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A Framework for Assessing the Impact of Chemical Exposures on Neurodevelopment in ECHO: Opportunities and Challenges

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Abstract

The Environmental influences on Child Health Outcomes (ECHO) Program is a research initiative funded by the National Institutes of Health that capitalizes on existing cohort studies to investigate the impact of early life environmental factors on child health and development from infancy through adolescence. In the initial stage of the program, extant data from 70 existing cohort studies are being uploaded to a database that will be publicly available to researchers. This new database will represent an unprecedented opportunity for researchers to combine data across existing cohorts to address associations between prenatal chemical exposures and child neurodevelopment. Data elements collected by ECHO cohorts were determined via a series of surveys administered by the ECHO Data Analysis Center. The most common chemical classes quantified in multiple cohorts include organophosphate pesticides, polychlorinated biphenyls, polybrominated diphenyl ethers, environmental phenols (including bisphenol A), phthalates, and metals. For each of these chemicals, at least four ECHO cohorts also collected behavioral data during infancy/early childhood using the Child Behavior Checklist. For these chemicals and this neurodevelopmental assessment (as an example), existing data from multiple ECHO cohorts could be pooled to address research questions requiring larger sample sizes than previously available. In addition to summarizing the data that will be available, the article also describes some of the challenges inherent in combining existing data across cohorts, as well as the gaps that could be filled by the additional data collection in the ECHO Program going forward.

Keywords

ECHO; neurodevelopment; prenatal chemical exposure; infancy; childhood

1. Introduction

The Environmental Influences on Child Health Outcomes (ECHO) Program is an ambitious research initiative funded by the National Institutes of Health that capitalizes on existing cohort studies across the US to investigate the impact of early life environmental factors – physical, chemical, biological, social, or behavioral – on child health and development from infancy through adolescence. Over 50,000 children are expected to be enrolled in the study. The ECHO Program represents an unprecedented opportunity to combine data across existing cohorts to address associations between environmental factors and child development. In particular, chemical exposures are one of the key risk factors to be investigated as a determinant of child development, including neurodevelopment (Bennett et al., 2016; Gore et al., 2015). Many ECHO cohorts have extant data documenting prenatal

and/or early postnatal chemical exposures as well as assessments of neurodevelopmental outcomes at multiple time points from infancy through adolescence. Our objective in this article is to review the chemical exposures and neurodevelopmental outcomes that have been assessed in ECHO cohorts to date, including the timing of both exposure and outcome assessment, with the goal of providing a roadmap that will allow interested investigators to determine what associations between chemical exposures and neurodevelopmental outcomes could be assessed in analyses combining data from multiple ECHO cohorts. Such analyses have the potential to greatly increase the power to detect such exposure-outcome associations including cognitive and behavioral outcomes and diagnoses such as attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Moreover, potential reasons for heterogeneous findings across studies could be identified.

The ECHO Program, with its large sample size, diverse set of cohorts, and extensive exposure, outcome, and covariate data, has the potential to address the following important questions:

- What is the impact of early life exposure to mixtures of environmental chemicals on neurodevelopmental outcomes?
- Are there periods of heightened neurodevelopmental susceptibility to chemical exposures or their mixtures?
- Are certain subpopulations more vulnerable or susceptible to the potential effects of environmental chemicals or their mixtures?
- Do nonchemical exposures mitigate or potentiate the effect of chemical exposures on neurodevelopmental outcomes?

We first highlight the importance of considering windows of susceptibility to environmental insults, and briefly summarize the existing literature for the subset of environmental chemicals measured by at least two ECHO cohorts. Including this information allows us to effectively highlight some of the key questions that remain unanswered and could potentially be addressed with ECHO data. We then present tables summarizing the existing exposure and outcome data available across the ECHO cohorts allowing readers to see the potential of the ECHO study to address these questions, and finally we include a discussion of some of the opportunities that exist and challenges that will come into play when combining data across these cohorts to address these data gaps.

1.1. Identifying windows of neurodevelopmental susceptibility to chemical exposures

Brain development is a complex and synchronized process that begins *in utero* and continues through adolescence. During embryonic development, the neural tube is the substrate for the embryonic central nervous system (CNS), and subsequent waves of cell proliferation, migration, and differentiation produce the neurons and glial cells that form the CNS. Differentiation of the CNS continues postnatally, and synaptogenesis, dendritic growth, myelination, apoptosis, synaptic pruning, and neurotransmitter system maturation continue to shape CNS organization and function throughout childhood, adolescence, and into early adulthood (de Graaf-Peters and Hadders-Algra, 2006; Uylings, 2006).

Because the CNS matures over such a long period, this creates a wide period of susceptibility to environmental insults, extending from the prenatal period through adolescence. Further complicating matters is the fact that different brain regions exhibit different developmental trajectories (Huttenlocher and Dabholkar, 1997). As a result, the timing of an insult may determine the effect on neurodevelopment, with the same chemical resulting in different outcomes depending on the timing of exposure (Shelton et al., 2014). Furthermore, a subtle disruption of neurodevelopmental processes at a given time may produce a cascade of adverse effects that alter the course of normal development and produce lasting deficits in CNS function (V. Anderson et al., 2011; Rice and Barone, 2000). The heightened sensitivity of the CNS to environmental exposures across developmental periods is illustrated by animal studies of neurotoxicants. Classic laboratory studies in animals revealed that methylazoxymethanol or radiation exposure disrupted cell proliferation in different brain regions or cell types depending on the timing of exposure, which in turn resulted in different behavioral outcomes (Rodier, 1986). For example, exposures occurring either early in CNS development when the Purkinje cells of the cerebellum are forming or late in development when the granule cells of the hippocampus are forming lead to hypoactivity, whereas exposures in midgestation, when the neurons of the cerebral cortex and striatum are forming, are more likely to lead to hyperactivity (Rodier, 1980).

The potential for the timing of exposure to modify the effect of chemicals on neurodevelopment necessitates epidemiological studies assessing exposures longitudinally across gestation and through infancy, childhood, and adolescence. For exposures with a short half-life, concentrations measured at several time points during pregnancy (e.g., trimesters of pregnancy), childhood, and adolescence should be considered. Several statistical approaches have been developed to examine susceptibility windows when exposures are highly correlated over time or measured with fine temporal resolution (Buckley et al., 2019). For example, multiple informant methods have been employed to identify periods of heightened susceptibility to neurotoxic effects of bisphenol A (BPA) and polybrominated diphenyl ethers (PBDEs) (Sánchez et al., 2011; Stacy et al., 2016; Vuong et al., 2017a, 2017b). Characterizing windows of heightened susceptibility may provide clues to the biological mechanisms for neurotoxicity, improve effect estimation by reducing exposure misclassification, and inform the design of targeted exposure reduction interventions. Furthermore, identifying windows of susceptibility to environmental exposures is highlighted in the latest National Institute of Environmental Health Sciences (NIEHS) strategic goals (NIEHS, 2018). The ECHO consortium is uniquely positioned to conduct novel etiologic and methodologic research characterizing susceptibility periods both in the immediate future by taking advantage of existing exposure and outcome data that have been collected across life stages in multiple cohorts, and in the longer term by leveraging new neurodevelopmental outcome data and biospecimens to be collected from a very large number of children through the ECHO-wide data collection protocol.

2. Chemicals With Available Exposure and Neurodevelopmental Outcome Data in ECHO

2.1. Organophosphorus insecticides

Organophosphorus insecticides (OPs) are a class of insecticides used in both agricultural and nonagricultural settings. OPs account for a large proportion of the insecticides used in the US, but several have been discontinued for any use (e.g., parathion) or just home use (e.g., chlorpyrifos) due to concerns over their toxicity. OPs are absorbed by inhalation and ingestion. Most are converted to dialkyl or diethyl phosphate metabolites, which can be used as biomarkers of exposure but are not considered to be toxic themselves (DuBois, 1971; Garcia-Repetto et al., 1995; Pasquet et al., 1976; Roberts and Aaron, 2007). These metabolites are excreted in the urine within 3-6 days (Bradway et al., 1977). The fetal brain can be exposed to OPs as they readily cross the placenta (Bradman et al., 2003; Whyatt et al., 2003) and blood brain barrier (Bradman et al., 2003). Postnatally, exposure to OPs may occur via breast milk or through diet as well as via hand-to-mouth behavior (Weldon et al., 2010; Zartarian et al., 2000).

There is a robust literature linking prenatal OP exposure to a variety of neurodevelopmental and behavioral outcomes in children. Studies based on geographic data have found associations between prenatal exposure to OPs and neurodevelopmental outcomes, including poorer cognitive functioning (Andersen et al., 2015; Jurewicz and Hanke, 2008; Rowe et al., 2016). Other studies have evaluated associations of OP concentrations in blood or OP metabolites in urine with neurodevelopmental and behavioral outcomes, reporting that elevated concentrations were associated with abnormal reflexes (Young et al., 2005), cognitive deficits (Bouchard et al., 2011; Engel et al., 2016; Eskenazi et al., 2007; Rauh et al., 2006), attention problems (Marks et al., 2010), developmental delay (Liu et al., 2016, 2015), tremor (Rauh et al., 2015), and social deficits and autism traits (Eskenazi et al., 2007; Furlong et al., 2014; Sagiv et al., 2018; Shelton et al., 2014). An analysis that pooled data from four birth cohorts found stronger adverse associations of total dialkyl and diethyl OP metabolite concentrations in prenatal maternal urine with 24-month mental development for carriers of the 192Q *PON*1 allele, especially among blacks and Hispanics (Engel et al, 2016), suggesting genetic and/or racial/ethnic differences in susceptibility to OP exposures. However, others have reported no association between prenatal OP urinary metabolites and neurobehavioral impairments (Donauer et al., 2016; Jusko et al., 2019; Millenson et al., 2017; Yolton et al., 2013).

In addition to performance on neuropsychological tests, neuroanatomical and neurophysiological differences have been reported in those exposed prenatally to OPs. For, example, one study found that prenatal exposure to OPs was associated with prolonged brainstem auditory evoked potential latencies in girls, suggesting that some of these outcomes may have a sex-specific pattern (Andersen et al., 2015). Chlorpyrifos concentrations in umbilical cord blood were associated with cortical thinning and region-specific cortical deformations measured with neuroanatomic imaging data acquired at 5.9-11.2 years of age (Rauh et al., 2012). Another study, using functional near-infrared spectroscopy, found that prenatal OP exposure was associated with altered brain activation

patterns during executive functioning and language comprehension tasks in 15- and 16-year-olds (Sagiv et al., 2019).

Several studies have assessed the relationship of postnatal exposure to OPs with neurobehavioral outcomes. Some cross-sectional and prospective studies have reported cognitive deficits as well as behavioral and neurodevelopmental disorders in children (Bouchard et al., 2010; Rohlman et al., 2005). However, others have reported no association between postnatal OP urinary metabolites and deficits in cognitive or motor function (Bouchard et al., 2011; Guodong et al., 2012). Finally, both prenatal and postnatal OP exposure were evaluated by several groups (Bouchard et al., 2011; Eskenazi et al., 2007; Liu et al., 2015, 2016). Bouchard et al. (2011) found that prenatal but not postnatal OP urinary metabolite concentrations were associated with poorer intellectual development in 7-year-old children. Eskenazi et al. (2007) found a negative association between prenatal OP urinary metabolite concentrations and mental development at 24 months but a positive association between postnatal concentrations and mental development at the same age. In contrast, both pre- and postnatal exposures were associated with pervasive developmental delay at age 2 (Liu et al., 2015, 2016), whereas postnatal exposure was associated with motor and social delays.

2.2. Pyrethroids

Pyrethroid pesticides are included in over 3,500 products registered with the US Environmental Protection Agency for use in and around homes, on pets, in mosquito control, and in agriculture (U.S. EPA, 2017). Pyrethroid pesticides have a short half-life (12-48 hours) in the body (Chrustek et al., 2018). An indicator of human exposure, 3-phenoxybenzoic acid (3-PBA), which is a common metabolite of six synthetic pyrethroids, was detected in 75% of urine samples from 2001-2002 in the National Health and Nutrition Examination Survey (NHANES), indicating widespread exposure (Barr, 2008; Barr et al., 2010); cis-3-(2,2-dichlorovinyl)-2,2-dimethyl-(1-cyclopropane) carboxylic acid (cis-DCCA) and trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-1-cyclopropane carboxylic acid (trans-DCCA) are less frequently detected isomeric metabolites of several pyrethroids. Exposure from agricultural applications can occur from residues on food, and indoor applications can result in dermal exposure (Trunnelle et al., 2014). Evidence from rodent studies shows that pyrethroids can cross the blood brain barrier (Gupta et al., 1999; Soderlund, 2012).

There are a number of published studies assessing the relationship between prenatal pyrethroid exposure as measured by maternal urinary metabolites and child cognition. A study in Mexico City found that higher 3-PBA concentrations in pregnancy urine samples were associated with lower mental development scores at 24 months, but not at 36 months (Watkins et al., 2016). A study with participants from low-income neighborhoods in New York City reported that pyrethroid pesticides measured in maternal plasma samples at delivery or via personal air monitors during pregnancy were not associated with child cognitive development at 36 months. However, higher concentrations of piperonyl butoxide, a pyrethroid synergist that inhibits cytochrome P450 and delays detoxification, were associated with lower mental development scores at 36 months (Horton et al., 2011). A study in France found no association between 3-PBA concentrations during pregnancy and

child intelligence quotient (IQ) at 6 years (Viel et al., 2015), but did report an association with increased internalizing behaviors at 6 years. In contrast, exposure to other pyrethroid metabolites during pregnancy was not associated with behavioral scores (Viel et al., 2017). One study from California's Salinas Valley investigated residential proximity to agricultural pesticide use and child IQ at 7 years, finding lower IQ scores for children whose mothers lived within 1 km of agricultural pyrethroid applications during pregnancy (Gunier et al., 2017b). Another study found that mothers living close to pyrethroid agricultural spraying in both preconception and prenatal periods were more likely to have a child diagnosed with ASD by 5 years of age (Shelton et al., 2014). A study in South Africa found that prenatal pyrethroid exposure was associated with impaired social-emotional development at 1 year and poorer language development at 2 years of age (Eskenazi et al., 2018).

There have been a number of cross-sectional studies that examined child urinary pyrethroid metabolites in relation to behavior. One study found that children's urinary pyrethroid metabolite concentrations at 6 years were associated with lower verbal comprehension and working memory scores (Viel et al., 2015). The same group found that 3-PBA concentrations in child urine were associated with increased externalizing behaviors at 6 years, but higher trans-DCCA concentrations were associated with decreased externalizing behaviors (Viel et al., 2017). An additional cross-sectional study observed an association between child urinary cis-DCCA and increased behavioral problems (Oulhote and Bouchard, 2013). Two cross-sectional analyses have used NHANES data to evaluate the association of pyrethroid exposure with ADHD, with mixed results. One found no relationship between urinary 3-PBA concentrations and ADHD using the 1999-2002 NHANES data (Quirós-Alcalá et al., 2014), while the other study utilized 2001-2002 NHANES data and did find an association of 3-PBA with ADHD (Wagner-Schuman et al., 2015).

2.3. Organochlorine pesticides

Organochlorine pesticides (OCPs), including dichlorodiphenyltrichloroethanes (p,p'-DDT, p,p'-DDE, o,p'-DDT) as well as aldrin, chlordane, dieldrin, endosulfan, endrin, heptachlor, hexachlorobenzene (HCB), hexachlorocyclohexanes, lindane, mirex, toxaphene, trans-nonachlor, and trichlorophenols, are a class of broad-spectrum insecticides introduced in the 1940s and are considered to be persistent organic pollutants (POPs). They were often sold as mixtures. Their use has largely been banned or restricted in the US, and worldwide through the Stockholm Convention, but use continues in some countries. Human exposure continues even in countries where these chemicals have been banned due to their lipophilic nature and long biological and environmental half-lives (Jayaraj et al., 2016). The primary source of exposure in the general population is through the diet, particularly the consumption of fatty foods (Centers for Disease Control and Prevention [CDC], 2009). Furthermore, OCPs can cross the placenta and are found in breast milk (Caspersen et al., 2016c; Dewan et al., 2013). The vast majority of studies examining OCPs and neurodevelopment have measured OCPs in prenatal maternal blood, cord blood, or breast milk.

Most studies estimating the association between OCP exposure and child neurodevelopment have reported adverse neurobehavioral associations with higher concentrations of OCPs, but

findings are not consistent across age groups, outcomes, or specific OCPs (Eskenazi et al., 2018, 2009; Jurewicz et al., 2013; Sagiv et al., 2012a, 2010; Rosas and Eskenazi, 2008). In addition, many studies report mixed findings within the same study population (Braun et al., 2014; Cheslack-Postava et al., 2013; Dallaire et al., 2012; Eskenazi et al., 2006; Gaspar et al., 2015; Lyall et al., 2017b; Sioen et al., 2013; Torres-Sánchez et al., 2007; Yamazaki et al., 2018), with significant associations at one age but not another, and/or associations with neurodevelopmental outcomes for one specific OCP but not others.

Most of the research on OCPs has focused on prenatal exposure to DDT and DDE. Although the findings are not uniform, the literature generally supports a lack of association between prenatal exposure and newborn behaviors (Engel et al., 2007; Fenster et al., 2007; Sagiv et al., 2008; Stewart et al., 2000). For outcomes at or after age 6 months, adverse impacts on cognitive and behavioral outcomes have been reported (Eskenazi et al., 2006; Ribas-Fitó et al., 2003; Torres-Sánchez et al., 2007). Data on outcomes at older ages are limited; one study reported no associations between DDE concentrations and memory and learning assessed at age 8 years (Orenstein et al., 2014). A few studies have suggested sex-specific associations with DDT or its metabolites on neurodevelopmental outcomes in early childhood (Gaspar et al., 2015; Pan et al., 2009; Sioen et al., 2013). One reported decreased motor scores in males only (Pan et al., 2009), while the others (Gaspar et al., 2015; Sioen et al., 2013) found deficits in IQ scores and behavioral difficulties in girls only. Evidence for associations between these chemicals and specific diagnoses is limited. Three studies have examined p,p’-DDT and/or DDE in association with ASD or ASD-related behaviors; two smaller studies suggested nonsignificant elevations in odds of ASD with higher concentrations of DDE (Cheslack-Postava et al., 2013) and for ASD-related traits with p’p’-DDT or p,p’-DDE (Braun et al., 2014), while a larger study reported no association between p,p’-DDE and ASD diagnosis (Lyall et al., 2017b). An additional study found associations of DDT/DDE with ADHD-related behaviors (Sagiv et al., 2012a, 2010)

One study examined whether genetic polymorphisms modify the association between OCPs and neurodevelopmental outcomes and found that p,p’-DDE was inversely associated with scores on a range of cognitive scales, executive functioning, and working memory (assessed at age 4) in those with glutathione S-transferase polymorphisms (any *GSTP1* Val-105 allele) (Morales et al., 2008). Interestingly, maternal concentrations of this OCP have been associated with maternal genes involved in xenobiotic and lipid metabolism (Traglia et al., 2017), suggesting future research considering genes involved in the metabolism of these chemicals may be fruitful in identifying potential susceptible subgroups.

A number of studies have examined prenatal HCB exposure specifically. Although high prenatal HCB (≥90th percentile) has been associated with decreased scores on cognitive scales at age 4 (Kyriklaki et al., 2016), other studies have reported no associations with cognitive or behavioral assessments at ages 1-8 (Braun et al., 2014; Ribas-Fitó et al., 2003; Sioen et al., 2013) or with ASD (Cheslack-Postava et al., 2013).

Only a few studies to date have examined prenatal exposure to a broader group of OCPs in association with child neurodevelopmental outcomes, and most findings have not been replicated. Mirex in the placenta has been inversely associated with cognitive scores at age 4

(Puertas et al., 2010). Higher concentrations of several chlordanes have been associated with a number of adverse outcomes, including poorer fine motor function (Boucher et al., 2013; Cordier et al., 2015), lower mental development scores (Yamazaki et al., 2018), and intellectual disability (Lyall et al., 2017b). One study reported stronger associations of both HCB and *trans*-nonachlor with autistic behaviors in girls (Braun et al., 2014), but another study found no associations with ASD diagnosis (Lyall et al., 2017b).

Few studies have examined postnatal exposure to OCPs in association with neurodevelopment. One study found a null prenatal association with HCB (Kim et al., 2018), while another found a significant association with chlordecone (Boucher et al., 2013), though neither reported any significant associations of these chemicals in breast milk with neurodevelopmental outcomes, but the sample sizes were small. Studies considering postnatal exposure to OCPs may need to consider neurodevelopmental outcomes at later age ranges, and in larger samples, to observe effects.

2.4. Herbicides and fungicides

In contrast to the extensive literature on insecticides, studies investigating the potential for herbicides and fungicides to impact children's behavior or cognition are remarkably scant. The most widely used herbicide formulations today are water-soluble and have half-lives on the order of days, rather than years (Székács and Darvas, 2012). Phosphinics (including glyphosate) represented 56% of herbicides used in 2010, followed by amides (17%), triazins (16%, including atrazine), and phenoxys (5% including 2,4-dichlorophenoxyacetic acid [2,4-D]) (Osteen and Fernandez-Cornejo, 2013). Despite a long history of extensive herbicide use, human data on the potential neurodevelopment impacts are sorely lacking (Myers et al., 2016; Vandenberg et al., 2017). We are unaware of any studies of human neurodevelopment in relation to glyphosate. Given the widespread use of this chemical, this is a critical data gap that could be addressed through analysis of archived biospecimens available for ECHO cohorts that have neurodevelopmental data. Most relevant health effects data come from studies of 2,4-D, which was a main ingredient in Agent Orange, the defoliant used during the Vietnam War. However, most of the long-term health consequences of Agent Orange exposure have been attributed to the other ingredients: 2,4,5-trichlorophenoxyacetic acid and tetrachloro-dibenzo-dioxin (Institute of Medicine [IOM], 2016).

Fungicides are used agriculturally to prevent foliar diseases on high-production field crops and reduce mold on plantations growing nuts, bananas, and plantains (Fernandez-Cornejo et al., 2014; van Wendel de Joode et al., 2014). Nonagricultural use of fungicides and other biocides include use in personal care products (Montes-Grajales et al., 2017) and household construction materials, such as paints and insulation (Bollmann et al., 2015).

To date, published investigations of human fungicide exposure and neurodevelopment are limited to mancozeb, a manganese-based fungicide. A longitudinal study of Latina women and their children living in an agricultural region of California studied exposure to mancozeb and children's neurodevelopment. Women's residential proximity to areas of heavy mancozeb application during pregnancy was associated with decrements in full-scale IQ and verbal comprehension at 7 years (Gunier et al., 2017b). Additionally, full-scale IQ was lower with proximity to higher concentrations of fumigant use (methyl bromide and chloropicrin)

(Gunier et al., 2017a). In a cross-sectional study of 140 children living in Costa Rica, 96% of children aged 6-9 years had detectible urinary ethylenethiourea, and higher exposure was associated with lower verbal learning ability among all children and with poorer working memory among boys, but not girls (van Wendel de Joode et al., 2016). Another study found that higher ethylenethiourea was associated with lower social-emotional development in 1-year-old girls, but not boys (Mora et al., 2018).

2.5. Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are a class of POPs once widely used in electrical equipment, hydraulic fluids, and building materials. As a result of health concerns, PCBs were banned in the 1970s in the US and other countries. However, PCBs are still measurable in blood and in breast milk (Sjödin et al., 2014; Woodruff et al., 2011), due to their long half-lives and lipophilic nature. PCBs differ in toxicity depending on the number and positions of chlorines on the molecule, and the lower-chlorinated class of PCBs may be more readily transferred across the placenta than higher-chlorinated PCBs (Mori et al., 2014; Tsuji et al., 2013). PCBs bioaccumulate in the food chain, and the primary source of exposure is through the consumption of fatty foods such as meat, dairy products, and certain types of fatty fish (CDC, 2009). The presence of PCBs in certain paints can also lead to inhalation exposure through volatilization from the paint. In addition, the presence of PCBs in building materials (such as caulk, fluorescent light ballasts, paints, and coatings) used in schools has also raised concerns about inhalation exposure in schoolchildren (Marek et al., 2017; U.S. EPA, 2016).

A wealth of literature has examined prenatal and early postnatal exposure to PCBs and neurodevelopmental outcomes, with the majority of studies suggesting adverse associations, particularly with cognitive development, as reviewed elsewhere (Dzwilewski and Schantz, 2015; Goodman et al., 2010; Grandjean and Landrigan, 2006; Jurewicz et al., 2013; Korrick and Sagiv, 2008; Polańska et al., 2013; Ribas-Fito et al., 2001; Schantz et al., 2003; Vrijheid et al., 2016). Key findings for prenatal exposure include language delays (Caspersen et al., 2016b), decrements in general cognitive abilities (Forns et al., 2012; Kyriklaki et al., 2016; Nakajima et al., 2017; Newman et al., 2009; Park et al., 2009), and lower verbal and non-verbal IQ scores (Stewart et al., 2008), poorer motor development, and a range of behavioral issues (Verner et al., 2015b). Increased odds of intellectual disability (as defined by cognitive test scores <70) with higher concentrations of certain congeners have also been reported (Lyall et al., 2017b). However, findings have not been uniformly adverse across all studies of prenatal exposure (Gray et al., 2005), nor have specific congeners or classes of PCBs (e.g., dioxin-like, ortho-substituted) been consistently identified as the primary biologically active compounds. Although a greater number of studies have reported associations with PCB153, this may be more a factor of its prevalence rather than greater potency. Some sexually dimorphic associations have been reported. For example, Sagiv et al. (2012a) reported neuropsychological deficits in boys only, and Caspersen et al. (2016a, 2016b) reported language effects that were stronger in girls.

Links with specific neurodevelopmental disorders have also been suggested, including ADHD and/or related symptoms (Sagiv et al., 2012a, 2010) and measures of impulsivity,

concentration, and alertness (Jacobson and Jacobson, 2003; Polańska et al., 2013), as well as ASD (Braun et al., 2014; Cheslack-Postava et al., 2013; Lyall et al., 2017b). Regarding ASD, two studies (Cheslack-Postava et al., 2013; Lyall et al., 2017b) have suggested increases in ASD or ASD-related behaviors with higher concentrations of either total PCB exposure or exposure to specific PCB congeners.

Findings for postnatal exposure have suggested associations with certain behavior problems (Wang et al., 2015) and attention deficits (Verner et al., 2015b), although other studies have found no adverse effects of postnatal exposure on neuropsychological function in early childhood (Forns et al., 2012). A few studies have compared the impact of prenatal and postnatal exposure on neurodevelopmental outcomes (Forns et al., 2012; Verner et al., 2015a), with inconsistent results. Attention to timing of exposure and outcome assessment will be critical for determining susceptibility related to exposure during specific windows of neurodevelopment.

2.6. Polybrominated diphenyl ethers

PBDEs are a class of POPs used as flame retardants in plastics, polyurethane foam, furniture, textiles, and electronics in the US and elsewhere. PBDEs were originally manufactured as three commercial mixtures – penta-, octa-, and deca-BDE – named according to the bromination of congeners within the mixture. In the US, penta- and octa-BDE formulations were phased out in 2004, and deca- was phased out in 2013, while all PBDEs were banned in the European Union by 2008. However, PBDE exposure persists through the continued use of older consumer products, the recycling of products containing PBDEs, and importation of new products containing deca-PBDEs, which may still be used in some countries. PBDEs are not chemically bound within materials, so they readily leach out of consumer products, and a primary source of exposure is through incidental ingestion of contaminated dust, with infants and children often having higher exposures due to crawling and hand-to-mouth behaviors (Hoffman et al., 2017). PBDEs are lipid-soluble and bioaccumulate; thus humans are also exposed to PBDEs through dietary intake of food with high fat content (Agency for Toxic Substances and Disease Registry [ATSDR], 2017). In humans, PBDEs are stored in body fat and have biological half-lives ranging from 15 days for deca-BDE to 2-4 years for many penta-BDE congeners and 14-16 years for BDE153 (Geyer et al., 2004). PBDEs can also accumulate in breast milk, a potential source of exposure for breastfeeding infants (J. Zhang et al., 2017). PBDE exposure is typically determined by measuring concentrations of BDE congeners in either plasma or serum (Children’s Health Exposure Analysis Resource [CHEAR], 2018).

A number of epidemiological studies have investigated associations between in utero exposure to PBDEs, indicated by concentrations in maternal serum during pregnancy or in cord blood serum, and aspects of neurobehavioral development. Several studies have reported relationships between measures of in utero penta- and hexa-PBDE exposure and decreased mental and psychomotor development from ages 1 to 3 years (Braun et al., 2017b; Herbstman et al., 2010), and lower full-scale, verbal, and performance IQ at ages 4-8 years (Braun et al., 2017b; Chen et al., 2014; Eskenazi et al., 2013; Herbstman et al., 2010; H. Zhang et al., 2017). Recently a systematic review and meta-analysis concluded that there

was sufficient evidence of an association between prenatal PBDE exposure and reductions in childhood IQ, but there was limited evidence of an association with ADHD (Lam et al., 2017).

In studies of children spanning ages 2 to 12 years, in utero penta- and hexa-BDE exposure (BDE-47, −85, −99, −100, −153, and −154) has been associated with poorer attention and increased hyperactivity on a continuous performance task and on parent and teacher reports of behavior (Chen et al., 2014; Cowell et al., 2015; Eskenazi et al., 2013; Gascon et al., 2011; Sagiv et al., 2015). Various penta-, hexa-, and octa-BDEs have also been associated with increased externalizing behaviors (Braun et al., 2017b; H. Zhang et al., 2017) and poorer behavioral regulation and emotional control (Vuong et al., 2016) throughout early and middle childhood, poorer language and social development in infancy (Ding et al., 2015), poorer motor coordination (Eskenazi et al., 2013; Gascon et al., 2011), poorer reading skills in middle childhood (H. Zhang et al., 2017), and poorer executive function in late childhood (Sagiv et al., 2015).

Studies analyzing breast milk to measure postnatal PBDE exposure have yielded inconsistent findings, showing associations between penta-BDE concentrations and increased externalizing behaviors and between BDE-28 and increased withdrawal at ages 2-3 years (Adgent et al., 2014; Hoffman et al., 2012), but better language and fine motor skills in relation to BDE-196 and BDE-209 (Adgent et al., 2014; Chao et al., 2011). Childhood penta-BDE exposure has also been associated with altered neurobehavioral functioning at ages 5-9 years, including poorer attention, executive function, and cognition (Eskenazi et al., 2013). Deca-BDE is difficult to measure accurately, and only two studies have reported associations of neurodevelopmental outcomes with the deca-BDE. These studies measured BDE-209 in breast milk and found poorer cognition or mental development at 12-14 months of age (Chao et al., 2011; Gascon et al., 2012). Interestingly, Sagiv et al. (2015) observed no sex differences in relationships between childhood PBDE concentrations and direct measures of attention or executive function, but associations between PBDEs and parent report of these behaviors were stronger in girls compared to boys (Sagiv et al., 2015).

Based on three studies, no clear association between either prenatal or childhood PBDE exposure and autistic behaviors or ASD diagnosis has been reported (Braun et al., 2014; Hertz-Picciotto et al., 2011; Lyall et al., 2017a). Thus, the evidence linking prenatal PBDE exposure to cognitive impairments is quite compelling, but the impact of pre- and postnatal PBDE exposure on neurodevelopmental disorders such as ADHD and ASD remains unclear.

2.7. Bisphenol A

BPA is used to make resins and polycarbonate plastics, and is one of the highest productive volume chemicals in the world (Chapin et al., 2008). Oral ingestion is the predominant exposure route since BPA can leach into food and beverages from containers; however, dermal absorption and inhalation may be additional routes of exposure (Carwile et al., 2011; Ehrlich et al., 2014; Hines et al., 2017). BPA is excreted in the urine as a glucuronide or sulfate conjugate, does not persist in the body, and has an estimated biological half-life of ~6 hours (Thayer et al., 2015). Human exposure is ubiquitous, with the vast majority of

pregnant women, infants, and children in Western countries having measureable urinary BPA concentrations (Arbuckle et al., 2014; Braun et al., 2011a; Casas et al., 2011; Stacy et al., 2016; Woodruff et al., 2011).

Eleven studies from seven prospective cohorts have reported that prenatal BPA exposure as measured by the concentration of maternal urinary metabolites during pregnancy is associated with various aspects of child behavior, but associations are not consistent, especially with regard to sex-specific effects (Braun et al., 2009, 2011b, 2014, 2017a; Casas et al., 2015; Evans et al., 2014; Harley et al., 2013; Perera et al., 2012b; Roen et al., 2015; Stacy et al., 2017). Several studies from different cohorts have reported that prenatal BPA exposure was associated with more internalizing behaviors in children, with stronger associations in boys than girls (Braun et al., 2017a; Evans et al., 2014; Harley et al., 2013; Perera et al., 2012b; Roen et al., 2015). In another cohort, prenatal BPA exposure was associated with more internalizing and externalizing behaviors in girls, but not boys (Braun et al., 2011b, 2009), and these associations persisted from 2 to 8 years of age (Braun et al., 2017b). In two separate cohorts, prenatal BPA exposure was not associated with parent-reported reciprocal social behaviors (Braun et al., 2014; Miodovnik et al., 2011). Four studies from three cohorts reported that maternal prenatal BPA urinary concentrations were not associated with child cognitive abilities between ages 3 and 8 years; however, one study reported that prenatal BPA exposure was associated with parent-reported executive function in 3-year-old girls (Braun et al., 2017a, 2011b; Stacy et al., 2017). Braun et al. (2017b) reported that urinary BPA concentrations during pregnancy were associated with persistent increases in ADHD-like behaviors among girls.

Studies of postnatal BPA exposure have reported inconsistent associations of BPA concentrations in child urine with child behavior or cognitive abilities (Arbuckle et al., 2016; Braun et al., 2011b; Harley et al., 2013; Hong et al., 2013; Perera et al., 2012b; Perez-Lobato et al., 2016; Roen et al., 2015; Stacy et al., 2017; Tewar et al., 2016). Some report that childhood BPA exposures were associated with more behavioral or learning problems, sometimes with sex-specific associations (Harley et al., 2013; Hong et al., 2013; Perera et al., 2012b; Roen et al., 2015; Tewar et al., 2016), while others report null associations between childhood BPA exposures and behavioral outcomes (Arbuckle et al., 2016; Braun et al., 2011b; Stacy et al., 2017). One study reported that the sex-specific associations between BPA exposure and neurobehavior depended on the timing of exposure during pregnancy or childhood (Stacy et al., 2017). Overall, there is some evidence that early life BPA exposures may adversely affect neurodevelopment, but there are inconsistencies across studies with respect to sex-specific associations and periods of heightened susceptibility.

2.8. Phthalates

Phthalates are a family of high-production-volume industrial chemicals non-covalently bonded to commercial materials to enhance flexibility and durability of polyvinyl chloride plastics and to facilitate scenting and coloring of personal care products (CDC, 2009). They are commonly found in plastics, cosmetics, soaps, and other personal care products and in flooring, food packaging and numerous other common household items. Phthalates have historically been chemically classified as groups of either high-molecular-weight phthalates

(high-MWP) or low-molecular-weight phthalates (low-MWP), which correlates with commercial use. High-MWP are commonly used in plastics, while low-MWP are more commonly found in personal care products (National Research Council [NRC], 2008). Because they are not chemically bound to plastics, phthalates can leach or volatilize into the environment (Latini et al., 2010, 2009). In the body, the phthalate diesters undergo hydrolysis and glucuronidation, and monoester metabolite(s) are excreted in urine (Calafat et al., 2006). Both parent diesters and monoester metabolites are biologically active (Ventrice et al., 2013). Phthalates have biological half-lives of 4-24 hours in adults depending on the specific metabolite (W. A. C. Anderson et al., 2011; Kessler et al., 2012; Koch et al., 2005; Koch and Angerer, 2007; Leng et al., 2014). Phthalate metabolites are typically measured in the urine to reduce the potential for exogenous contamination during sample collection or processing (Calafat, 2016). Phthalate exposure can occur through ingestion, inhalation, dermal absorption, and parenteral routes (CDC, 2009).

Substantial information exists on the neurodevelopmental effects of prenatal exposure to phthalates during infancy and early childhood, and a recent systematic review provides an overview of this work (Zhang et al., 2019).

Inverse associations between phthalate metabolites in maternal urine and various cognitive outcomes including general cognitive ability have been reported (Doherty et al., 2017; Factor-Litvak et al., 2014; Hyland et al., 2019; Kim et al., 2018, 2011; Téllez-Rojo et al., 2013; Whyatt et al., 2012). Associations were found between high prenatal phthalate concentrations and lower mental development scores in 24-month-old girls (Doherty et al., 2017) and in girls 24-36 months of age (Téllez-Rojo et al., 2013). Likewise, Whyatt et al. (2012) reported a significantly stronger association between maternal phthalate concentrations and lower mental development scores in 3-year-old girls compared to boys. In contrast, Kim et al. (2011) found that maternal prenatal phthalate concentrations were associated with lower mental development scores in 6-month-old boys, but not girls. Associations of prenatal phthalate exposure with decrements in full-scale IQ were found in both boys and girls at 7 years of age (Factor-Litvak et al., 2014). Other studies have shown prenatal phthalate exposure to be associated with delayed language development in boys, but not girls (Bornehag et al., 2018; Olesen et al., 2018), deficits in recognition memory (Ipapo et al., 2017), impaired executive function (Engel et al., 2010), reduced social cognition (Miodovnik et al., 2011), and at 16 years of age, slightly increased IQ scores among girls but lower IQ scores among boys (Hyland et al., 2019).

Several associations have been found between prenatal phthalate exposure and behavioral problems in children, including internalizing/externalizing behaviors (Engel et al., 2010; Hyland et al., 2019; Lien et al., 2015; Whyatt et al., 2012), conduct problems, aggression, and inattention (Engel et al., 2010; Kobrosly et al., 2014). Higher prenatal urinary phthalate metabolites were associated with increasing internalizing behaviors in 3-year-old girls, but not boys (Whyatt et al., 2012), while Kobrosly et al. (2014) found that higher prenatal urinary phthalate metabolite concentrations were associated with impaired attention, increased aggression and conduct problems in boys 6-10 years of age. Lien et al. (2015) showed that prenatal phthalate exposure was associated with increasing externalizing behaviors in both boys and girls 8 years old. Likewise, Engel et al. (2010) reported that

increased aggression, inattention, and externalizing behaviors in boys and girls 4-9 years old were associated with increased prenatal phthalate concentrations. Hyland et al. (2019) found suggestive associations between higher prenatal phthalate concentrations and more parent-reported and self-reported internalizing problems at 16 years of age.

Some studies have found no significant associations between prenatal exposure to phthalates and cognition (Huang et al., 2015; Kim et al., 2017; Nakiwala et al., 2018) or behavior problems (Gascon et al., 2015), and one study reported more rapid motor and behavioral maturation in early infancy (Stroustrup et al., 2018). Among studies that have found associations between phthalate exposure and neurodevelopment, the results are inconsistent. The discrepancies may be due to differences in which phthalate metabolites were used as biomarkers of exposure, how cognitive and behavioral effects were assessed, and/or the age at which they were assessed. It is also important to note that many associations are sex-specific, suggesting that prenatal phthalate exposure influences neurobehavioral outcomes differently for males and females.

2.9. Per- and polyfluoroalkyl substances

Per- and polyfluoroalkyl substances (PFAS) are a family of chemicals used in the manufacture of consumer and industrial products, including oil-resistant coatings for food packaging, non-stick cookware, and stain-resistant fabrics. PFAS are persistent in the environment and have biological half-lives of approximately 3-5 years in humans (Olsen et al., 2007). PFAS concentrations are universally detected in the US population (Calafat et al., 2007). Diet and the indoor environment are the most common sources of human PFAS exposure. Breastfeeding is an important route of exposure among children (Kingsley et al., 2018; Mogensen et al., 2015).

Prospective birth cohort studies that measure prenatal PFAS have reported inconsistent findings with respect to neurodevelopment, with some studies reporting poorer gross motor skills at age 2 (Chen et al., 2013), and, at school age, poorer visual motor abilities (Høyer et al., 2018), more behavior problems, particularly hyperactivity (Høyer et al., 2018, 2015), and poorer executive function (Vuong et al., 2016). Harris et al. (2018) found that both prenatal and childhood exposure to PFAS was associated with lower visual motor abilities at 6.6-10.9 years of age. Other studies report no associations (Fei et al., 2008; Fei and Olsen, 2011; Forns et al., 2015; Liew et al., 2018, 2015; Ode et al., 2014; Stein et al., 2013; Strøm et al., 2014) or associations with more favorable cognitive and behavioral scores (Braun et al., 2014; Harris et al., 2018; Lien et al., 2016; Lyall et al., 2018; Quaak et al., 2016; Stein et al., 2013; Zhang et al., 2018).

Studies of childhood PFAS exposure report higher risk for ADHD and related behaviors (Hoffman et al., 2010; Stein and Savitz, 2011, Gump et al., 2011, Vuong et al., 2018). In addition, a recent study that measured both prenatal and postnatal PFASs reported associations of these chemicals in childhood with more behavior problems, including hyperactivity, peer relationship problems, and conduct problems, and null associations of prenatal PFASs with these outcome measures (Oulhote et al., 2016). However, a study conducted in a community exposed to high concentrations of perfluorooctanoate via contaminated drinking water found null or favorable associations with parent- or teacher-

reported executive function, ADHD-related behavior, and other behavioral problems (Stein et al., 2013). Another study found that both prenatal and postnatal PFAS exposures were associated with better children's reading scores at ages 5 and 8 years (Zhang et al., 2018). Results point to the childhood period as a potentially more sensitive window for PFAS exposure than the prenatal period. However, there are many inconsistencies across studies, and as in the case of phthalates, studies differ with respect to which PFAS are measured and the particular mix of PFAS, which varies over time and geographically.

2.10. Perchlorate, thiocyanate, and nitrate

Perchlorate is an inorganic anion that occurs naturally in soil and water in certain areas of the world, and is manufactured for use in rocket fuel, fireworks, vehicle airbags, fertilizers, and other materials. In the US, exposure to perchlorate is widespread and occurs primarily through ingestion of contaminated food and water (Maffini et al., 2016; Steinmaus, 2016), such that perchlorate can be detected in essentially all urine samples tested despite its short half-life of approximately 8 hours (Blount et al., 2007). Thiocyanate is present in cigarette smoke and cruciferous vegetables, and nitrate is commonly found in vegetables, cured meats, and contaminated water. Ingestion of thiocyanate and nitrate through diet and drinking water has led to ubiquitous exposure in the US (Blount and Valentin-Blasini, 2006). Perchlorate, thiocyanate, and nitrate are all known to inhibit iodine uptake at the sodium/iodide symporter, a transmembrane glycoprotein responsible for transporting iodide into follicular thyroid cells for use in thyroid hormone synthesis (Steinmaus, 2016).

To date, only one study has examined relationships between in utero perchlorate exposure and neurodevelopment. Taylor et al. (2014) reported that children of women in the highest 10% of urinary perchlorate concentrations during the first trimester of pregnancy had three times higher odds of being in the lowest 10% for verbal IQ at 3 years of age compared to the rest of the study population. These findings remained after adjustment for iodine and thyroid status of the mother during pregnancy. However, this study was based on a subset of participants in a randomized controlled trial and included only women with suboptimal thyroid function (but not known thyroid disease), so it is unknown whether the findings are generalizable to women with normal thyroid function. Longitudinal studies that consider combined early life exposure to perchlorate, thiocyanate, and nitrate in relation to neurobehavioral outcomes in childhood are clearly needed given widespread exposure to these compounds and the importance of thyroid hormones to brain development.

2.11. Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are formed from incomplete combustion of organic material or the production of fossil fuels. PAH concentrations are more likely to be elevated in urban environments with high vehicular traffic. PAHs are also produced in the grilling of foods and are one of the many components of cigarette smoke. While PAHs may come from several sources, and exposure can be oral or via inhalation, studies have primarily focused on PAHs coming from vehicular exhaust. Measurement of PAH exposure can be carried out indirectly, through the use of air filter methods, or via validated urinary metabolites or DNA adducts.

Evaluation of the effects of prenatal PAHs using DNA adducts as the exposure measure has revealed associations of increased DNA adducts with decreased cognitive ability, and with increased odds of cognitive developmental delay at 3 years of age in a cohort from New York City (Perera et al., 2007). Longitudinal follow-up of this same cohort showed lasting effects of prenatal PAH exposure on IQ assessed at age 3 and on attention, anxiety, and depression at ages 6-7 (Perera et al., 2012a, 2006). Furthermore, in a subset of these children, increasing prenatal PAHs, measured via personal air monitoring, was associated with reductions in white matter volume at ages 7-9 years, as well as with deficits in processing speed, increased ADHD symptoms, and more frequent externalizing problems (Peterson et al., 2015).

Findings from Poland and China support that increasing prenatal PAH exposure is associated with decreases in children's cognitive ability (Edwards et al., 2010; Jedrychowski et al., 2015; J. Lee et al., 2017). Two reports from Poland, using the same PAH DNA adduct measures in the studies described above, found increased prenatal PAH exposure to be associated with poorer cognitive ability at age 5 and decreased IQ at age 7 (Edwards et al., 2010; J. Lee et al., 2017). In China, increasing PAH DNA adducts were inversely associated with IQ at age 5 (J. Lee et al., 2017).

While the above mentioned studies focused largely on prenatal PAH exposure, more recent research has begun to focus on exposure during childhood. A report from Spain examined the relationship of measured indoor and outdoor PAH concentrations at schools with brain volume and ADHD among 8-12-year-old children. The authors report associations between total PAH measures and decreased brain volume, but nonstatistically significant associations with ADHD (Mortamais et al., 2017). These results are broadly consistent with the study from New York City reporting white matter deficits associated with postnatal PAH exposure (Peterson et al., 2015). However, a US study that used NHANES data to examine the association of concurrent urinary PAH metabolites with report of ADHD, learning disability, or use of special education services showed only a marginal association between a single PAH urinary metabolite and use of special education services, no associations with reported learning disability, and inverse associations with ADHD (Abid et al., 2014).

2.12. Mercury and methylmercury

Mercury (Hg) is a naturally occurring metal that can be found in the environment in several forms—elemental Hg, a liquid metal, inorganic Hg compounds, and organic forms—with methylmercury (MeHg) being the most common form (Counter and Buchanan, 2004). Hg is derived from natural sources such as volcanic emissions, industrial sources such as coal-fired power plants, and commercial products such as fluorescent light bulbs or Hg-containing thermometers. In health care, dental amalgam is an important source of Hg exposure (Bellinger et al., 2007). Other sources of Hg include skin lightening creams and other cosmetic products (Counter and Buchanan, 2004; NRC, 2000). Hg is converted to MeHg by organisms in aquatic systems and concentrates in fish at the top of the food chain. MeHg is a chemical of global concern, and a key exposure pathway is consumption of contaminated fish (Goldman et al., 2001). MeHg can be detected in human blood, breast milk, placental tissues, umbilical cord blood, and hair. Blood concentrations reflect recent

exposure, but hair accumulates Hg as the strand grows, creating a historical record of exposure, and about 90% of Hg in hair is MeHg (Counter and Buchanan, 2004; NRC, 2000). The half-life of MeHg in human blood is approximately 50 days (Kershaw et al., 1980).

Early studies of very high MeHg exposure in Japan and Iraq found that prenatally exposed infants had few symptoms at birth, but by 6 months of age, severe neurodevelopmental deficits became evident, including cerebral palsy-like signs, mental retardation, seizure disorders, deafness, blindness, dysarthria, and other cerebellar symptoms (NRC, 2000). Lower levels of exposure to MeHg during pregnancy can also lead to subtle neurodevelopmental effects that may not be evident in infancy but may be observed at older ages (Grandjean et al., 2014). In the Faroe Islands, children had subtle developmental effects that were dose-related and evident at age 7. Abnormalities were observed in memory, attention, and language (NRC, 2000). Additional studies found that higher prenatal MeHg concentrations in maternal hair were associated with memory deficits in infants (Oken et al., 2005) and greater risk for ADHD-related behaviors such as inattention and hyperactivity/impulsivity in children (Sagiv et al., 2012b). Similarly, a study of the New Zealand cohort of children exposed to MeHg in utero who were examined at age 6 with a battery of cognitive tests found decreases in performance in children exposed to concentrations higher than 6 ppm (Kjellstrom et al., 1989; NRC, 2000). These findings were not evident in the Seychelles Islands cohort among children exposed to similar concentrations of MeHg as the Faroe Island cohort. This discrepancy may be due to diet differences between the two cohorts. Children from the Faroe Island cohort had increased MeHg exposure from maternal consumption of whale meat (Grandjean et al., 1997); participants from the Seychelles Islands consumed fish that contained nutrients such as omega-3 fatty acids, selenium, choline, and vitamin D that are important for healthy neurodevelopment and may have played a role in counteracting adverse MeHg effects (Davidson et al., 2008).

Elemental Hg and inorganic Hg compounds can be toxic, but their neurodevelopmental effects are less clear. Dental amalgam in children can lead to increased Hg concentrations in urine and blood (Counter and Buchanan, 2004; Pesch et al., 2002). However, longitudinal studies of children with one or more amalgam dental fillings in the Seychelles Islands or in the New England Children's Amalgam Trial did not find evidence of increased risk for negative effects in neuropsychological function within a 5-year follow-up (Bellinger et al., 2007; Watson et al., 2013).

2.13. Arsenic, manganese, and lead

Arsenic (As), manganese (Mn), and lead (Pb) are naturally occurring metals mostly existing in the earth's crust in trace amounts, with higher concentrations in some parts of the US due to human activities such as metal mining and burning of fossil fuel (Bellinger, 2011; Bowler et al., 2006; Jaishankar et al., 2014; Williams et al., 2012). Primary sources of exposure to these metals include drinking water for As; inhalation of air and dust for Mn; and soil, dust, and paint in old homes for Pb (Jaishankar et al., 2014; Williams et al., 2012). Other sources of exposure can be through contaminated food (e.g., rice containing As, or foods packaged in Pb-based containers), cosmetics (for Pb and Mn), contaminated drinking water (Pb), and toys (often imported, either constructed with Pb or painted with Pb-based paints) (Bellinger,

2011; Jaishankar et al., 2014; Wani et al., 2015; Williams et al., 2012). In addition, coal combustion and wind-blown dusts from sources such as mine waste can result in inhalation exposures. These metals and metalloids can pass from mother to child through the placenta.

Prenatal exposure to As and Pb has been associated with deficits in various verbal and nonverbal cognitive measures, including IQ, executive functioning, and attention, as well as behavioral problems (Bellinger, 2008a, 2011; Bellinger et al., 2017; Chung et al., 2015; Lin et al., 2013). Associations between excessive prenatal Mn and developmental outcomes have been less consistent than those reported for Pb and As, with only some studies showing adverse effects (Coetzee et al., 2016; Gunier et al., 2015; Mora et al., 2015b).

Associations have been reported between postnatal As exposure, measured by biomonitoring of hair, urine, blood, or environmental exposure source concentrations in drinking water or soil, and different measures of cognition and executive functioning (Bellinger, 2013; Tolins et al., 2014; von Ehrenstein et al., 2007; Wasserman et al., 2014). For example, exposure via drinking water exceeding 5 μg/L As (50% of USEPA maximum contaminant level for drinking water) has been associated with decreases in IQ, working memory, verbal comprehension, and perceptual reasoning scores (Wasserman et al., 2014). Associations have also been reported between As concentrations in urine and blood and several cognitive measures including visual-spatial reasoning, verbal IQ, memory, letter sequencing, math skills, and processing speed (Hamadani et al., 2011; Rosado et al., 2007). Recent studies have indicated, however, that the proportional relationship of two important As metabolites —monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA)—may be a more accurate predictor of neurotoxicity than total As in urine, with a higher ratio of MMA to DMA potentially increasing the risk for neurotoxicity (Gomez-Rubio et al., 2012; Hall et al., 2007; Laine et al., 2015). One study observed associations between As exposure and behavioral problems, including oppositional behavior and ADHD (Roy et al., 2011); however, the results of some studies suggest that As-associated behavioral problems may be the result of deficits in attention and cognition, as controlling for cognitive scores weakened the association between exposure and behavioral problems (Bellinger, 2013; Roy et al., 2011). Although this evidence suggests that certain developmental domains (e.g., cognitive) may be more affected by As exposure, more research is required to confirm the differential effects of As on different neurodevelopmental domains.

Childhood Pb exposure is consistently associated with lower IQ, poorer school performance, and behavioral difficulties (Bellinger, 2008a, 2008b; Braun et al., 2012; Finkelstein et al., 1998; Lanphear et al., 2005; Wigle and Lanphear, 2005). Young children are particularly vulnerable because of greater opportunities for exposure due to their activities (e.g., crawling, putting contaminated objects in their mouth) and increased level of absorption (Bearer, 1995; Ferguson et al., 2017; Selevan et al., 2000). Early childhood Pb exposure has also been associated with ADHD, conduct disorder, and risk of criminal arrests in adulthood (Braun et al., 2006; Froehlich et al., 2009; Wright et al., 2008). Chronic exposure during the prenatal and early postnatal periods may have especially detrimental effects on cognitive and behavioral functioning (Wani et al., 2015).

Associations between postnatal Mn exposure and neurodevelopment are less consistent. Nevertheless, Mn exposure, whether modeled from drinking water concentrations or measured through biomonitoring, has been associated with decreased cognitive and verbal performance (Khan et al., 2012; Menezes-Filho et al., 2011; Mora et al., 2015a) and increased behavioral and attention problems (Khan et al., 2011; Menezes-Filho et al., 2014; Mora et al., 2015a) in early childhood.

3. Available Data to Assess Chemical Exposures and Neurodevelopmental Outcomes in ECHO

As the above summary highlights, there are a large number of potentially neurotoxic chemicals to which the fetus, infant, and child may be chronically exposed. Although research has contributed greatly to our understanding of the neurodevelopmental risks associated with many of these chemicals, many uncertainties remain, even for the more extensively studied compounds. As outlined below, the ECHO Program provides a unique opportunity both to combine existing data across cohorts and to use new data that will be collected through the ECHO Program to make progress in resolving these uncertainties. Research conducted in the ECHO Program adheres to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and has been approved by a centralized institutional review board (Western Institutional Review Board) and/or the local institutional review boards of the participating institutions.

Data elements collected by ECHO cohorts were determined via a series of surveys administered by the ECHO Data Analysis Center. Data are included from 70 of 71 ECHO cohorts with available responses to survey modules assessing neurodevelopmental outcomes (module 03, release date Oct. 3, 2018) as well as existing chemical assays and banked biospecimens (module 04a, release date May 15, 2018). If data elements were ever collected, the cohorts provided the life stage(s) of data collection. Information on cohort sample size was not available. We conducted cohort-level descriptive statistics using SAS software version 9.3.

Among ECHO cohorts with each neurodevelopmental assessment collected at any life stage, we examined the number and proportion of cohorts that also have prenatal or delivery chemical assay data (Table 1). The most common chemical classes quantified by these cohorts are OPs, PCBs, PBDEs, environmental phenols (including BPA), phthalates, and metals. Among ECHO cohorts with infant/toddler neurodevelopmental assessments, the child behavior checklist, and gross motor development, at least four cohorts also have early life assays of PCBs, PBDEs, environmental phenols, phthalates, or metals (Table 1). For these chemicals and neurodevelopmental assessments, existing data from ECHO cohorts could be pooled to address key gaps requiring larger sample sizes than previously available. For chemicals such as pyrethroids, herbicides and fungicides, and perchlorate and other anions, the minimal overlap of early life assays with available neurodevelopmental assessments could be addressed by expanded chemical biomonitoring in ECHO cohorts. Such biomonitoring can be facilitated by ECHO’s Human Health Exposure Analysis

Resource (HHEAR) Program supplement and its state-of-the-art laboratory network specializing in chemical exposure assessment.

A substantial proportion of ECHO cohorts with neurodevelopmental assessments also have banked prenatal or delivery biospecimens (Table 2), representing opportunities to quantify additional chemicals of interest for studies of their effects on neurodevelopment. For ASD-related phenotype, attention disorders-related phenotype, brain MRI, infant/toddler development, IQ, language development, externalizing/internalizing behavior, executive function testing, gross motor development, and fine motor skills, there are at least five ECHO cohorts that have banked blood (blood, whole blood, serum, plasma, or umbilical cord blood) and urine (Table 2). We also assessed life stages of neurodevelopmental assessments among 41 ECHO cohorts with at least one banked biospecimen collected during gestation or at delivery (Table 3). These results suggest strong potential to examine early life chemical exposures in relation to outcomes assessed during infancy and childhood, with less data currently available during middle childhood and adolescence. Future study visits conducted according to the ECHO-wide data collection protocol are poised to fill gaps with respect to the neurodevelopmental assessments during these later childhood life stages.

4. Challenges and Opportunities in ECHO

Below we highlight some of the major challenges related to exposure assessment and neurodevelopmental testing faced in environmental epidemiology studies, as well as opportunities for addressing them within the ECHO Program. Moreover, we discuss the unique challenges that will be faced when using data from ECHO cohorts to address questions related to chemicals and neurodevelopment. Traditional challenges such as confounding and selection bias are of concern in any observational study; analytical challenges for pooled studies such as ECHO are discussed at length elsewhere (Lesko et al., 2018). Notably, all ECHO cohorts are providing data on key covariates that are traditionally considered in studies of developmental neurotoxicology—such as maternal age, race/ethnicity, socioeconomic status, marital status, perinatal factors (e.g., parity), tobacco use during pregnancy, breastfeeding, and pregnancy complications— to address confounding and selection bias using advanced analytic techniques. Additional covariates, including parental IQ and mental health, quality and quantity of caregiving, pre- and postnatal diet, and geographic location, are available in some cohorts and could be considered.

4.1. Challenges and Opportunities in Exposure Assessment

Assessing exposure to environmental chemicals remains one of the biggest challenges in environmental epidemiology and ECHO. Broadly, these challenges are related to the chemical exposure assessment method, variability of chemical exposures within individuals over time, potential for periods of heightened susceptibility, exposures to chemical mixtures, and comparability of exposures and exposure-outcome associations across cohorts.

4.1.1. Biomonitoring: Biomonitoring can include single urine samples, 24-hour urine collection, hair, blood (serum, plasma, or whole), breastmilk, meconium, shed deciduous teeth, or toenails, with each medium capturing different time frames and metabolic processes (Arora and Austin, 2013; Needham, 2005; Needham et al., 2008). The optimal biologic

matrix used to assess exposure to an environmental toxicant will depend on the properties of the chemical as well as its metabolism. Moreover, laboratories may differ in methodology used to measure the same chemicals, and there may be differences across laboratories in sensitivity (limits of detection) and volume of sample required for the analysis. In addition, differences in concentrations across studies may result from using different analytical techniques to assess exposure. As an example, PAH exposure has been assessed using DNA adducts, metabolites, and air monitoring; these methods likely reflect different exposure sources, as well as the body's response to exposure (Jedrychowski et al., 2013). An additional challenge to assessing exposure is the potential for exogenous contamination of samples because many chemicals of concern are present in clinic or office settings, or used in medical and laboratory equipment (Calafat, 2016). Prior to the collection of samples, it is critical to verify that the collection containers and apparatus are free of chemical contaminants; otherwise, specimen contamination may invalidate the exposure measurement (Guidry et al., 2015). Finally, creating multiple small aliquots of blood and urine is optimal and can prevent repeated freeze-thaw cycles, which could affect the integrity of samples. However, this requires more processing and storage space, and can be difficult in the context of individual studies. The ECHO biorepository will provide the unique opportunity for long-term storage of multiple aliquots of biological samples collected and processed using uniform materials and procedures across all participating ECHO cohorts. Additionally, chemicals assayed using ECHO's HHEAR supplement will ensure that future measurements for ECHO cohorts are conducted by the same laboratory using standardized protocols.

4.1.2. Within-Person Variation: As noted above, some chemicals have short half-lives, and exposure occurs episodically. For these rapidly metabolized compounds, a single measure per individual in each life stage, as will be available in ECHO, may not be adequate; however, measurement error correction techniques have been developed to correct for this exposure measurement error (Perrier et al., 2016). There is also variability by cohort in the timing of specimen collections within a life stage (e.g., first versus third trimester of pregnancy) that may reflect different windows of susceptibility to neurotoxicants and presents a challenge to harmonization. Nevertheless, a strength of ECHO is the availability of multiple, repeated measurements from the same individual across pregnancy, infancy, and childhood to represent exposure across multiple life stages.

4.1.3. Mixtures: Human populations are not exposed to a single chemical but to multiple chemicals at once. The "one chemical at a time" approach has left us with insufficient knowledge about the interactive and cumulative health effects of chemical mixtures (Braun et al., 2016). Until recently, most studies have not identified individual agents responsible for neurodevelopmental toxicity or quantified the additive or synergistic effects of multiple chemical exposures. One concern with examining chemical mixtures is that different populations may have "mixture profiles" unique to their location, history, and sociodemographics (Kalloo et al., 2018; W. Lee et al., 2017; Robinson et al., 2015). ECHO provides an incredible opportunity to advance our knowledge in the field of chemical mixtures by 1) measuring a common set of chemicals in multiple ECHO cohorts and multiple life stages, 2) comparing profiles of the same set of chemicals across multiple studies, and 3) determining if there are unique profiles of exposure associated with particular

neurodevelopmental outcomes. A variety of new statistical methods have emerged to quantify the effect of chemical mixtures, allowing for more sophisticated modeling of multiple chemical exposures (Hamra and Buckley, 2018; Taylor et al., 2016). ECHO presents a large study population to apply these innovative methods, many of which require large sample sizes, to provide new insights into the etiology of neurodevelopmental outcomes.

4.1.4. Exposure and Effect Measure Comparability Across Cohorts:

Differences in the range of exposure across studies in ECHO creates some challenges and opportunities to quantify associations across multiple cohorts. Most notably, the combined ECHO cohorts will provide a rich data resource with greater racial, demographic and geographic diversity than any one cohort. This provides the opportunity to investigate how an array of sociodemographic, built environment, or contextual factors modify the association between chemical exposures and neurodevelopment. Of direct relevance to chemical exposures, the different range (or central tendency) in exposure could arise because of variations in the source and history of exposures in a cohort, as well as the sociodemographic, behavioral, and lifestyle factors of the participants. One related challenge is that differences in exposure levels could obscure the association between chemical exposure and neurodevelopment if these relations are non-linear (e.g., Mn) (Claus Henn et al., 2010). Thus, consideration of non-linearity and appropriate methods to account for this need to be employed (Lanphear et al., 2005). While differences in exposure levels present a challenge, they are also an opportunity to explore dose-response relationships across a wider range of exposure concentrations for some chemicals. For instance, concentrations of As vary dramatically across the US due to differences in local geology and source of drinking water (i.e., private-well vs. public supply), thus providing the opportunity to examine dose-response across a wide range of exposure. Finally, observing heterogeneous associations across cohorts is a challenge of interpretation. However, the ability to estimate the potential effect of various chemicals on neurodevelopment in multiple cohorts provides the opportunity to consider whether there are factors that either modify these associations or interact with chemical exposures to increase or decrease the negative impact of an exposure. These could include biological sex, sociodemographic, nutritional, psychosocial, or built environment characteristics, all of which are being measured in ECHO. The ability in ECHO to stratify on such factors, including multiple factors simultaneously, will greatly enhance the identification and understanding of vulnerable populations, opening the door to targeting interventions.

4.2. Challenges and opportunities in neurodevelopmental assessment

Appropriate assessment of neurodevelopment is critical in studies estimating the potential effect of early-life chemical exposures on children’s neurobehavior. Neurodevelopmental test batteries include direct assessment by an examiner (e.g., IQ test), computer-assisted tests (e.g., continuous performance tasks), or questionnaires (e.g., behavioral ratings). The choice of psychometric tests is often dictated by the time and resources available to conduct the assessment, and potentially by the specific hypotheses being tested. Considerations need to be made regarding the appropriateness of the psychometric tests available for the age, language, and culture of the participants, level of skill and qualifications required of the test

administrator, and blinding of the examiners to the participants exposure. The standardized measurement of multiple neurodevelopmental domains across the life course by ECHO cohorts provides unique opportunities to better understand the impact of environmental chemicals on brain development from infancy to adolescence.

4.2.1. Standard Assessments: While many of the ECHO cohorts have already assessed an array of neurodevelopmental domains, all cohorts will follow a common protocol to administer a standard battery of age-appropriate, valid, and reliable measurements of developmental milestones, temperament, emotional and behavioral functioning, cognition, social cognition, and academic abilities. This battery encompasses many neurobehavioral domains that have been previously associated with environmental chemicals and are important predictors of later life health and wellbeing (e.g., IQ). The use of a standard neurodevelopmental assessment battery across all of the ECHO cohorts is a major strength, since previous studies attempting to estimate the effect of environmental pollutants on neurodevelopment have faced challenges with the array of different tests used to assess a given neurodevelopmental domain (Goodman et al., 2010).

Another major strength is that individual cohorts will review children's medical records across the life course, allowing investigators to determine whether environmental chemicals are associated with clinical diagnoses (e.g., ADHD). This represents another strength of the ECHO Program: Previous studies have primarily focused on examining whether environmental chemical exposures are associated with subtle shifts in the distribution of neurobehavioral traits; rarely has there been the opportunity to determine whether these shifts are accompanied by increased risk of neurodevelopmental disorders in the same cohort of children. However, one challenge is that case identification and verification of clinical diagnoses are critical to consider given that ECHO cohorts vary in terms of geography, calendar time, socioeconomic status, and other factors that may be related to the probability of being diagnosed. Ideally, the probability of an individual being diagnosed (or not diagnosed) with a neurodevelopmental disorder should be the same with regard to factors such as socioeconomic status, geography, exposure, and calendar time. However, in reality, children living in areas with more specialized medical services may be more likely to receive a clinical diagnosis than those living in an area with less of these services, even if the prevalence of this disorder is the same in both areas.

4.2.2. Longitudinal Measurements: Child neurodevelopment is dynamic, but studies of environmental chemicals generally do not consider whether exposure influences children's neurodevelopmental trajectories (Bellinger et al., 2016). With this type of longitudinal analysis that will be inherent in ECHO, it is possible to determine whether the potential effects of environmental chemical exposures persist, emerge, or wane over time (Braun et al., 2017b). Identifying persistent effects is important as chemical-induced deficits early in life may be a prelude to more severe impairments later in life, as is the case with Pb (Desrochers-Couture et al., 2019; Wright et al., 2008). Alternatively, chemical-associated deficits that manifest in infancy or early childhood may not persist if the plasticity of the developing brain allows for recovery from early life insults. The ECHO Program will assess the above mentioned domains at multiple times during infancy, early childhood, middle

childhood, and adolescence. This will allow the ECHO Program to not only characterize typical and atypical patterns of neurodevelopment across infancy and childhood, but also determine whether these trajectories are disrupted by chemical exposures.

4.3. Challenges Unique to ECHO

Investigators may face challenges related to data harmonization, missing data, and contextual and methodological factors when using multiple ECHO cohorts to study chemical exposures and child neurodevelopment. First, harmonizing exposure, outcome, and covariate data presents a unique set of challenges since the ECHO cohorts have measured these variables with different instruments or at different ages. Achieving inferential equivalence of variables intended to measure the same neurodevelopmental trait or covariate or assess chemical exposure will require substantive knowledge of these variables (Fortier et al., 2010). For instance, the ECHO cohorts have measured children's ADHD-related behaviors with a variety of instruments. Thus, when evaluating whether these instruments measure the same trait, it is essential to consider the individual items from these instruments to ensure that they contain similar content, and that scores are correlated across instruments to confirm they are measuring the same trait, and to be aware of nuances that might influence harmonization, such as different versions of the same instrument. As another example, harmonizing a chemical exposure biomarker will require investigators to consider the comparability of biomarker assays measured at different laboratories or at different ages. The latter could be a concern with non-persistent chemicals, since exposure patterns may change with time because of age-related changes in behaviors that predict exposure (e.g., triclosan or PFASs). While data harmonization is a key challenge for ECHO, it is also an opportunity to contribute to the development of innovative methodological tools to address complexities of collaborative study designs (Lesko et al., 2018).

Missing data could present a second challenge to combining ECHO cohort data. This is especially critical when considering and controlling for potential confounders, which may be missing at the individual-level, cohort-level, or both. For example, collection of data related to diet, caregiving environment, and parental IQ or psychopathology is likely to vary in ascertainment, method of assessment, and degree of completeness. The extent of missing data (and the nature of the missingness, such as missing at random, missing completely at random, or nonignorable missingness) will need to be considered as the methods to impute missing data make assumptions about the prevalence and nature of missingness. Additionally, the predictors of missingness are likely to differ by cohort, necessitating different missing data models for each cohort (Lesko et al., 2018). For variables missing at the cohort level, ECHO can apply novel methods such as those developed to draw on the covariate correlation structure from an external population for sensitivity analyses of unmeasured variables (Chatterjee et al., 2016).

Finally, contextual and methodological factors will need to be considered when interpreting associations and considering sources of bias. For instance, the patterns and correlates of chemical exposures and neurodevelopmental outcomes may change over time in ways that influence the pattern of associations across different cohorts. As an example, low socioeconomic status has been found to be associated with smoking during pregnancy in

later born cohorts, but not in older cohorts (Keyes et al., 2013). Smoking during pregnancy is also a risk factor for ADHD (Huang et al., 2018). Other factors, such as variations in the relative contribution of exposure sources to chemical body burden as well as the presence and severity of modifying factors (e.g., stress), need to be considered. For example, many ECHO cohorts have collected information on maternal prenatal chemical exposures and psychosocial stressors (Padula et al., 2019). Pooling individual-level data to examine effect modifiers is an important benefit over meta-analyses of individual study results that may not report information on modifiers of interest.

In terms of methodology, specific attention will need to be paid to the selection of participants into individual ECHO cohorts, particularly for cohorts that selected participants because they are at increased risk of a neurodevelopmental disorder (e.g., enriched risk cohorts) or related conditions (e.g. preterm cohorts) (Newschaffer et al., 2012). While these cohorts give ECHO a much larger sample size to study rare outcomes, it is important to consider potential biases and interrogate cohort influences on estimates using weighting, stratification, leave-one-out, or other approaches. The ability to directly study and characterize reasons for cohort-level differences in associations is a major strength of ECHO.

5. Summary and Conclusions

In summary, the ECHO Program provides an unprecedented opportunity to combine data across a large number of already existing cohorts of children to address associations between environmental factors and child neurodevelopment. While chemical exposures are one of the key risk factors impacting neurodevelopment, Section 2 above highlights that there are many inconsistencies and unanswered questions in the current literature. As outlined in Section 3, many ECHO cohorts have existing prenatal and/or childhood chemical exposure data as well as assessments of neurodevelopmental outcomes at multiple life stages from infancy through adolescence. Combining existing data from multiple existing cohort studies will present challenges, but will also provide incredible opportunities to address unanswered questions that require larger sample sizes and greater racial, demographic, and geographic diversity than has been feasible in previous individual studies. In addition to existing data, new data collection beginning in 2019 across all of the ECHO cohorts using standard protocols for collection of both biological samples and outcome variables will expand even further the opportunities of this unique research initiative to address complex research questions about the impact of chemical exposures on neurodevelopment.

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Appendix

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Table 1.

Number of ECHO cohorts with neurodevelopmental assessments and existing maternal prenatal or child delivery chemical assays, *n* (%)[a]

Neurodevelopmental Assessment	*N*[b]	OPs	Pyrethroids	OCPs	Herbicides and fungicides	PCBs	PBDEs	Environmental phenols	Phthalates	PFASs	Perchlorate and other anions	PAHs	Metals or metalloids
ASD-related phenotype													
ASD clinical diagnosis[c]	21	2 (9.5)	1 (4.8)	2 (9.5)	0	3 (14.3)	3 (14.3)	4 (19.0)	4 (19.0)	2 (9.5)	0	1 (4.8)	4 (19.0)
Social Responsiveness Scale	15	2 (13.3)	2 (13.3)	2 (13.3)	0	3 (20.0)	3 (20.0)	2 (13.3)	4 (26.7)	0	2 (13.3)	2 (13.3)	2 (13.3)
Attention disorders-related phenotype													
ADHD clinical diagnosis[c]	22	2 (9.1)	1 (4.5)	1 (4.5)	0	2 (9.1)	2 (9.1)	3 (13.6)	3 (13.6)	2 (9.1)	0	1 (4.5)	4 (18.2)
CBRS	5	1 (20.0)	1 (20.0)	1 (20.0)	0	1 (20.0)	1 (20.0)	1 (20.0)	1 (20.0)	0	1 (20.0)	1 (20.0)	2 (40.0)
Continuous performance test	4	1 (25.0)	1 (25.0)	1 (25.0)	0	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	0	1 (25.0)	1 (25.0)	2 (50.0)
Brain magnetic resonance imaging	17	2 (11.8)	1 (5.9)	1 (5.9)	0	1 (5.9)	1 (5.9)	4 (23.5)	3 (17.6)	1 (5.9)	1 (5.9)	2 (11.8)	1 (5.9)
Infant/toddler development													
BSID	18	3 (16.7)	2 (11.1)	4 (22.2)	1 (5.6)	4 (22.2)	4 (22.2)	3 (16.7)	3 (16.7)	3 (16.7)	1 (5.6)	3 (16.7)	3 (16.7)
Other developmental assessment	27	3 (11.1)	2 (7.4)	5 (18.5)	1 (3.7)	5 (18.5)	5 (18.5)	8 (29.6)	8 (29.6)	4 (14.8)	1 (3.7)	4 (14.8)	5 (18.5)
Intelligence quotient													
WISC or WPPSI	13	1 (7.7)	1 (7.7)	1 (7.7)	0	1 (7.7)	1 (7.7)	2 (15.4)	2 (15.4)	1 (7.7)	2 (15.4)	1 (7.7)	2 (15.4)
Peabody Picture Vocabulary Test	4	1 (25.0)	0	1 (25.0)	0	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	2 (50.0)	0	0	2 (50.0)
Language development													
MacArthur-Bates CDI	12	1 (8.3)	0	2 (16.7)	0	2 (16.7)	3 (25.0)	3 (25.0)	3 (25.0)	2 (16.7)	0	1 (8.3)	1 (8.3)
Preschool language test	13	2 (15.4)	1 (7.7)	2 (15.4)	0	2 (15.4)	3 (23.1)	3 (23.1)	3 (23.1)	2 (15.4)	1 (7.7)	1 (7.7)	2 (15.4)
Speech and language assessment scale	18	2 (11.1)	1 (5.6)	2 (11.1)	0	2 (11.1)	3 (16.7)	4 (22.2)	4 (22.2)	3 (16.7)	1 (5.6)	1 (5.6)	3 (16.7)
Externalizing/internalizing behavior scoring													
Child Behavior Checklist	26	3 (11.5)	2 (7.7)	3 (11.5)	0	4 (15.4)	4 (15.4)	5 (19.2)	6 (23.1)	2 (7.7)	2 (7.7)	3 (11.5)	4 (15.4)
BASC	9	1 (11.1)	1 (11.1)	1 (11.1)	0	1 (11.1)	2 (22.2)	1 (11.1)	2 (22.2)	1 (11.1)	1 (11.1)	1 (11.1)	3 (33.3)
Depression scale (any)	14	1 (7.1)	1 (7.1)	1 (7.1)	0	1 (7.1)	1 (7.1)	1 (7.1)	2 (14.3)	1 (7.1)	1 (7.1)	2 (14.3)	4 (28.6)

Neurodevelopmental Assessment	N[b]	OPs	Pyrethroids	OCPs	Herbicides and fungicides	PCBs	PBDEs	Environmental phenols	Phthalates	PFASs	Perchlorate and other anions	PAHs	Metals or metalloids
Child Depression Inventory	8	1 (12.5)	1 (12.5)	1 (12.5)	0	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	0	1 (12.5)	1 (12.5)	2 (25.0)
Executive function test													
BRIEF	18	1 (5.6)	1 (5.6)	1 (5.6)	0	1 (5.6)	2 (11.1)	3 (16.7)	3 (16.7)	3 (16.7)	1 (5.6)	2 (11.1)	3 (16.7)
Gross motor development (any)	34	4 (11.8)	3 (8.8)	4 (11.8)	1 (2.9)	5 (14.7)	5 (14.7)	6 (17.6)	6 (17.6)	4 (11.8)	1 (2.9)	4 (11.8)	7 (20.6)
Fine motor skills (any)	21	2 (9.5)	2 (9.5)	3 (14.3)	1 (4.8)	3 (14.3)	4 (19.0)	4 (19.0)	4 (19.0)	4 (19.0)	1 (4.8)	4 (19.0)	6 (28.6)
Pegboard	9	1 (11.1)	1 (11.1)	1 (11.1)	0	1 (11.1)	1 (11.1)	2 (22.2)	2 (22.2)	2 (22.2)	1 (11.1)	2 (22.2)	2 (22.2)

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; BASC, Behavior Assessment System for Children; BSID, Bayley Scales of Infant Development; BRIEF, Behavior Rating Inventory of Executive Function; CBRS, Conners Comprehensive Behavior Rating Scales; CDI, Communicative Development Inventories; OCPs, organochlorine pesticides; OPs, organophosphorus insecticides; PAHs, polycyclic aromatic hydrocarbons; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PFASs, per- and polyfluoroalkyl substances; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

[a]Number (%) of ECHO cohorts with the specified chemical assay among those with the neurodevelopmental assessment at any life stage.

[b]Number of ECHO cohorts with the neurodevelopmental assessment at any life stage.

[c]Diagnosis based on clinician assessment or parent report of a clinical diagnosis.

Table 2.

Number of ECHO cohorts with neurodevelopmental assessments and existing banked maternal prenatal or delivery biospecimens, *n* (%)[a]

Neurodevelopmental Assessment	*N*[b]	Maternal prenatal biospecimen						Umbilical cord blood
		Blood	Whole blood	Serum	Plasma	Urine	Blood at delivery	
ASD-related phenotype								
ASD clinical diagnosis[c]	21	9 (42.9)	9 (42.9)	8 (38.1)	10 (47.6)	8 (38.1)	2 (9.5)	7 (33.3)
Social Responsiveness Scale	15	5 (33.3)	3 (20.0)	4 (26.7)	4 (26.7)	6 (40.0)	2 (13.3)	4 (26.7)
Attention disorders-related phenotype								
ADHD clinical diagnosis[c]	22	8 (36.4)	8 (36.4)	7 (31.8)	9 (40.9)	8 (36.4)	3 (13.6)	7 (31.8)
CBRS	5	0	0	0	0	1 (20.0)	1 (20.0)	1 (20.0)
Continuous performance test	4	1 (25.0)	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)	1 (25.0)	1 (25.0)
Brain magnetic resonance imaging	17	4 (23.5)	4 (23.5)	5 (29.4)	4 (23.5)	5 (29.4)	2 (11.8)	2 (11.8)
Infant/toddler development								
BSID	18	3 (16.7)	3 (16.7)	4 (22.2)	4 (22.2)	6 (33.3)	3 (16.7)	5 (27.8)
Other developmental assessment	27	14 (51.9)	11 (40.7)	13 (48.1)	14 (51.9)	14 (51.9)	4 (14.8)	11 (40.7)
Intelligence quotient								
WISC or WPPSI	13	4 (30.8)	3 (23.1)	4 (30.8)	5 (38.5)	5 (38.5)	1 (7.7)	2 (15.4)
Stanford-Binet Intelligence Scales	2	1 (50.0)	0	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
Peabody Picture Vocabulary Test	4	2 (50.0)	1 (25.0)	1 (25.0)	2 (50.0)	1 (25.0)	0	1 (25.0)
Language development								
MacArthur-Bates CDI	12	4 (33.3)	5 (41.7)	5 (41.7)	5 (41.7)	5 (41.7)	1 (8.3)	3 (25.0)
Preschool language test	13	3 (23.1)	4 (30.8)	4 (30.8)	4 (30.8)	5 (38.5)	2 (15.4)	3 (23.1)
Speech and language assessment scale	18	4 (22.2)	3 (16.7)	4 (22.2)	4 (22.2)	5 (27.8)	2 (11.1)	3 (16.7)
Externalizing/internalizing behavior scoring								
Child Behavior Checklist	26	8 (30.8)	6 (23.1)	9 (34.6)	9 (34.6)	11 (42.3)	4 (15.4)	7 (26.9)
BASC	9	4 (44.4)	3 (33.3)	3 (33.3)	3 (33.3)	4 (44.4)	2 (22.2)	3 (33.3)
Depression scale (any)	14	3 (21.4)	1 (7.1)	2 (14.3)	2 (14.3)	4 (28.6)	2 (14.3)	4 (28.6)
Child Depression Inventory	8	0	0	0	0	1 (12.5)	1 (12.5)	1 (12.5)
Executive function test								
Wisconsin or other card sorting test	2	2 (100)	1 (50.0)	2 (100)	2 (100)	1 (50.0)	0	0
BRIEF	18	6 (33.3)	3 (16.7)	5 (27.8)	6 (33.3)	7 (38.9)	4 (22.2)	7 (38.9)

Neurodevelopmental Assessment	N[b]	Maternal prenatal biospecimen						Umbilical cord blood
		Blood	Whole blood	Serum	Plasma	Urine	Blood at delivery	
Gross motor development (any)	34	13 (38.2)	11 (32.4)	9 (26.5)	14 (41.2)	13 (38.2)	5 (14.7)	12 (35.3)
Fine motor skills (any)	21	8 (38.1)	7 (33.3)	7 (33.3)	9 (42.9)	10 (47.6)	5 (23.8)	10 (47.6)
Pegboard	9	2 (22.2)	0	1 (11.1)	2 (22.2)	3 (33.3)	2 (22.2)	3 (33.3)

[a]Number (%) of ECHO cohorts with the specified biospecimen among those with the neurodevelopmental assessment at any life stage.

[b]Number of ECHO cohorts with the neurodevelopmental assessment at any life stage.

[c]Diagnosis based on clinician assessment or parent report of a clinical diagnosis.

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Table 3.

Neurodevelopmental assessments among 41 ECHO cohorts with a banked prenatal or delivery biospecimen by life stage, *n* (%)[a]

Neurodevelopmental Assessment	Collected (ever)[b]	Infancy (birth to <12 months)	Childhood (1 to <5 years)	Middle childhood (5 to <12 years)	Adolescence (≥12 years)
ASD-related phenotype					
ASD clinical diagnosis[c]	11 (26.8)	5 (12.2)	8 (19.5)	3 (7.3)	2 (4.9)
Social Responsiveness Scale	6 (14.6)	1 (2.4)	5 (12.2)	2 (4.9)	1 (2.4)
Attention disorders-related phenotype					
ADHD clinical diagnosis[c]	11 (26.8)	5 (12.2)	8 (19.5)	3 (7.3)	2 (4.9)
CBRS	1 (2.4)	NA	NA	1 (2.4)	1 (2.4)
Continuous performance test	3 (7.3)	0	1 (2.4)	2 (4.9)	1 (2.4)
Brain magnetic resonance imaging	6 (14.6)	4 (9.8)	4 (9.8)	2 (4.9)	1 (2.4)
Infant/toddler development					
BSID	7 (17.1)	5 (12.2)	7 (17.1)	0	0
Other developmental assessment	19 (46.3)	13 (31.7)	14 (34.1)	3 (7.3)	0
Intelligence quotient					
WISC or WPPSI	6 (14.6)	NA	4 (9.8)	4 (9.8)	0
Stanford-Binet Intelligence Scales	1 (2.4)	NA	1 (2.4)	0	0
Peabody Picture Vocabulary Test	2 (4.9)	NA	2 (4.9)	0	0
Language development					
MacArthur-Bates CDI	5 (12.2)	1 (2.4)	4 (9.8)	NA	NA
Preschool language test	5 (12.2)	2 (4.9)	5 (12.2)	1 (2.4)	NA
Speech and language assessment scale	5 (12.2)	NA	5 (12.2)	2 (4.9)	0
Externalizing/internalizing behavior scoring					
Child Behavior Checklist	11 (26.8)	1 (2.4)	11 (26.8)	2 (4.9)	1 (2.4)
BASC	5 (12.2)	0	2 (4.9)	3 (7.3)	0
Depression scale (any)	5 (12.2)	3 (7.3)	4 (9.8)	2 (4.9)	2 (4.9)
Child Depression Inventory	1 (2.4)	NA	NA	1 (2.4)	1 (2.4)
Executive function test					
Wisconsin or other card sorting test	2 (4.9)	NA	NA	2 (4.9)	0
BRIEF	8 (19.5)	NA	6 (14.6)	4 (9.8)	0

Neurodevelopmental Assessment	Collected (ever)[b]	Infancy (birth to <12 months)	Childhood (1 to <5 years)	Middle childhood (5 to <12 years)	Adolescence (≥12 years)
Gross motor development (any)	17 (41.5)	13 (31.7)	10 (24.4)	5 (12.2)	1 (2.4)
Fine motor skills (any)	12 (29.3)	10 (24.4)	8 (19.5)	3 (7.3)	0
Pegboard	4 (9.8)	NA	3 (7.3)	2 (4.9)	0

NA indicates that assessment is not applicable to this life stage and was not ascertained by the ECHO Data Analysis Center.

[a]Restricted to cohorts that collected maternal blood, whole blood, serum, plasma, or urine during gestation or maternal blood or umbilical cord blood at delivery.

[b]Number (%) of ECHO cohorts with the neurodevelopmental assessment at any life stage.

[c]Diagnosis based on clinician assessment or parent report of a clinical diagnosis.