment in the environmental influences on child health outcomes program. *Curr Opin Pediatr* 2018; 30: 285–291. [PubMed: 29406438]
25. Wang A, Padula A, Sirota M, Woodruff TJ. Environmental influences on reproductive health: the importance of chemical exposures. *Fertil Steril* 2016; 106: 905–929. [PubMed: 27513554]
26. Pellizzari ED, Woodruff TJ, Boyles RR, Kannan K, Beamer PI, Buckley JP et al. Identifying and Prioritizing Chemicals with Uncertain Burden of Exposure: Opportunities for Biomonitoring and Health-Related Research. *Environ Health Perspect* In press; doi 10.1289/EHP5133.
27. Adgate JL, Church TR, Ryan AD, Ramachandran G, Fredrickson AL, Stock TH et al. Outdoor, indoor, and personal exposure to VOCs in children. *Environ Health Perspect* 2004; 112: 1386–1392. [PubMed: 15471730]

28. Choi H, Perera F, Pac A, Wang L, Flak E, Mroz E et al. Estimating individual-level exposure to airborne polycyclic aromatic hydrocarbons throughout the gestational period based on personal, indoor, and outdoor monitoring. *Environ Health Perspect* 2008; 116: 1509–1518. [PubMed: 19057704]
29. Chuang JC, Callahan PJ, Lyu CW, Wilson NK. Polycyclic aromatic hydrocarbon exposures of children in low-income families. *J Expo Anal Environ Epidemiol* 1999; 9: 85–98. [PubMed: 10321348]
30. Andrew Clayton C, Pellizzari ED, Whitmore RW, Quackenboss JJ, Adgate J, Sefton K. Distributions, associations, and partial aggregate exposure of pesticides and polynuclear aromatic hydrocarbons in the Minnesota Children's Pesticide Exposure Study (MNCPEs). *J Expo Anal Environ Epidemiol* 2003; 13: 100–111. [PubMed: 12679790]
31. Delfino RJ, Staimer N, Tjoa T. Personal endotoxin exposure in a panel study of school children with asthma. *Environ Health* 2011; 10: 69. [PubMed: 21810249]
32. Delfino RJ, Staimer N, Tjoa T, Gillen D, Kleinman MT, Sioutas C et al. Personal and ambient air pollution exposures and lung function decrements in children with asthma. *Environ Health Perspect* 2008; 116: 550–558. [PubMed: 18414642]
33. Geyh AS, Xue J, Ozkaynak H, Spengler JD. The Harvard Southern California Chronic Ozone Exposure Study: assessing ozone exposure of grade-school-age children in two Southern California communities. *Environ Health Perspect* 2000; 108: 265–270.
34. Gordon SM, Callahan PJ, Nishioka MG, Brinkman MC, O'Rourke MK, Lebowitz MD et al. Residential environmental measurements in the national human exposure assessment survey (NHEXAS) pilot study in Arizona: preliminary results for pesticides and VOCs. *J Expo Anal Environ Epidemiol* 1999; 9: 456–470. [PubMed: 10554148]
35. Hoh E, Hites RA. Brominated flame retardants in the atmosphere of the East-Central United States. *Environ Sci Technol* 2005; 39: 7794–7802. [PubMed: 16295839]
36. Kim JH, Stevens RC, MacCoss MJ, Goodlett DR, Scherl A, Richter RJ et al. Identification and characterization of biomarkers of organophosphorus exposures in humans In: Reddy S (ed) *Paraoxonases in Inflammation, Infection, and Toxicology*. Humana Press: New York, 2010, pp 61–71.
37. Kinney PL, Chillrud SN, Ramstrom S, Ross J, Spengler JD. Exposures to multiple air toxics in New York City. *Environ Health Perspect* 2002; 110 (Suppl 4): 539–546. [PubMed: 12194883]
38. La Guardia MJ, Schreder ED, Uding N, Hale RC. Human indoor exposure to airborne halogenated flame retardants: influence of airborne particle size. *Int J Environ Res Public Health* 2017; 14: 507.
39. Lee T, Grinshpun SA, Martuzevicius D, Adhikari A, Crawford CM, Reponen T. Culturability and concentration of indoor and outdoor airborne fungi in six single-family homes. *Atmos Environ (1994)* 2006; 40: 2902–2910. [PubMed: 18458748]
40. Liou PJ, Fan Z, Zhang J, Georgopoulos P, Wang SW, Ohman-Strickland P et al. Personal and Ambient Exposures to Air Toxics in Camden, New Jersey. Health Effects Research Institute: Boston, MA, 2011 Report no.: 1041–5505.
41. O'Rourke MK, Van de Water PK, Jin S, Rogan SP, Weiss AD, Gordon SM et al. Evaluations of primary metals from NHEXAS Arizona: distributions and preliminary exposures. National Human Exposure Assessment Survey. *J Expo Anal Environ Epidemiol* 1999; 9: 435–445. [PubMed: 10554146]
42. Payne-Sturges DC, Burke TA, Breyse P, Diener-West M, Buckley TJ. Personal exposure meets risk assessment: a comparison of measured and modeled exposures and risks in an urban community. *Environ Health Perspect* 2004; 112: 589–598. [PubMed: 15064166]
43. Ryan PH, Brokamp C, Fan ZH, Rao MB. Analysis of personal and home characteristics associated with the elemental composition of PM_{2.5} in indoor, outdoor, and personal air in the RIOPA Study. *Res Rep Health Eff Inst* 2015 3–40. [PubMed: 26934775]
44. Sheldon L, Clayton A, Keever J, Perritt R, Whitaker D. PTEAM: Monitoring of Phthalates and PAHs in Indoor and Outdoor Air Samples in Riverside, California. Research Triangle Institute, Durham, NC, 1992 Report no.: No. PB-93–205649/XAB.

45. Shendell DG, Winer AM, Stock TH, Zhang L, Zhang JJ, Maberti S et al. Air concentrations of VOCs in portable and traditional classrooms: results of a pilot study in Los Angeles County. *J Expo Anal Environ Epidemiol* 2004; 14: 44–59. [PubMed: 14726944]
46. Suh H, Koutrakis P, Chang L-T. Characterization of the composition of personal, indoor, and outdoor particulate exposures. California Air Resources Board: Sacramento, CA, 2003 <https://ww3.arb.ca.gov/research/apr/past/98-330.pdf>.
47. Wilson NK, Chuang JC, Morgan MK, Lordo RA, Sheldon LS. An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare. *Environ Res* 2007; 103: 9–20. [PubMed: 16750524]
48. Venier M, Audy O, Vojta Š, Be anová J, Romanak K, Melymuk L et al. Brominated flame retardants in the indoor environment—Comparative study of indoor contamination from three countries. *Environ Int* 2016; 94: 150–160. [PubMed: 27248661]
49. Wilson NK, Chuang JC, Lyu C. Levels of persistent organic pollutants in several child day care centers. *J Expo Anal Environ Epidemiol* 2001; 11: 449–458. [PubMed: 11791162]
50. Batterman S, Su F-C, Li S, Mukherjee B, Jia C. Personal exposure to mixtures of volatile organic compounds: modeling and further analysis of the RIOPA data. *Res Rep Health Eff Inst* 2014 3.
51. Pellizzari ED, Clayton CA, Rodes CE, Mason RE, Piper LL, Fort B et al. Particulate matter and manganese exposures in Indianapolis, Indiana. *J Expo Anal Environ Epidemiol* 2001; 11: 423–440. [PubMed: 11791160]
52. Tonne CC, Whyatt RM, Camann DE, Perera FP, Kinney PL. Predictors of personal polycyclic aromatic hydrocarbon exposures among pregnant minority women in New York City. *Environ Health Perspect* 2004; 112: 754–759. [PubMed: 15121521]
53. Weisel CP. Assessing exposure to air toxics relative to asthma. *Environ Health Perspect* 2002; 110(Suppl 4): 527–537.
54. Whyatt RM, Barr DB, Camann DE, Kinney PL, Barr JR, Andrews HF et al. Contemporary- use pesticides in personal air samples during pregnancy and blood samples at delivery among urban minority mothers and newborns. *Environ Health Perspect* 2003; 111: 749–756. [PubMed: 12727605]
55. Williams MK, Rundle A, Holmes D, Reyes M, Hoepner LA, Barr DB et al. Changes in pest infestation levels, self-reported pesticide use, and permethrin exposure during pregnancy after the 2000–2001 US Environmental Protection Agency restriction of organophosphates. *Environ Health Perspect* 2008; 116: 1681–1688. [PubMed: 19079720]
56. Imm P, Knobeloch L, Buelow C, Anderson HA. Household exposures to polybrominated diphenyl ethers (PBDEs) in a Wisconsin Cohort. *Environ Health Perspect* 2009; 117: 1890–1895. [PubMed: 20049208]
57. Kanazawa A, Saito I, Araki A, Takeda M, Ma M, Saijo Y et al. Association between indoor exposure to semi-volatile organic compounds and building-related symptoms among the occupants of residential dwellings. *Indoor Air* 2010; 20: 72–84. [PubMed: 20028434]
58. Kim JL, Elfman L, Mi Y, Wieslander G, Smedje G, Norback D. Indoor molds, bacteria, microbial volatile organic compounds and plasticizers in schools--associations with asthma and respiratory symptoms in pupils. *Indoor Air* 2007; 17: 153–163. [PubMed: 17391238]
59. Mandin C, Mercier F, Rarnalho O, Lucas JP, Gilles E, Blanchard O et al. Semi-volatile organic compounds in the particulate phase in dwellings: A nationwide survey in France. *Atmospheric Environment* 2016; 136: 82–94.
60. Otake T, Yoshinaga J, Yanagisawa Y. Exposure to phthalate esters from indoor environment. *J Expo Anal Environ Epidemiol* 2004; 14: 524–528. [PubMed: 15039795]
61. Pang Y, MacIntosh DL, Camann DE, Ryan PB. Analysis of aggregate exposure to chlorpyrifos in the NHEXAS-Maryland investigation. *Environ Health Perspect* 2002; 110: 235–240. [PubMed: 11882473]
62. Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. *Environ Sci Technol* 2003; 37: 4543–4553. [PubMed: 14594359]

63. Stapleton HM, Allen JG, Kelly SM, Konstantinov A, Klosterhaus S, Watkins D et al. Alternate and new brominated flame retardants detected in U.S. house dust. *Environ Sci Technol* 2008; 42: 6910–6916. [PubMed: 18853808]
64. Zota AR, Schaidler LA, Ettinger AS, Wright RO, Shine JP, Spengler JD. Metal sources and exposures in the homes of young children living near a mining-impacted Superfund site. *J Expo Sci Environ Epidemiol* 2011; 21: 495–505. [PubMed: 21587306]
65. Xue J, Wan Y, Kannan K. Occurrence of bisphenols, bisphenol A diglycidyl ethers (BADGEs), and novolac glycidyl ethers (NOGEs) in indoor air from Albany, New York, USA, and its implications for inhalation exposure. *Chemosphere* 2016; 151: 1–8. [PubMed: 26923236]
66. Li H, Lydy MJ, You J. Pyrethroids in indoor air during application of various mosquito repellents: Occurrence, dissipation and potential exposure risk. *Chemosphere* 2016; 144: 2427–2435. [PubMed: 26615491]
67. Abb M, Stahl B, Lorenz W. Analysis of brominated flame retardants in house dust. *Chemosphere* 2011; 85: 1657–1663. [PubMed: 21724229]
68. Abou-Elwafa Abdallah M, Pawar G, Harrad S. Human dermal absorption of chlorinated organophosphate flame retardants; implications for human exposure. *Toxicol Appl Pharmacol* 2016; 291: 28–37. [PubMed: 26712466]
69. Abdallah MA, Harrad S. Personal exposure to HBCDs and its degradation products via ingestion of indoor dust. *Environ Int* 2009; 35: 870–876. [PubMed: 19344952]
70. Abraham JH, Gold DR, Dockery DW, Ryan L, Park JH, Milton DK. Within-home versus between-home variability of house dust endotoxin in a birth cohort. *Environ Health Perspect* 2005; 113:1516–1521. [PubMed: 16263505]
71. Bjorklund JA, Sellstrom U, de Wit CA, Aune M, Lignell S, Darnerud PO. Comparisons of polybrominated diphenyl ether and hexabromocyclododecane concentrations in dust collected with two sampling methods and matched breast milk samples. *Indoor Air* 2012; 22: 279–288. [PubMed: 22212125]
72. Boros K, Fortin D, Jayawardene I, Chenier M, Levesque C, Rasmussen PE. Comparison of gastric versus gastrointestinal PBET extractions for estimating oral bioaccessibility of metals in house dust. *Int J Environ Res Public Health* 2017; 14: 92.
73. Castorina R, Butt C, Stapleton HM, Avery D, Harley KG, Holland N et al. Flame retardants and their metabolites in the homes and urine of pregnant women residing in California (the CHAMACOS cohort). *Chemosphere* 2017; 179: 159–166. [PubMed: 28365501]
74. Cowell WJ, Stapleton HM, Holmes D, Calero L, Tobon C, Perzanowski M et al. Prevalence of historical and replacement brominated flame retardant chemicals in New York City homes. *Emerg Contam* 2017; 3: 32–39. [PubMed: 28989983]
75. Deutsche T, Reiter R, Butte W, Heinzow B, Keck T, Riechelmann H. A controlled challenge study on di(2-ethylhexyl) phthalate (DEHP) in house dust and the immune response in human nasal mucosa of allergic subjects. *Environ Health Perspect* 2008; 116: 1487–1493. [PubMed: 19057701]
76. Deziel NC, Colt JS, Kent EE, Gunier RB, Reynolds P, Booth B et al. Associations between self-reported pest treatments and pesticide concentrations in carpet dust. *Environ Health* 2015; 14: 27. [PubMed: 25889489]
77. Dodge LE, Williams PL, Williams MA, Missmer SA, Toth TL, Calafat AM et al. Paternal urinary concentrations of parabens and other phenols in relation to reproductive outcomes among couples from a fertility clinic. *Environ Health Perspect* 2015; 123: 665–671. [PubMed: 25767892]
78. Fang M, Webster TF, Gooden D, Cooper EM, McClean MD, Carignan C et al. Investigating a novel flame retardant known as V6: measurements in baby products, house dust, and car dust. *Environ Sci Technol* 2013; 47: 4449–4454. [PubMed: 23565680]
79. Horick N, Weller E, Milton DK, Gold DR, Li RF, Spiegelman D. Home endotoxin exposure and wheeze in infants: Correction for bias due to exposure measurement error. *Environ Health Perspect* 2006; 114: 135–140. [PubMed: 16393671]
80. Johnson PI, Stapleton HM, Mukherjee B, Hauser R, Meeker JD. Associations between brominated flame retardants in house dust and hormone levels in men. *Sci Total Environ* 2013; 445:177–184. [PubMed: 23333513]

81. Johnson-Restrepo B, Kannan K. An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. *Chemosphere* 2009; 76: 542–548. [PubMed: 19349061]
82. Kubwabo C, Stewart B, Zhu J, Marro L. Occurrence of perfluorosulfonates and other perfluorochemicals in dust from selected homes in the city of Ottawa, Canada. *J Environ Monit* 2005; 7: 1074–1078. [PubMed: 16252056]
83. Lioy PJ, Freeman NCG, Millette JR. Dust: A metric for use in residential and building exposure assessment and source characterization. *Environ Health Perspect* 2002; 110: 969–983. [PubMed: 12361921]
84. Meeker JD, Johnson PI, Camann D, Hauser R. Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men. *Sci Total Environ* 2009; 407: 3425–3429. [PubMed: 19211133]
85. Park JH, Spiegelman DL, Burge HA, Gold DR, Chew GL, Milton DK. Longitudinal study of dust and airborne endotoxin in the home. *Environ Health Perspect* 2000; 108: 1023–1028. [PubMed: 11102291]
86. Robertson GL, Lebowitz M, O'Rourke M, Gordon S, Moschandreas D. The National Human Exposure Assessment Survey (NHEXAS) study in Arizona—introduction and preliminary results. *J Expo Anal Environ Epidemiol* 1999; 9: 427–434. [PubMed: 10554145]
87. Sahlstrom LM, Sellstrom U, de Wit CA, Lignell S, Darnerud PO. Estimated intakes of brominated flame retardants via diet and dust compared to internal concentrations in a Swedish mother-toddler cohort. *Int J Hyg Environ Health* 2015; 218: 422–432. [PubMed: 25850971]
88. Sordillo JE, Alwis UK, Hoffman E, Gold DR, Milton DK. Home characteristics as predictors of bacterial and fungal microbial biomarkers in house dust. *Environ Health Perspect* 2011; 119: 189–195. [PubMed: 20965804]
89. Ward MH, Colt JS, Deziel NC, Whitehead TP, Reynolds P, Gunier RB et al. Residential levels of polybrominated diphenyl ethers and risk of childhood acute lymphoblastic leukemia in California. *Environ Health Perspect* 2014; 122: 1110–1116. [PubMed: 24911217]
90. Wu N, Herrmann T, Paepke O, Tickner J, Hale R, Harvey LE et al. Human exposure to PBDEs: associations of PBDE body burdens with food consumption and house dust concentrations. *Environ Sci Technol* 2007; 41: 1584–1589. [PubMed: 17396645]
91. Dodson RE, Van den Eede N, Covaci A, Perovich LJ, Brody JG, Rudel RA. Urinary biomonitoring of phosphate flame retardants: levels in California adults and recommendations for future studies. *Environ Sci Technol* 2014; 48: 13625–13633.
92. Kubwabo C, Kosarac I, Lalonde K. Determination of selected perfluorinated compounds and polyfluoroalkyl phosphate surfactants in human milk. *Chemosphere* 2013; 91: 771–777. [PubMed: 23498060]
93. Camann D, Colt J, Teitelbaum S, Rudel R, Hart R, Gammon M (eds). Pesticide and PAH distributions in house dust from seven areas of USA. Paper 570 Society of Environmental Toxicology and Chemistry; Nashville, TN, 2000.
94. Larsson K, Berglund M. Children's exposure to chemicals in indoor environments—a literature survey of chemicals in dust. Swedish Environmental Protection Agency, 2018 <http://www.diva-portal.org/smash/get/diva2:1220692/FULLTEXT01.pdf>.
95. Karásková P, Venier M, Melymuk L, Be anová J, Vojta Š, Prokeš R et al. Perfluorinated alkyl substances (PFASs) in household dust in Central Europe and North America. *Environ Int* 2016; 94: 315–324. [PubMed: 27295048]
96. Subedi B, Sullivan KD, Dhungana B. Phthalate and non-phthalate plasticizers in indoor dust from childcare facilities, salons, and homes across the USA. *Environ Pollut* 2017; 230: 701–708. [PubMed: 28728088]
97. Kumarathilaka P, Oze C, Indraratne S, Vithanage M. Perchlorate as an emerging contaminant in soil, water and food. *Chemosphere* 2016; 150: 667–677. [PubMed: 26868023]
98. Benotti M, Fisher S, Terracciano S. Occurrence of pharmaceuticals in shallow ground water of Suffolk County, New York, 2002–2005 U.S. Geological Survey Open-File Report 2006–1297, 2006 <https://pubs.usgs.gov/of/2006/1297/OFR2006-1297.pdf>.

99. Blomquist JD, Denis JM, Cowles J, Hetrick JA, Jones RD, Birchfield NB. Pesticides in selected water-supply reservoirs and finished drinking water, 1999–2000: Summary of results from a pilot monitoring program. US Geological Survey Open-File Report 2001–456: Washington, DC, 2001 <https://pubs.er.usgs.gov/publication/ofr01456>.
100. Hu XC, Andrews DQ, Lindstrom AB, Bruton TA, Schaidler LA, Grandjean P et al. Detection of poly-and perfluoroalkyl substances (PFASs) in US drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. *Environmental science & technology letters* 2016; 3: 344–350. [PubMed: 27752509]
101. Moran MJ, Lapham WW, Rowe BL, Zogorski JS. Volatile organic compounds in ground water from rural private wells, 1986 to 1999. *Journal of the American Water Resources Association* 2004; 40: 1141–1157.
102. Rowe BL, Toccalino PL, Moran MJ, Zogorski JS, Price CV. Occurrence and potential human-health relevance of volatile organic compounds in drinking water from domestic wells in the United States. *Environ Health Perspect* 2007; 115: 1539–1546. [PubMed: 18007981]
103. EPA (US Environmental Protection Agency). Compliance Monitoring Data. Washington, DC: Environmental Protection Agency, 1993-2006 <https://www.epa.gov/dwsixyearreview/six-year-review-3-compliance-monitoring-data-2006-2011>; <https://www.epa.gov/dwsixyearreview/six-year-review-2-contaminant-occurrence-data-1998-2005> and <https://www.epa.gov/dwsixyearreview/six-year-review-1-contaminant-occurrence-data-1993-1997>.
104. USDA (U.S. Department of Agriculture). Pesticide Data Program 2010–2015. Washington, DC: U.S. Department of Agriculture National Organic Program, 2012 <https://www.ams.usda.gov/datasets/pdp>
105. USDA (U.S. Department of Agriculture). Pesticide Data Program: Databases and Annual Summary Reports, 2010–2016. Washington, DC: US Department of Agriculture, 2017 <https://www.ams.usda.gov/datasets/pdp/pdpdata>.
106. Guo J, Romanak K, Westenbroek S, Hites RA, Venier M. Current-use flame retardants in the water of Lake Michigan tributaries. *Environ Sci Technol* 2017; 51: 9960–9969. [PubMed: 28817260]
107. EPA (US Environmental Protection Agency). Six-Year Review 1, 2 and 3 Compliance Monitoring Data. Washington, DC: US Environmental Protection Agency, Office of Water, 2016 <https://www.epa.gov/dwsixyearreview/six-year-review-3-compliance-monitoring-data-2006-2011>; <https://www.epa.gov/dwsixyearreview/six-year-review-2-contaminant-occurrence-data-1998-2005> and <https://www.epa.gov/dwsixyearreview/six-year-review-1-contaminant-occurrence-data-1993-1997>.
108. FDA (US Food and Drug Administration). Total Diet Study Market Baskets 2004–1 through 2005–4. College Park, MD: U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition <https://www.fda.gov/downloads/Food/FoodScienceResearch/TotalDietStudy/UCM291685.pdf>.
109. Roszko M, Szerk A, Szymczyk K, Waszkiewicz-Robak B. PAHs, PCBs, PBDEs and pesticides in cold-pressed vegetable oils. *J Am Oil Chem* 2012; 89: 389–400.
110. Schecter A, Colacino J, Haffner D, Patel K, Opel M, Papke O et al. Perfluorinated compounds, polychlorinated biphenyls, and organochlorine pesticide contamination in composite food samples from Dallas, Texas, USA. *Environ Health Perspect* 2010; 118: 796–802. [PubMed: 20146964]
111. Schecter A, Haffner D, Colacino J, Patel K, Pöpke O, Opel M et al. Polybrominated diphenyl ethers (PBDEs) and hexabromocyclodecane (HBCD) in composite US food samples. *Environ Health Perspect* 2010; 118: 357–362. [PubMed: 20064778]
112. Schecter A, Lorber M, Guo Y, Wu Q, Yun SH, Kannan K et al. Phthalate concentrations and dietary exposure from food purchased in New York State. *Environ Health Perspect* 2013; 121:473–494. [PubMed: 23461894]
113. Schecter A, Pöpke O, Harris TR, Tung K, Musumba A, Olson J et al. Polybrominated diphenyl ether (PBDE) levels in an expanded market basket survey of US food and estimated PBDE dietary intake by age and sex. *Environ Health Perspect* 2006; 114: 1515–1520. [PubMed: 17035135]

114. Schecter A, Szabo DT, Miller J, Gent TL, Malik-Bass N, Petersen M et al. Hexabromocyclododecane (HBCD) stereoisomers in U.S. food from Dallas, Texas. *Environ Health Perspect* 2012; 120: 1260–1264. [PubMed: 22647707]
115. FDA (US Food and Drug Administration). Total Diet Study. U.S. Food and Drug Administration: Washington, DC <https://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/ucm184293.htm>.
116. CDC (U.S. Centers for Disease Control and Prevention). Biomonitoring Summaries. 2017.
117. Ferguson KK, Colacino JA, Lewis RC, Meeker JD. Personal care product use among adults in NHANES: associations between urinary phthalate metabolites and phenols and use of mouthwash and sunscreen. *J Expo Sci Environ Epidemiol* 2017; 27: 326–332. [PubMed: 27168391]
118. Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). *Reprod Toxicol* 2007; 24: 139–177. [PubMed: 17825522]
119. Chen D, Kannan K, Tan H, Zheng Z, Feng YL, Wu Y et al. Bisphenol analogues other than BPA: environmental occurrence, human exposure, and toxicity—a review. *Environ Sci Technol* 2016; 50: 5438–5453. [PubMed: 27143250]
120. Register Federal. Indirect Food Additives: Polymers. Office of the Federal Register NAA. 2012 pp 41899–41902. <https://www.gpo.gov/fdsys/granule/FR-2012-07-17/2012-17366>.
121. FDA (US Food and Drug Administration). Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use. Final rule. *Fed Regist* 2016; 81: 61106–61130.
122. Calafat AM. Contemporary issues in exposure assessment using biomonitoring. *Curr Epidemiol Rep* 2016; 3: 145–153. [PubMed: 28884070]
123. Guidry VT, Longnecker MP, Aase H, Eggesbo M, Zeiner P, Reichborn-Kjennerud T et al. Measurement of total and free urinary phenol and paraben concentrations over the course of pregnancy: assessing reliability and contamination of specimens in the Norwegian Mother and Child Cohort Study. *Environ Health Perspect* 2015; 123: 705–711. [PubMed: 25782115]
124. Rodriguez-Gomez R, Martin J, Zafra-Gomez A, Alonso E, Vilchez JL, Navalon A. Biomonitoring of 21 endocrine disrupting chemicals in human hair samples using ultra-high performance liquid chromatography-tandem mass spectrometry. *Chemosphere* 2017; 168: 676–684. [PubMed: 27839885]
125. Ye X, Wong LY, Kramer J, Zhou X, Jia T, Calafat AM. Urinary concentrations of Bisphenol A and three other bisphenols in convenience samples of U.S. adults during 2000–2014. *Environ Sci Technol* 2015; 49: 11834–11839.
126. Giovanoulis G, Bui T, Xu F, Papadopoulou E, Padilla-Sanchez JA, Covaci A et al. Multipathway human exposure assessment of phthalate esters and DINCH. *Environ Int* 2018; 112: 115–126. [PubMed: 29272775]
127. Gaspar FW, Castorina R, Maddalena RL, Nishioka MG, McKone TE, Bradman A. Phthalate exposure and risk assessment in California child care facilities. *Environ Sci Technol* 2014; 48: 7593–7601. [PubMed: 24870214]
128. Consumer Product Safety Commission. Rule 82 FR 49938. Prohibition of Children’s Toys and Child Care Articles Containing Specified Phthalates. 2017.
129. Public Law 110 – 314 - Consumer Product Safety Improvement Act of 2008. Consumer Product Safety Commission 2008.
130. Johns LE, Cooper GS, Galizia A, Meeker JD. Exposure assessment issues in epidemiology studies of phthalates. *Environ Int* 2015; 85: 27–39. [PubMed: 26313703]
131. Renner R. Growing concern over perfluorinated chemicals. *Environ Sci Technol* 2001; 35: 154A–160A.
132. OECD (Organisation for Economic Co-operation and Development). Potential Designated Chemicals: Perfluoroalkyl and Polyfluoroalkyl Substances (PFASs), 2015 <https://biomonitoring.ca.gov/sites/default/files/downloads/PotenDesigPFASs031315.pdf>.
133. Gutzkow KB, Haug LS, Thomsen C, Sabaredzovic A, Becher G, Brunborg G. Placental transfer of perfluorinated compounds is selective—a Norwegian Mother and Child sub-cohort study. *Int J Hyg Environ Health* 2012; 215: 216–219. [PubMed: 21937271]

134. Needham LL, Grandjean P, Heinzow B, Jorgensen PJ, Nielsen F, Patterson DG Jr. et al. Partition of environmental chemicals between maternal and fetal blood and tissues. *Environ Sci Technol* 2011; 45: 1121–1126. [PubMed: 21166449]
135. Winkens K, Vestergren R, Berger U, Cousins IT. Early life exposure to per- and polyfluoroalkyl substances (PFASs): A critical review. *Emerg Contam* 2017; 3: 55–68.
136. 3M Company. Phase-out Plan for POSF-Based Products Letter from William Weppner (3M Company) to Charles Auer (U.S. EPA). 7 July 2000. U.S. EPA docket AR-226–0600: Washington, DC, 2000 <http://www.fluoridealert.org/wp-content/pesticides/pfos.fr.final.docket.0009.pdf>.
137. EPA (US Environmental Protection Agency). Fact Sheet: 2010/2015 PFOA Stewardship Program. 2018.
138. Ritter S. Fluorochemicals Go Short. *Chemical & Engineering News* 2010; 88: 12–17.
139. CDC (U.S. Centers for Disease Control and Prevention). An Overview of Perfluoroalkyl and Polyfluoroalkyl Substances and Interim Guidance for Clinicians Responding to Patient Exposure Concerns. 2017.
140. Alves A, Jacobs G, Vanermen G, Covaci A, Voorspoels S. New approach for assessing human perfluoroalkyl exposure via hair. *Talanta* 2015; 144: 574–583. [PubMed: 26452864]
141. Wang Y, Zhong Y, Li J, Zhang J, Lyu B, Zhao Y et al. Occurrence of perfluoroalkyl substances in matched human serum, urine, hair and nail. *J Environ Sci (China)* 2018; 67: 191–197. [PubMed: 29778152]
142. Ritscher A, Wang Z, Scheringer M, Boucher JM, Ahrens L, Berger U et al. Zurich statement on future actions on per- and polyfluoroalkyl substances (PFASs). *Environ Health Perspect* 2018; 126: 84502.
143. EPA (US Environmental Protection Agency). Development of a Relative Potency Factor (Rpf) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (External Review Draft). 2010.
144. Costa LG. Organophosphorus compounds at 80: some old and new issues. *Toxicol Sci* 2018; 162: 24–35. [PubMed: 29228398]
145. Hertz-Picciotto I, Sass JB, Engel S, Bennett DH, Bradman A, Eskenazi B et al. Organophosphate exposures during pregnancy and child neurodevelopment: Recommendations for essential policy reforms. *PLoS Med* 2018; 15: e1002671.
146. Needham LL. Assessing exposure to organophosphorus pesticides by biomonitoring in epidemiologic studies of birth outcomes. *Environ Health Perspect* 2005; 113: 494–498. [PubMed: 15811842]
147. Beamer PI, Canales RA, Ferguson AC, Leckie JO, Bradman A. Relative pesticide and exposure route contribution to aggregate and cumulative dose in young farmworker children. *Int J Environ Res Public Health* 2012; 9: 73–96. [PubMed: 22470279]
148. Silva MJ, Wong LY, Samandar E, Preau JL Jr., Jia LT, Calafat AM. Exposure to di-2- ethylhexyl terephthalate in the U.S. general population from the 2015–2016 National Health and Nutrition Examination Survey. *Environ Int* 2019; 123: 141–147. [PubMed: 30529838]
149. Silva MJ, Jia T, Samandar E, Preau JL Jr., Calafat AM. Environmental exposure to the plasticizer 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH) in U.S. adults (2000–2012). *Environ Res* 2013; 126: 159–163. [PubMed: 23777640]
150. BASF. BASF doubles production capacity of Hexamoll DINCH to 200,000 metric tons, 2014 <https://www.basf.com/en/company/news-and-media/news-releases/2014/05/p-14-231.html>
151. Silva MJ, Wong LY, Samandar E, Preau JL, Calafat AM, Ye X. Exposure to di-2- ethylhexyl terephthalate in a convenience sample of U.S. adults from 2000 to 2016. *Arch Toxicol* 2017; 91: 3287–3291. [PubMed: 28314884]
152. Covaci A, Harrad S, Abdallah MA, Ali N, Law RJ, Herzke D et al. Novel brominated flame retardants: a review of their analysis, environmental fate and behaviour. *Environ Int* 2011; 37: 532–556. [PubMed: 21168217]
153. van der Veen I, de Boer J. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere* 2012; 88: 1119–1153. [PubMed: 22537891]

154. Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A et al. Detection of organophosphate flame retardants in furniture foam and U.S. house dust. *Environ Sci Technol* 2009; 43: 7490–7495. [PubMed: 19848166]
155. de Boer J, Ballesteros-Gomez A, Leslie HA, Brandsma SH, Leonards PEG. Flame retardants: Dust - And not food - Might be the risk. *Chemosphere* 2016; 150: 461–464. [PubMed: 26765313]
156. Hoffman K, Garantziotis S, Birnbaum LS, Stapleton HM. Monitoring indoor exposure to organophosphate flame retardants: hand wipes and house dust. *Environ Health Perspect* 2015; 123:160–165. [PubMed: 25343780]
157. Hoffman K, Butt CM, Chen A, Limkakeng AT, Stapleton HM. High exposure to organophosphate flame retardants in infants: associations with baby products. *Environ Sci Technol* 2015; 49: 14554–14559.
158. Wei GL, Li DQ, Zhuo MN, Liao YS, Xie ZY, Guo TL et al. Organophosphorus flame retardants and plasticizers: sources, occurrence, toxicity and human exposure. *Environ Pollut* 2015; 196: 29–46. [PubMed: 25290907]
159. Schreder ED, Uding N, La Guardia MJ. Inhalation a significant exposure route for chlorinated organophosphate flame retardants. *Chemosphere* 2016; 150: 499–504. [PubMed: 26775187]
160. Liu X, Yu G, Cao Z, Wang B, Huang J, Deng S et al. Occurrence of organophosphorus flame retardants on skin wipes: Insight into human exposure from dermal absorption. *Environ Int* 2017; 98: 113–119. [PubMed: 28029386]
161. Xu F, Tay JH, Covaci A, Padilla-Sanchez JA, Papadopoulou E, Haug LS et al. Assessment of dietary exposure to organohalogen contaminants, legacy and emerging flame retardants in a Norwegian cohort. *Environ Int* 2017; 102: 236–243. [PubMed: 28335995]
162. Shi Z, Zhang L, Li J, Zhao Y, Sun Z, Zhou X et al. Novel brominated flame retardants in food composites and human milk from the Chinese Total Diet Study in 2011: Concentrations and a dietary exposure assessment. *Environ Int* 2016; 96: 82–90. [PubMed: 27619751]
163. Zhang X, Zou W, Mu L, Chen Y, Ren C, Hu X et al. Rice ingestion is a major pathway for human exposure to organophosphate flame retardants (OPFRs) in China. *J Hazard Mater* 2016; 318:686–693. [PubMed: 27484948]
164. Butt C, Congleton J, Hoffman K, Fang M, Stapleton HM. Metabolites of Organophosphate Flame Retardants and 2-Ethylhexyl Tetrabromobenzoate (EH-TBB) in Urine from Paired Mothers and Toddlers. *Environ Sci Technol* 2014; doi 10.1021/es5025299.
165. Hoffman K, Daniels JL, Stapleton HM. Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. *Environ Int* 2014; 63: 169–172. [PubMed: 24316320]
166. Hoffman K, Fang M, Horman B, Patisaul HB, Garantziotis S, Birnbaum LS et al. Urinary tetrabromobenzoic acid (TBBA) as a biomarker of exposure to the flame retardant mixture Firemaster® 550. *Environ Health Perspect* 2014; 122: 963–969. [PubMed: 24823833]
167. Meeker JD, Cooper EM, Stapleton HM, Hauser R. Exploratory analysis of urinary metabolites of phosphorus-containing flame retardants in relation to markers of male reproductive health. *Endocr Disruptors (Austin)* 2013; 1: e26306.
168. Crump D, Chiu S, Kennedy SW. Effects of tris(1,3-dichloro-2-propyl) phosphate and tris(1-chloropropyl) phosphate on cytotoxicity and mRNA expression in primary cultures of avian hepatocytes and neuronal cells. *Toxicol Sci* 2012; 126: 140–148. [PubMed: 22268003]
169. Hoffman K, Butt CM, Webster TF, Preston EV, Hammel SC, Makey C et al. Temporal trends in exposure to organophosphate flame retardants in the United States. *Environ Sci Technol Lett* 2017; 4: 112–118. [PubMed: 28317001]
170. Urbansky E. Perchlorate chemistry: implications for analysis and remediation. *Bioremediation J* 1998; 2: 81–95.
171. El Aribi H, Le Blanc YJ, Antonsen S, Sakuma T. Analysis of perchlorate in foods and beverages by ion chromatography coupled with tandem mass spectrometry (IC-ESI- MS/MS). *Anal Chim Acta* 2006; 567: 39–47. [PubMed: 17723377]
172. Dyke JV, Ito K, Obitsu T, Hisamatsu Y, Dasgupta PK, Blount BC. Perchlorate in dairy milk. Comparison of Japan versus the United States. *Environ Sci Technol* 2007; 41: 88–92. [PubMed: 17265931]

173. Kirk AB, Dyke JV, Martin CF, Dasgupta PK. Temporal patterns in perchlorate, thiocyanate, and iodide excretion in human milk. *Environ Health Perspect* 2007; 115: 182–186. [PubMed: 17384762]
174. Guruge KS, Wu Q, Kannan K. Occurrence and exposure assessment of perchlorate, iodide and nitrate ions from dairy milk and water in Japan and Sri Lanka. *J Environ Monit* 2011; 13: 2312–2320. [PubMed: 21738937]
175. ATSDR (Agency for Toxic Substances and Disease Registry). Nitrates/nitrites poisoning: Patient Education Care Instruction Sheet, 2013 <http://www.atsdr.cdc.gov/csem/nitrate2013/docs/nitratepatient-education.pdf>
176. Zil -a Rubab, Rahman MA. Serum thiocyanate levels in smokers, passive smokers and never smokers. *J Pak Med Assoc* 2006; 56: 323–326. [PubMed: 16900714]
177. Crump KS, Gibbs JP. Benchmark calculations for perchlorate from three human cohorts. *Environ Health Perspect* 2005; 113: 1001–1008. [PubMed: 16079070]
178. Oldi JF, Kannan K. Analysis of perchlorate in human saliva by liquid chromatography- tandem mass spectrometry. *Environ Sci Technol* 2009; 43: 142–147. [PubMed: 19209597]
179. Oldi JF, Kannan K. Perchlorate in human blood serum and plasma: Relationship to concentrations in saliva. *Chemosphere* 2009; 77: 43–47. [PubMed: 19564037]
180. Kirk AB, Martinelango PK, Tian K, Dutta A, Smith EE, Dasgupta PK. Perchlorate and iodide in dairy and breast milk. *Environ Sci Technol* 2005; 39: 2011–2017. [PubMed: 15871231]
181. EPA (US Environmental Protection Agency). Pyrethrins and Pyrethroids. 2017 <https://www.epa.gov/ingredients-used-pesticide-products/pyrethrins-and-pyrethroids>.
182. EPA (US Environmental Protection Agency). Reevaluation: Pyrethrins and Pyrethroids. Pesticides: Regulating Pesticides, 2010 <http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html>
183. Trunnelle KJ, Bennett DH, Tulve N, Clifton MS, Davis M, Calafat A et al. Urinary pyrethroid and chlorpyrifos metabolite concentrations in northern California families and their relationship to indoor residential insecticide levels, part of SUPERB. *Environ Sci Technol* 2014; 48: 1931–1939. [PubMed: 24422434]
184. Parsons PJ. Atomic spectrometry in clinical chemistry In: Evenson MA (ed) *Encyclopedia of Analytical Chemistry, Applications, Theory and Instrumentation*, vol. 2. John Wiley & Sons, Inc.: Chichester, UK, 2000, pp 1091–1123.
185. Parsons PJ, Barbosa F Jr. Atomic spectrometry and trends in clinical laboratory medicine. *Spectrochim Acta Part B At Spectrosc* 2007; 62: 992–1003.
186. Verdon CP, Caldwell KL, Fresquez MR, Jones RL. Determination of seven arsenic compounds in urine by HPLC-ICP-DRC-MS: a CDC population biomonitoring method. *Anal Bioanal Chem* 2009; 393: 939–947. [PubMed: 19082583]
187. Davis WC, Vander Pol SS, Schantz MM, Long SE, Day RD, Christopher SJ. An accurate and sensitive method for the determination of methylmercury in biological specimens using GC-ICP-MS with solid phase microextraction. *J Anal At Spectrom* 2004; 19: 1546–1551.
188. McShane WJ, Steven Pappas R, Paschal D. Analysis of total arsenic, total selenium and total chromium in urine by inductively coupled plasma-dynamic reaction cell-mass spectrometry. *J Anal At Spectrom* 2007; 22: 630–635.
189. Jarrett JM, Xiao G, Caldwell KL, Henahan D, Shakirova G, Jones RL. Eliminating molybdenum oxide interference in urine cadmium biomonitoring using ICP-DRC-MS. *J Anal At Spectrom* 2008; 23: 962–967.
190. Praamsma ML, Arnason JG, Parsons PJ. Monitoring Mn in whole blood and urine: a comparison between electrothermal atomic absorption and inorganic mass spectrometry. *J Anal At Spectrom* 2011; 26: 1224–1232.
191. Parsons PJ, Palmer CD, Caldwell KL, Jones RL. Determination of total mercury in urine by inductively coupled plasma mass spectrometry (ICP-MS) In: Holland G, Bandura D (eds). *Plasma Source Mass Spectrometry: Proceedings of the 9th International Conference on plasma source mass spectrometry*. Royal Society of Chemistry: London, 2005, pp 59–71.

192. Taylor A, Jones R, Leblanc A, Mazarrasa O, Lee M-Y, Parsons P et al. Instability of mercury in specimens of human urine for external quality assessment. *Accredit Qual Assur* 2009; 14: 461–466.
193. Arora M, Austin C, Sarrafpour B, Hernandez-Avila M, Hu H, Wright RO et al. Determining prenatal, early childhood and cumulative long-term lead exposure using microspatial deciduous dentine levels. *PLoS One* 2014; 9: e97805.
194. Matt GE, Quintana PJ, Destailats H, Gundel LA, Sleiman M, Singer BC et al. Thirdhand tobacco smoke: emerging evidence and arguments for a multidisciplinary research agenda. *Environ Health Perspect* 2011; 119: 1218–1226. [PubMed: 21628107]
195. Ashford K, Wiggins A, Rayens E, Assef S, Fallin A, Rayens MK. Perinatal biochemical confirmation of smoking status by trimester. *Nicotine Tob Res* 2017; 19: 631–635. [PubMed: 28403470]
196. Llaquet H, Pichini S, Joya X, Papaseit E, Vall O, Klein J et al. Biological matrices for the evaluation of exposure to environmental tobacco smoke during prenatal life and childhood. *Anal Bioanal Chem* 2010; 396: 379–399. [PubMed: 19466395]
197. Hecht SS, Stepanov I, Carmella SG. Exposure and metabolic activation biomarkers of carcinogenic tobacco-specific nitrosamines. *Acc Chem Res* 2016; 49: 106–114. [PubMed: 26678241]
198. Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev* 2005; 57: 79–115. [PubMed: 15734728]
199. Jones IA, St Helen G, Meyers MJ, Dempsey DA, Havel C, Jacob P 3rd et al. Biomarkers of secondhand smoke exposure in automobiles. *Tob Control* 2014; 23: 51–57. [PubMed: 23349229]
200. Avila-Tang E, Al-Delaimy WK, Ashley DL, Benowitz N, Bernert JT, Kim S et al. Assessing secondhand smoke using biological markers. *Tob Control* 2013; 22: 164–171. [PubMed: 22940677]
201. Carmella SG, Ming X, Olvera N, Brookmeyer C, Yoder A, Hecht SS. High throughput liquid and gas chromatography-tandem mass spectrometry assays for tobacco-specific nitrosamine and polycyclic aromatic hydrocarbon metabolites associated with lung cancer in smokers. *Chem Res Toxicol* 2013; 26: 1209–1217. [PubMed: 23837805]
202. Wei B, Blount BC, Xia B, Wang L. Assessing exposure to tobacco-specific carcinogen NNK using its urinary metabolite NNAL measured in US population: 2011–2012. *J Expo Sci Environ Epidemiol* 2016; 26: 249–256. [PubMed: 25564369]
203. Li XF, Mitch WA. Drinking water disinfection byproducts (DBPs) and human health effects: multidisciplinary challenges and opportunities. *Environ Sci Technol* 2018; 52: 1681–1689. [PubMed: 29283253]
204. ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological Profile for Bromoform and Chlorodibromomethane. U.S. Department of Health and Human Services, Public Health Service: Atlanta, GA, 2005 <https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=713&tid=128>.
205. Dick D, Ng KM, Sauder DN, Chu I. In vitro and in vivo percutaneous absorption of 14C-chloroform in humans. *Hum Exp Toxicol* 1995; 14: 260–265. [PubMed: 7779456]
206. Leavens TL, Blount BC, DeMarini DM, Madden MC, Valentine JL, Case MW et al. Disposition of bromodichloromethane in humans following oral and dermal exposure. *Toxicol Sci* 2007; 99: 432–445. [PubMed: 17656487]
207. Ashley DL BB, Singer PC, Depaz E, Wilkes C, Gordon S. et al. Changes in blood trihalomethanes concentrations resulting from differences in water quality and water use activities. *Arch Environ Occup Health* 2005; 60: 7–15. [PubMed: 16961003]
208. Backer LC, Ashley DL, Bonin MA, Cardinali FL, Kieszak SM, Wooten JV. Household exposures to drinking water disinfection by-products: whole blood trihalomethane levels. *J Expo Anal Environ Epidemiol* 2000; 10: 321–326. [PubMed: 10981726]
209. Bradman A, Whyatt RM. Characterizing exposures to nonpersistent pesticides during pregnancy and early childhood in the National Children’s Study: a review of monitoring and measurement methodologies. *Environ Health Perspect* 2005; 113: 1092–1099. [PubMed: 16079084]

210. Bradman A, Barr DB, Claus Henn BG, Drumheller T, Curry C, Eskenazi B. Measurement of pesticides and other toxicants in amniotic fluid as a potential biomarker of prenatal exposure: a validation study. *Environ Health Perspect* 2003; 111: 1779–1782. [PubMed: 14594631]
211. CDC (U.S. Centers for Disease Control and Prevention). Fourth National Report on Human Exposure to Environmental Chemicals: Atlanta, GA, 2009.
212. Li YF, Venkatesh S, Li D. Modeling global emissions and residues of pesticides. *Environ Model Assess* 2004; 9: 237–243.
213. Fromme H, Becher G, Hilger B, Volkel W. Brominated flame retardants - Exposure and risk assessment for the general population. *Int J Hyg Environ Health* 2016; 219: 1–23. [PubMed: 26412400]
214. UNEP (United Nations Environment Programme). All POPs listed in the Stockholm Convention, 2008 <http://chm.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx>.
215. Parry E, Zota AR, Park JS, Woodruff TJ. Polybrominated diphenyl ethers (PBDEs) and hydroxylated PBDE metabolites (OH-PBDEs): A six-year temporal trend in Northern California pregnant women. *Chemosphere* 2017; 195: 777–783. [PubMed: 29289024]
216. Zota AR, Mitro SD, Robinson JF, Hamilton EG, Park JS, Parry E et al. Polybrominated diphenyl ethers (PBDEs) and hydroxylated PBDE metabolites (OH-PBDEs) in maternal and fetal tissues, and associations with fetal cytochrome P450 gene expression. *Environ Int* 2018; 112: 269–278. [PubMed: 29316516]
217. Tšechová E, Vojta Š, Kukuška P, Koňan A, Trnovec T, Murínová L' et al. Legacy and alternative halogenated flame retardants in human milk in Europe: Implications for children's health. *Environ Int* 2017; 108: 137–145. [PubMed: 28843142]
218. Abdallah MA, Harrad S. Dermal contact with furniture fabrics is a significant pathway of human exposure to brominated flame retardants. *Environ Int* 2018; 118: 26–33. [PubMed: 29787899]
219. Sjödin A, Patterson DG Jr., Bergman A. A review on human exposure to brominated flame retardants--particularly polybrominated diphenyl ethers. *Environ Int* 2003; 29: 829–839. [PubMed: 12850099]
220. ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological Profile for Polychlorinated Biphenyls (PCBs). U.S. Department of Health and Human Services, Public Health Service: Atlanta, GA, 2000 <https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=142&tid=26>.
221. Batterman SA, Chernyak S, Su FC. Measurement and comparison of organic compound concentrations in plasma, whole blood, and dried blood spot samples. *Front Genet* 2016; 7: 64. [PubMed: 27148360]
222. Grandjean P, Budtz-Jorgensen E, Barr DB, Needham LL, Weihe P, Heinzow B. Elimination half-lives of polychlorinated biphenyl congeners in children. *Environ Sci Technol* 2008; 42: 6991–6996. [PubMed: 18853821]
223. Shirai JH, Kissel JC. Uncertainty in estimated half-lives of PCBs in humans: impact on exposure assessment. *Sci Total Environ* 1996; 187: 199–210. [PubMed: 8711465]
224. Tylavsky FA, Ferrara A, Catellier DJ, Oken E, Li X, Law A et al. Understanding childhood obesity in the US: the NIH environmental influences on child health outcomes (ECHO) program. *Int J Obes (Lond)* 2019; e-pub ahead of print 2019/10/28; doi 10.1038/s41366-019-0470-5.
225. Braun JM, Gennings C, Hauser R, Webster TF. What can epidemiological studies tell us about the impact of chemical mixtures on human health? *Environ Health Perspect* 2016; 124: A6–9. [PubMed: 26720830]
226. Carlin DJ, Rider CV, Woychik R, Birnbaum LS. Unraveling the health effects of environmental mixtures: an NIEHS priority. *Environ Health Perspect* 2013; 121: A6–8. [PubMed: 23409283]
227. Hamra GB, Buckley JP. Environmental exposure mixtures: questions and methods to address them. *Curr Epidemiol Rep* 2018; 5: 160–165. [PubMed: 30643709]
228. Stafoggia M, Breitner S, Hampel R, Basagana X. Statistical approaches to address multi-pollutant mixtures and multiple exposures: the state of the science. *Curr Environ Health Rep* 2017; 4: 481–490. [PubMed: 28988291]
229. Braun JM, Gray K. Challenges to studying the health effects of early life environmental chemical exposures on children's health. *PLoS Biol* 2017; 15: e2002800.

230. Buckley JP, Hamra GB, Braun JM. Statistical approaches for investigating periods of susceptibility in children's environmental health research. *Curr Environ Health Rep* 2019.
231. Moschet C, Anumol T, Lew BM, Bennett DH, Young TM. Household dust as a repository of chemical accumulation: new insights from a comprehensive high-resolution mass spectrometric study. *Environ Sci Technol* 2018; 52: 2878–2887. [PubMed: 29437387]
232. Buckley JP, Engel SM, Braun JM, Whyatt RM, Daniels JL, Mendez MA et al. Prenatal phthalate exposures and body mass index among 4- to 7-year-old children: a pooled analysis. *Epidemiology* 2016; 27: 449–458. [PubMed: 26745610]
233. Engel SM, Bradman A, Wolff MS, Rauh VA, Harley KG, Yang JH et al. Prenatal organophosphorus pesticide exposure and child neurodevelopment at 24 months: an analysis of four birth cohorts. *Environ Health Perspect* 2016; 124: 822–830. [PubMed: 26418669]
234. Harley KG, Engel SM, Vedar MG, Eskenazi B, Whyatt RM, Lanphear BP et al. Prenatal exposure to organophosphorous pesticides and fetal growth: pooled results from four longitudinal birth cohort studies. *Environ Health Perspect* 2016; 124: 1084–1092. [PubMed: 26685281]
235. Casas M, Nieuwenhuijsen M, Martinez D, Ballester F, Basagana X, Basterrechea M et al. Prenatal exposure to PCB-153, p,p'-DDE and birth outcomes in 9000 mother-child pairs: exposure-response relationship and effect modifiers. *Environ Int* 2015; 74: 23–31. [PubMed: 25314142]
236. Iszatt N, Stigum H, Verner MA, White RA, Govarts E, Murinova LP et al. Prenatal and postnatal exposure to persistent organic pollutants and infant growth: a pooled analysis of seven European birth cohorts. *Environ Health Perspect* 2015; 123: 730–736. [PubMed: 25742056]
237. Forn J, Stigum H, Hoyer BB, Sioen I, Sovcikova E, Nowack N et al. Prenatal and postnatal exposure to persistent organic pollutants and attention-deficit and hyperactivity disorder: a pooled analysis of seven European birth cohort studies. *Int J Epidemiol* 2018; 47: 1082–1097. [PubMed: 29912347]

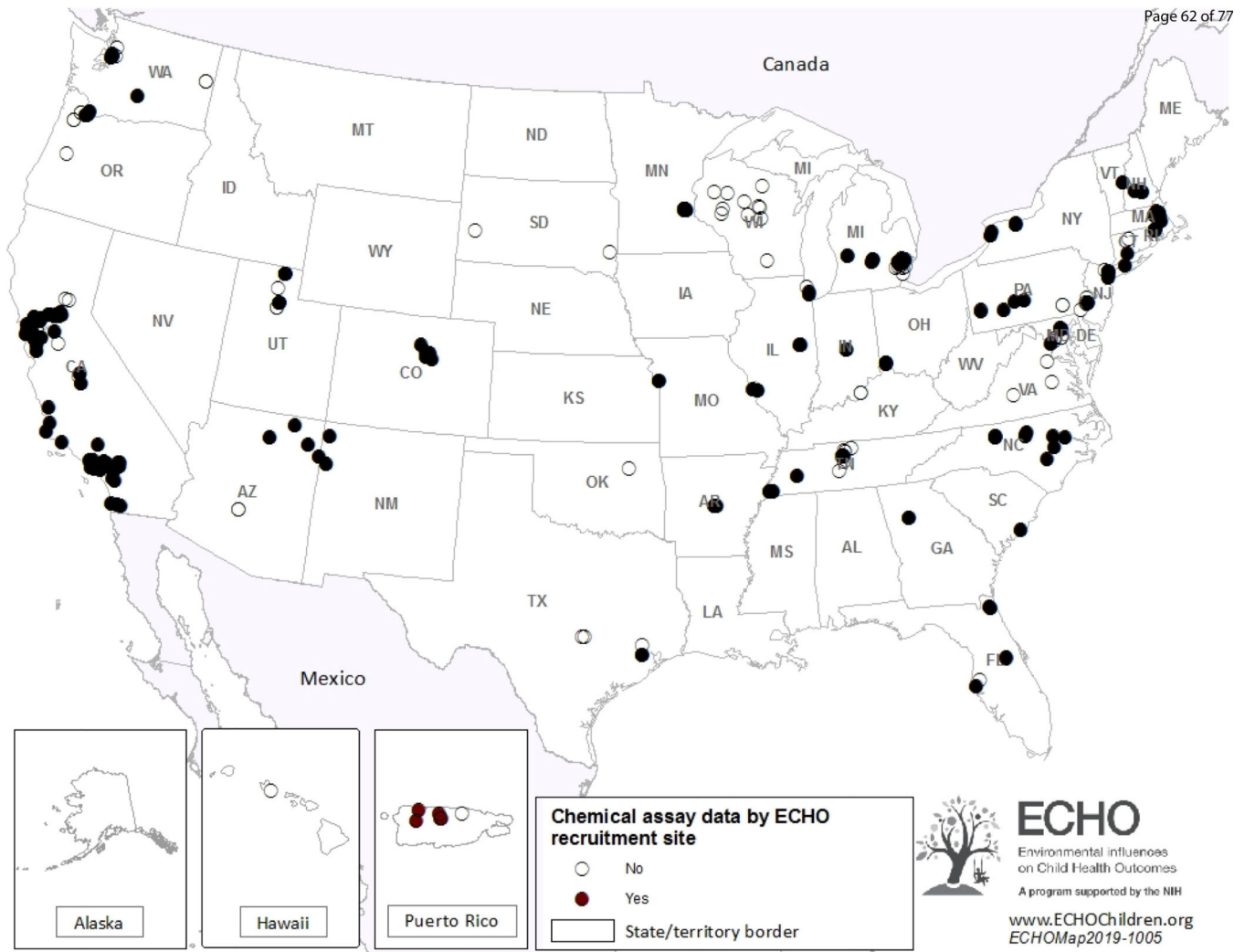


Figure 1. Existing or planned chemical assay data available for mothers or children by ECHO recruitment site.

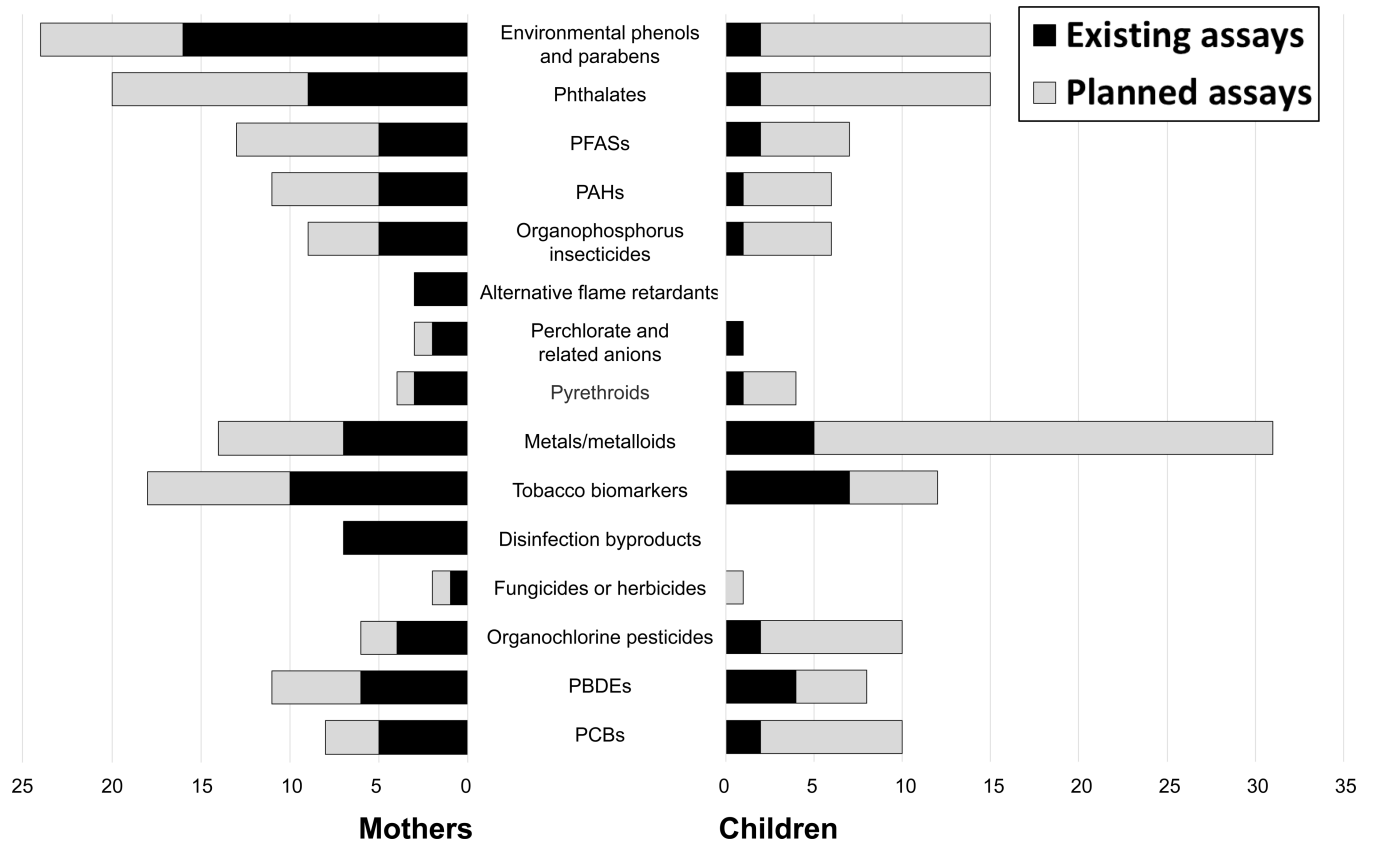


Figure 2.

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).

Table 1.

Number of 70 ECHO cohorts with existing or planned chemical class assays by participant and life stage¹

Chemical Class	Mother					Child				
	Collected (any) (n=70)	Pre-Conception (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	2	
Organophosphorus insecticides	9	1	11	1	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	1	1	0	0	0	0	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.

¹Life 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).

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

Life stage of the child	Number of cohorts ¹	Blood ²	Urine	Hair	Toenails
Samples collected from the mother					
Preconception	50	2	9	7	0
Prenatal	69	27 ³	23 ³	10 ⁴	3 ³
Delivery/infancy (birth to <12 months)	70	11 ⁴	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 ⁴	8	35 ⁴	0
Infancy (1 to <12 months)	70	10 ⁴	8 ³	5 ⁴	1 ³
Early childhood (1 to <5 years)	68	28 ⁴	12 ³	6 ³	1 ³
Middle childhood (5 to <12 years)	60	9 ³	5 ³	3 ³	1 ³
Adolescence (12 to <18 years)	30	5 ³	2 ³	2 ³	0 ³

¹Number of cohorts that collected any data at each life stage.

²Cohorts are included if they banked serum, plasma, whole blood, or umbilical cord blood.

³Specimens in this life stage are essential data elements in the ECHO-wide data collection protocol.

⁴Specimens in this life stage are recommended data elements in the ECHO-wide data collection protocol

Table 3
Number of 70 ECHO cohorts with existing or planned environmental monitoring by participant and life stage¹

Environmental monitoring	Mother				Child					
	Collected (any) (n=70)	Pre-Conception (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.

¹Life 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).

Number of 70 ECHO cohorts with existing or planned questionnaire data on chemical exposure sources by participant and life stage¹

Table 4.

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 ²	12	2	11	10	8	7	3	2
Farm animal contact	7	2	6	10	9	8	3	1
Pets in household ²	21	4	19	48	39	42	21	7
Type of residence ²	28	5	19	40	28	28	16	4
Attached garage ²	2	0	2	3	3	2	1	0
Renovations ²	17	8	16	16	14	14	5	2
Primary heating source ²	24	3	22	30	18	20	7	5
Wood stove or fireplace ²	11	1	10	22	11	19	7	5
Gas stove ²	15	1	13	19	12	12	10	5
Cook stove type ²	11	1	11	15	10	6	4	2
Burning candles or incen	5	1	5	2	2	2	1	1
Air fresheners ²	13	0	13	2	2	2	2	1
Cleaning agents ²	18	1	18	6	6	5	2	1
Personal care products ²	12	2	12	9	8	7	2	1
Ventilation ²	18	1	18	21	19	18	8	5
Mold in household ²	24	3	22	29	19	21	6	6
Carpeting in household ²	21	3	21	26	25	11	7	5
Furniture type/condition	10	1	9	1	1	1	0	0
Primary source of water ²	20	12	20	13	12	7	2	1
Fast food ²	12	1	11	11	7	9	5	3

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)
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.

¹Life 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)

²Data collection by questionnaire is essential or recommended in the ECHO-wide data collection protocol.