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Prenatal Chemical Exposures and Child Language Development

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Abstract

The goal of this review is to summarize the evidence that prenatal and/or early postnatal exposure to certain chemicals, both man made (insulating materials, flame retardants, pesticides) and naturally occurring (e.g. lead, mercury), may be associated with delays or impairments in language development. We focus primarily on a subset of more extensively studied chemicals—polychlorinated biphenyls (PCBs), lead, and methyl mercury—for which a reasonable body of literature on neurodevelopmental outcomes is available. We also briefly summarize the smaller body of evidence for other chemicals including polybrominated diphenyl ether flame retardants (PBDEs) and organophosphate pesticides. Very few studies have used specific assessments of language development and function. Therefore, we included discussion of aspects of cognitive development such as overall intellectual functioning and verbal abilities that rely on language, as well as aspects of cognition such as verbal and auditory working memory that are critical underpinnings of language development. A high percentage of prospective birth cohort studies of PCBs, lead and mercury have reported exposure-related reductions in overall IQ and/or verbal IQ that persist into middle or late childhood. Given these findings, it is important that clinicians and researchers in communication sciences and disorders are aware of the potential for environmental chemicals to impact language development.

Keywords

language development; prenatal exposure; polychlorinated biphenyls; lead; mercury

1. Introduction

In the 1960s, Rachel Carson published her influential book, *Silent Spring*, a watershed moment that opened our eyes to the detrimental impact environmental chemicals could have on human health. Coincidentally, it was at about the same time that the drug thalidomide—used to alleviate morning sickness in pregnant women—was linked to birth defects,

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dispelling the long-held belief that the placenta was a protective armor, virtually impervious to drugs and chemicals (Grandjean, 2013).

Today it is widely accepted that most drugs and chemicals are readily transported across the placenta to the developing fetus, and there is a large body of literature linking prenatal exposures to environmental chemicals to adverse neurodevelopmental outcomes (e.g., see Grandjean and Landrigan, 2014). A majority of this research has focused on measuring the association between prenatal exposures and overall cognitive functioning. There are relatively few studies evaluating specific cognitive domains, and language development, in particular, has received very little emphasis. In addition, what limited evidence is available has not migrated into the mainstream literature within communication sciences and disorders where it has the potential to directly impact clinical practice (Rogers et al., this issue).

The importance of both biological and experiential contributions to child language development are well recognized; however, recently the focus has shifted to the interplay between a person's genetic makeup and the environment in which they are raised (Roth, 2013). It is now recognized that, in addition to social experience, various environmental agents including dietary components, drugs, and chemicals can interact with an individual's genetic make-up to produce a particular phenotype (Weikum et al., 2012).

Over the past several decades, it has become increasingly clear that the prenatal and early postnatal period is a critical window of time when experiences (or exposures) could impact language development (e.g., see Weikum et al., 2012). Hearing begins at the onset of the third trimester of pregnancy (Hepper and Shahidullah, 1994), and researchers have used changes in fetal heart rate to show that late-term fetuses can detect and discriminate between vowel sounds (Zimmer et al., 1993), and can also process the temporal features of speech (Granier-Deferre et al., 2011). Moreover, newborns respond to vowel sounds from their own language differently than vowel sounds from an unfamiliar language, demonstrating that the human fetus can learn phonetic information in utero (Moon et al., 2013). In the first few months of life, infants can group vowels and consonants from their native language into perceptual categories (Kuhl et. al., 1992). This research highlights the importance of the late prenatal and early postnatal periods for language development. It stands to reason that chemical exposures occurring during this critical window, when the brain is rapidly developing and the early, foundational stages of language acquisition are underway, could result in long-lasting effects on language abilities.

The goal of this review is to summarize the evidence that prenatal and/or early postnatal exposure to chemicals may be associated with delays or impairments in language development. The term "chemical" is used broadly to refer to substances foreign to the human body, whether manmade (insulating materials, flame retardants, pesticides) or occurring naturally (e.g. lead, mercury). In general, these chemicals were either recently synthesized or recently released into the environment due to industrial processes. Thus, the human body has not evolved mechanisms to detoxify them. We chose to focus on a subset of more extensively studied chemicals—polychlorinated biphenyls (PCBs), lead, and methyl mercury—for which a reasonable body of literature on neurodevelopmental outcomes is available. We also briefly summarize the smaller body of evidence for other chemicals

including polybrominated diphenyl ethers flame retardants (PBDEs) and organophosphate pesticides.

2. Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are a group of persistent environmental contaminants that were widely used in industry until their production was banned in the 1970s. PCB residues found their way into major water bodies, including the Great Lakes, where they continue to persist. PCBs are currently detectable in the blood of most people, and an important source of exposure is consumption of fish from polluted waters (Crinnion, 2011). PCBs are also present in air, particularly indoor air of older buildings, as a result of their use in caulking, paint, and fluorescent light ballasts (MacIntosh et al., 2012). As fat-soluble compounds, PCBs persist in the body and bioaccumulate with repeated exposure (Crinnion, 2011; La Rocca & Mantovani, 2006). Exposure during the perinatal period is a concern because PCBs readily cross the placenta, and are transferred to the newborn postnatally via breast milk (Jacobson et al., 1984).

PCBs are among the most extensively studied environmental toxicants. Animal studies suggest they can affect nervous system development by multiple mechanisms including disrupting thyroid hormones, which are critical for brain development, altering calcium signaling in neurons, and reducing the concentrations of dopamine, an important neurotransmitter in the brain (Fonnum & Mariussen, 2009). Perinatal exposure to PCBs has been assessed in prospective birth cohort studies in Massachusetts, Michigan, North Carolina and upstate New York, and in the Canadian Arctic, Slovakia, the Netherlands, Germany and the Faroe Islands. The health impacts of PCB exposure also have been evaluated following poisoning episodes in Japan and Taiwan (Guo et al., 1995; Yoshimura, 2012) and in other cross-sectional studies (e.g., Bouchard et al., 2014; Everett et al., 2011; Hagmar, 2003). However, in these cross-sectional studies, direct measures of prenatal or early postnatal PCB exposure typically are not available. Because exposures during this critical early developmental window are more likely to disrupt brain development, we chose to focus this review on evidence from prospective birth cohort studies.

2.1. Cognition and IQ

One of the most consistent findings across studies is the association between higher prenatal PCB exposure and lower full scale and verbal IQ scores later in childhood. While these are not direct measures of language development and/or ability, language skills are integral to performance on these tests and impairments in language development could be a contributing factor, particularly on tests of verbal IQ.

2.1.1. Infants and toddlers—Unlike later childhood (see below), most assessments of infants and toddlers using the Bayley Scales for Infant Development (BSID, Bayley, 1969; BSID-II, Bayley, 1993) reported a lack of association between prenatal PCB exposure and cognition (See Table 1). The BSID and BSID-II yielded two composite scores. The psychomotor development index (PDI) assesses fine and gross motor skills, while the mental development index (MDI) assesses cognition and language, and thus is relevant to this discussion. Cohorts in North Carolina, the Netherlands, Quebec, and Duisburg, Germany

were assessed at multiple ages using the BSID or BSID-II, and no associations between MDI scores and either prenatal or postnatal PCB exposure were observed (Gladen et al., 1988; Gladen & Rogan, 1991; Koopman-Esseboom et al., 1996; Boucher et al., 2014; Wilhelm at al., 2008). In contrast, one study in Dusseldorf, Germany found a negative correlation between perinatal PCB exposure and MDI scores (Winneke et al., 1998; Walkowiak et al., 2001). For purposes of comparison of PCB exposure levels across cohorts, serum concentrations of PCB congener 153 are shown in Table 2.

2.1.2. Early childhood—Cognition was assessed during early childhood using the Kaufman Assessment Battery (K-ABC) in the Dutch and Dusseldorf, Germany cohorts (Kaufman & Kaufman, 1983) and the McCarthy Scales of Children's Abilities (McCarthy, 1972) in the North Carolina, Michigan and upstate New York cohorts, as well as in a later follow-up of the Dutch cohort. Although these early childhood assessments produced mixed results, they provide somewhat stronger evidence for a negative association between prenatal PCB exposure and cognitive function than do the assessments in infancy (see Table 1). The K-ABC was used in the Dutch cohort at 3.5 years, and the Dusseldorf, Germany cohort at 3.5 and 6 years. Higher prenatal PCB exposure was associated with lower overall cognitive scale scores at 3.5 years in both cohorts (Patandin et al., 1999; Walkowiak et al., 2001), but not at 6 years in the German cohort (Winneke et al., 2005). Interestingly, in the Dutch cohort, the significant association at 3.5 years was seen in formula-fed but not breast-fed children (Patandin et al., 1999).

The McCarthy Scales were used in the Michigan cohort at 4 years, the upstate New York cohort at 3 and 4.5 years, and the North Carolina cohort at 3, 4, and 5 years. There were no associations between PCB exposure and McCarthy scores in the North Carolina cohort (Gladen & Rogan, 1991), but there were negative associations between PCB exposure and McCarthy general cognitive index (GCI) and word knowledge scores at 3, but not 4.5 years in the New York cohort (Stewart et al., 2003) and between PCB exposure and GCI scores at 4 years in the Michigan cohort (Jacobson, Jacobson and Humphrey, 1990). Of particular relevance to language development, in the Michigan cohort, associations were found between higher prenatal PCB exposure and lower scores on the verbal and memory subscales of the McCarthy (Jacobson, Jacobson, and Humphrey, 1990). Interestingly, a reanalysis of the Michigan data that divided the children into breastfed and formula-fed groups showed that, similar to the Dutch cohort, a significant association was only seen in children who were not breast-fed (Jacobson & Jacobson, 2002). Finally, children from the Dutch cohort were re-assessed at 6.5 years of age using the McCarthy Scales, and an association between higher prenatal PCB exposure and lower McCarthy GCI scores was observed, but only in children born to younger mothers or to parents with lower verbal IQ scores (Vreugdenhil et al., 2002). These findings, together with those related to breast feeding, highlight the fact that various social and experiential factors can modify the impact of environmental contaminants on cognitive development.

2.1.3. Later childhood—A clearer picture emerged when the children were assessed at older ages (Table 1). Stewart and colleagues found an association between prenatal PCB exposure and both full-scale and verbal IQ scores at 9 years in the New York cohort

(Stewart et al., 2008). Similarly, children in the Michigan cohort were assessed using the Wechsler Intelligence Scale for Children – Revised (WISC-R; Wechsler, 1974) at 11 years, and higher prenatal PCB exposure was associated with lower full-scale and verbal, but not performance IQ scores. When separated into quintiles based on PCB exposure, the most highly exposed children averaged 6.2 points lower on overall IQ than the other 4 groups and were 3 times more likely to have a low average IQ score. The pattern was similar for verbal IQ (Jacobson & Jacobson 1996). Overall, these findings suggest a long-lasting effect of prenatal exposure to PCBs on cognition and on verbal abilities in particular.

2.2. Language Abilities

Direct studies of the link between language and PCB exposure have focused on measures of comprehension. In two of the PCB cohorts, decreased language comprehension was related to higher prenatal exposure to PCBs (Table 1). The Dutch cohort was assessed at 3.5 years using the Reynell Language Development Scales (Patandin et al., 1999), and higher prenatal but not postnatal PCB exposure was associated with decreased verbal comprehension. Comprehension was assessed later, at 11 years, in the Michigan cohort using the WISC-R as well as the Woodcock Reading Mastery Tests – Revised (Woodcock, 1987; Jacobson & Jacobson, 1996). Prenatal PCB exposure was associated with lower verbal comprehension scores on the WISC-R as well as lower word and passage comprehension scores on the Woodcock. The most highly exposed children were twice as likely to be two or more years behind their peers in reading comprehension. In both studies, associations with comprehension were only found for prenatal and not for postnatal PCB exposure. This was also true of the effect of PCBs on overall cognition, suggesting the developing brain may be more sensitive to these chemicals prenatally. Expressive language has also been studied in association with prenatal PCB exposure Although not a standard measure of language ability because it was developed to assess adult language use after neurological insults, the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) was used at 7 years in the Faroe Islands cohort (Grandjean et al., 2001). Higher prenatal PCB exposure was associated with increased reaction time (worse performance) on both non-cued and cued naming.

2.3. Verbal and auditory learning and memory

Verbal learning and memory have been assessed in a number of the PCB cohorts (Table 1). At 4 years, prenatal PCB exposure was negatively associated with scores on the verbal memory subtest of the McCarthy Scales in children from the Michigan cohort (Jacobson, Jacobson and Humphrey, 1990). At 11 years, the Michigan children were assessed for verbal and auditory working memory using the Digit Span task from the WISC-R, and the Seashore Rhythm Test, in which the child is asked to determine if pairs of tone sequences are the same (Reitan & Wolfson, 1993; Jacobson & Jacobson, 2003). Prenatal PCB exposure was associated with poorer performance on both of these tasks, but not on a task of visuospatial working memory. In the Faroe Islands cohort, PCB exposure was not associated with verbal learning and memory, which were assessed at 7 years using the California Verbal Learning Test (Children; CVLT; Delis et al., 1994; Grandjean et al., 2001). Higher prenatal PCB exposure was associated with decreased long-term recall (Grandjean et al., 2001). Vreugdenhil and colleagues (2004) assessed children in the Dutch cohort at 9 years using an Auditory-Verbal Learning Task (Rey, 1958; Kalverboer & Deelman, 1964) and did not find

an association between prenatal PCB exposure and short- or long-term verbal memory. In a New Bedford, Massachusetts cohort, there was no association between prenatal PCB exposure and learning or verbal memory as measured by the Wide Range Assessment of Memory and Learning (WRAML) at 8 years of age (Sheslow & Adams, 1990; Orenstein et al., 2014).

2.4. Summary

Overall, results from these prospective birth cohorts suggest that perinatal exposure to PCBs is associated with decrements in aspects of cognition that are closely related to language development including verbal IQ, verbal and auditory working memory, comprehension and word knowledge. Interestingly, the results from assessments during infancy were mostly null, with a clearer picture of PCB-related deficits emerging later in childhood. This could stem from the fact that prenatal PCB exposure appears to be associated with deficits in verbal IQ and verbal learning and memory—aspects of cognition that are harder to measure accurately at very early ages. In contrast to early assessmensts using the BSID, later assessments using standardized IQ tests revealed negative associations between prenatal PCB exposure and IQ scores in four of five cohorts. The lack of effects on IQ in the North Carolina cohort cannot be explained by PCB exposure as concentrations of the marker congener, PCB 153, in that cohort were comparable to other cohorts where negative impacts were reported (Table 2). Importantly, in both the Michigan and Dutch cohorts negative effects of prenatal PCB exposure on cognition were only present in infants that were not breastfed. Over 80% of the women in the North Carolina cohort breastfed their infants. Thus, the positive impact of breastfeeding could explain the lack of effects in that cohort.

3. Lead

Lead is an extensively studied environmental contaminant that is associated with decreased intellectual functioning in childhood (Schwartz, 1994; Wakefield, 2002). The toxicity of lead stems from its ability to substitute for calcium and zinc in the molecular machinery of living cells, disrupting a number of cellular mechanisms (Garza et al., 2006). The historical use of lead as an additive in paint and gasoline resulted in widespread contamination of air, dust, and soil (Levin et al., 2008). There is a critical period of lead exposure from 6 months to 2 years of age due to mouthing behaviors, and children’s blood lead concentrations typically peak at around 2 years of age (Levin et al., 2008). However, perinatal exposure also occurs as lead freely crosses the placental barrier and is transferred from maternal tissue to breast milk (Ong et al., 1985). Although the concentrations of lead in children’s blood have declined dramatically since lead was phased out of gasoline in the 1970s, children are still exposed to low levels of lead on a daily basis, and those living in poor inner city neighborhoods are most at risk (Chandran & Cataldo, 2010; Levin et al., 2008). The effects of childhood lead exposure have been assessed in a large number of cross-sectional and prospective birth cohort studies (Jurewicz et al., 2013; Koyashiki et al., 2010). Discussed here is evidence from prospective studies assessing the effects of prenatal and early childhood lead exposure on cognitive measures that may be related to language development.

3.1. Cognition and IQ

The neurodevelopmental sequelae of early lead exposure have been studied even more extensively than perinatal PCB exposure (Tables 3 and 4). Interestingly, unlike PCB exposure where early assessments using the BSID were not very sensitive, negative associations between lead exposure and cognition are present consistently across childhood, from infancy through adolescence.

3.1.1. Infants and toddlers—Associations between higher prenatal lead exposure and lower MDI scores were observed at every age of assessment in cohorts in Boston, China, and Poland (Bellinger et al., 1987; Liu et al., 2014; Jedrychowski et al., 2009), at 24 to 36 months in cohorts in Mexico City, Port Pirie, Yugoslavia, and Taiwan (Hu et al., 2006; Tellez-Rojo et al., 2006; Wigg et al., 1988; Wasserman et al., 1992; Huang et al., 2012), and at 3 and 6, but not 24 months in Cincinnati (Dietrich et al., 1987; Dietrich et al, 1990). In contrast, there was no association between prenatal lead exposure and MDI scores at 11 months of age in a cohort in Quebec (Boucher et al., 2014) or at 6, 12, or 24 months of age in a Cleveland cohort (Ernhart & Greene, 1990). Overall, eight studies found an association between early lead exposure and lower MDI scores at one or more ages and only two saw no association at any age. Unfortunately, the results were not reported in a way that allows determination of whether the lower MDI scores were driven by deficits on the language portions of the test.

3.1.2. Early childhood—Many of the same studies (and a few others) assessed cognitive abilities during early childhood (Table 3). Children in a Rochester, New York cohort were assessed using the Stanford-Binet Intelligence Scale (fourth edition; Thorndike, Hagen, & Sattler, 1986) at 3 and 5 years (Canfield et al., 2003). An association was found between early lead exposure and lower full-scale IQ scores at both ages. Subscale scores were not reported. In the Boston cohort, children were assessed at 4 years, 9 months using the McCarthy Scales (Bellinger et al., 1991). An association between early lead exposure and lower GCI scores was driven primarily by decreases in visual-spatial and visual-motor integration scores. There were associations between early lead exposure and McCarthy GCI at 4 years in both the Mexico City and the Port Pirie cohorts (Braun et al., 2012; Tong et al., 1998). In Port Pirie, GCI was an average of 7.2 points lower in children in the highest quartile of lead exposure (McMichael et al., 1988). McCarthy subscale scores were not reported for either cohort.

In the Yugoslavia cohort, there was no association between early exposure to lead and McCarthy GCI scores at 3 years of age, but there were negative associations with all of the McCarthy sub-scales (verbal, quantitative, motor, perceptual-performance, memory, and GCI) at 4 years (Wasserman et al., 1994; Wasserman et al., 2000). Early exposure to lead was also associated with lower full-scale, performance, and verbal IQ on the Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R; Wechsler, 1989) at 5 years (Wasserman et al., 1997). In the Taiwanese cohort, there were associations between early lead exposure and lower full-scale, verbal, and performance IQ scores on the WPPSI-R at 5-6 years (Huang et al., 2012).

Dietrich and colleagues (1991; 1992) found associations between early lead exposure and scores on the K-ABC simultaneous processing and nonverbal scales in the Cincinnati cohort at 4 and 5 years, and between early lead exposure and both full-scale and performance IQ scores, but not verbal IQ scores on the WISC-R at 6.5 years (Dietrich et al., 1993). In addition, there were significant associations at 4 years between early lead exposure and all of the sub-scales of the K-ABC in the poorest children among the cohort. This again highlights the importance of social factors in mitigating the effects of environmental exposures on cognitive development. In the Cleveland cohort, there were no associations between lead and scores on the Stanford-Binet Intelligence Scale (Form L-M; Terman & Merrill, 1973) at 3 years or the WPPSI (Wechsler, 1967) at 4 years, 10 months (Ernhart et al., 1989; Ernhart & Greene, 1990).

In summary, of the eight studies that assessed cognition during early childhood, all but one (the Cleveland study) found that higher early lead exposure was associated with reductions in overall cognitive functioning. In the majority of these studies, scores on individual subscales that could provide more specific information about language abilities were not reported.

3.1.3. Later childhood—The associations between lead exposure and cognition were found to continue into later childhood in 4 studies that followed the children beyond 6 years of age. In the Boston cohort, there was an association between higher early lead exposure and full-scale and verbal IQ on the WISC-R at 10 years (Bellinger, Stiles, & Needleman, 1992). This association persisted into adulthood when the cohort was assessed using the Wechsler Abbreviated Scale of Intelligence, although the association between early lead exposure and verbal IQ in adulthood was only marginal (WASI; Wechsler, 1999; Mazumdar et al., 2011). In the Port Pirie Cohort, there were associations between early lead exposure and WISC-R full-scale and verbal IQ at 7 years, and WISC-R full-scale, performance, and verbal IQ at 11-13 years (Baghurst et al., 1992; Tong et al., 1996). In the Yugoslavia cohort, there were associations between early lead exposure and full-scale, performance, and verbal IQ on the WISC-III at 7 years (Wechsler, 1991; Wasserman et al., 1997). This study also reported negative associations of early lead exposure with scores on the perceptual organization, freedom from distractability and verbal comprehension subscales of the WISC-III at 7 years. There was an association with full-scale IQ, but not with verbal and performance IQ on the WISC-III at 8-9 years in the Taiwanese cohort (Huang et al., 2012). In summary, all four of the studies found negative associations between early lead exposure and IQ scores at one or more ages during later childhood. A majority only reported results in terms of full-scale, performance and verbal IQ. Subscale scores were typically not reported.

3.2. Language Abilities

A small number of studies assessed children using measures more directly related to language development. The Cleveland cohort was evaluated using the Sequenced Inventory of Communication Development (SICD) at 12, 24, and 36 months of age (Ernhart & Greene, 1990). At 12 and 24 months, there were no associations between early exposure to lead and receptive or expressive language. However, there was an association of lead with worse expressive language scores at 36 months. At 24 months, researchers also recorded a sample

of spontaneous speech, and found an association between prenatal lead exposure and a decreased mean length of utterance (MLU).

Central auditory processing of children in the Cincinnati cohort was assessed at 5 years using the Screening Test for Auditory Processing Disorders (Dietrich et al., 1992). There was not an association between early lead exposure and the auditory figure-ground subtest, but there was an association between exposure and poorer performance on the filtered word subtest. Children who had higher early lead exposure were worse at recognizing muffled or altered words.

Verbal comprehension was assessed in two of the prospective cohorts. In the Yugoslavia cohort, there was an association between childhood lead exposure and lower scores on the verbal comprehension subscale of the WISC-III at 7 years of age (Wasserman et al., 1997). In the Boston cohort, there was an association between higher lead exposure and lower overall composite, mathematics composite, and spelling composite scores on the Kaufman Test of Educational Achievement at 10 years (K-TEA; Kaufman & Kaufman, 1985; Bellinger, Stiles, & Needleman, 1992). In North Carolina, a large study linking early childhood lead exposure with end-of-grade standardized testing found an association between lead exposure and scores on both mathematics and reading achievement tests in the fourth grade (Miranda et al., 2007). Although not a measure of language ability per se, scores on spelling and reading achievement tests may suggest an impact on overall language abilities.

During early adulthood, participants from the Cincinnati cohort were asked to perform a verbal generation task during functional magnetic resonance imaging (fMRI; Yuan et al., 2006). Participants with higher early lead exposure showed lower activation of the left frontal cortex including parts of Broca's area, and of the left middle temporal gyrus including parts of Wernicke's area. They also showed greater activation of the right temporal gyrus including portions homologous to Wernicke's area. These altered patterns of activation suggest a long-lasting effect of early lead exposure on the organization and activation of brain areas relevant to language production.

3.4. Summary

Results from these prospective studies suggest that there is an association between early lead exposure and decrements in overall cognition, as well as auditory processing, verbal comprehension, and reading and spelling achievement. Although these measures may be related to language development and abilities, language has only been specifically assessed in the Cleveland cohort (Ernhart & Greene, 1990). Interestingly, significant associations between lead exposure and specific measures of language development were observed, even though there were no significant associations of lead with overall cognitive function in this cohort. This suggests that direct measures of language development may detect effects that are not reflected in measures of overall cognitive ability. Persistent changes in brain structure and function related to language were found in a separate cohort (Yuan et al., 2006). Additional research is needed to determine whether the effects of early lead exposure on overall cognition may be mediated by an association between lead exposure and language

development, as well as to determine whether underlying functional changes in language areas of the brain contribute to decrements in language ability.

4. Mercury

The health effects of prenatal methyl mercury (MeHg) exposure first became a concern after an outbreak of severe neurological symptoms in Minamata, Japan in the 1950s was traced to MeHg contamination of fish in Minamata Bay (Ekino et al., 2007; Harada, 1995). Mercury is a heavy metal emitted into the atmosphere during manufacturing. Some of these emissions settle into aquatic environments where the mercury is converted into organic forms, particularly MeHg, which are more neurotoxic (Kim & Zoh, 2012). MeHg can bioaccumulate in fish, leading to human exposure (Kim & Zoh, 2012), and it readily crosses the placenta leading to prenatal exposure (Kim & Zoh, 2012). Research has identified three primary mechanisms of MeHg action - disruption of calcium homeostatis, induction of oxidative stress, and interactions with sulfhydryl groups in cells (Ceccatelli et al., 2010).

Given the harmful neurological effects of MeHg observed in Minamata Bay and in a later incident in Iraq where people consumed MeHg contaminated grain (Clarkson et al., 1976), several prospective birth cohorts were established to study the impact of lower level prenatal exposure to MeHg through maternal fish consumption. Two cohorts, one in the Faroe Islands and one in the Republic of Seychelles, have provided much of the knowledge regarding the neurodevelopmental effects of prenatal MeHg exposure. Cohorts were established in these areas because of the high rates of fish consumption (Grandjean et al., 1997; Myers et al., 2003). In the Seychelle Islands, there have been three phases of study, with pilot, main, and follow-up cohorts (Davidson et al., 2008). The follow-up cohort was established to assess the effects of prenatal MeHg exposure, while controlling for the beneficial influence of a diet high in ocean fish. Researchers have also assessed the association between maternal dental amalgam (which contains a less toxic form of mercury) and neurodevelopmental outcomes in the Seychelles cohorts (Watson et al., 2011; Watson et al., 2012; Watson et al., 2013). Discussed here are results from the Seychelles, Faroe Islands, and other cohort studies that have assessed prenatal MeHg exposure and neurodevelopment.

4.1. Cognition and IQ

As with PCBs and lead, the impact of prenatal MeHg exposure on overall cognitive development has been studied across development from infancy to later childhood/ adolescence. However, the results are less consistent than for the other two contaminants. Tables 5 and 6 summarize the results and the exposure levels, respectively.

4.1.1. Infants and toddlers—Overall cognition was assessed in infants and toddlers using either the BSID or the Denver Developmental Screening Test (Table 5). In the Seychelle Islands, there were no associations between prenatal MeHg exposure or maternal dental amalgams and overall cognition on either the Denver Developmental Screening Test – Revised (Frankenburg et al., 1990) or the BSID MDI (Davidson et al., 2006; Davidson et al., 2008; Myers et al., 1995b; Stokes-Riner et al., 2011; Strain et al., 2008; Watson et al., 2012). Early life assessments were not conducted in the Faroe Island study.

Other studies that assessed cognition in the infant/toddler period include one in New York City which found no association between prenatal mercury exposure and the BSID MDI at 36 months (Lederman et al., 2008), and one in Spain that found no association at 14 months (Llop et al., 2012). In a Quebec cohort, researchers found no association between prenatal MeHg exposure and BSID-II MDI at 11 months (Boucher et al., 2014). The BSID-III was used in recent studies in Italy and Taiwan to assess children at 18 or 36 months, respectively. There were no associations between prenatal MeHg exposure and BSID-III cognitive, language, social-emotional, or adaptive behavior scores at 18 months in the Italian cohort (Valent et al., 2013). In contrast, in the Taiwanese cohort, there was an association between early MeHg exposure and lower expressive language scale scores, but no associations with other BSID-III scales (cognitive, receptive language, fine motor, and gross motor; Hsi et al., 2014).

In the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom, there were no associations between prenatal mercury exposure and outcomes on the Denver Developmental Screening Test at 18 months (Daniels et al., 2004). In contrast, there was an association between maternal and child fish consumption and higher scores, highlighting the beneficial impact maternal fish consumption can have on neurodevelopment (Daniels et al., 2004).

In summary, the results of studies assessing the relationship between prenatal mercury exposure and cognition during infancy have been mostly negative with only 1 of 8 studies reporting an association between prenatal mercury exposure and cognition during infancy. Interestingly, the one study showing a significant effect used the BSID-III, which includes measures of expressive and receptive language, and lower scores were limited to the expressive language scale.

4.1.2. Early childhood—Overall cognition was also assessed during early childhood in a few of the mercury studies (Table 5). In the Seychelles main cohort, there was no association between prenatal MeHg exposure and overall cognition as measured by the McCarthy GCI at 5.5 years of age (Davidson et al., 2006). There was also no association between prenatal MeHg exposure and scores on the McCarthy memory sub-scale at 5.5 years of age (Davidson et al., 2006). Similarly, there was no association between maternal amalgam history and McCarthy GCI at 5.5 years (Watson et al., 2011).

Children in the New York City cohort were assessed at 4 years using the WPPSI-R (Lederman et al., 2008), and there was an association between prenatal mercury exposure and lower full-scale, performance, and verbal IQ scores. Boys in a cohort in Spain were also assessed at 4 years, but using the McCarthy Scales (Freire et al., 2010). There was an association between postnatal mercury exposure and lower scores on the McCarthy GCI, and on the memory and verbal subscales, but no association with quantitative, perceptual-performance, or motor sub-scale scores.

4.1.3. Later childhood—In several of the mercury cohorts, IQ was assessed during later childhood using the WISC, and in one cohort IQ was assessed in adulthood using the Kaufman Brief Intelligence Test (Table 5). There were no associations between prenatal

MeHg and global cognition as measured by the WISC-III at 9 years of age, or the Kaufman Brief Intelligence Test at 19 years of age in the Seychelles main cohort (Davidson et al., 2006; van Wijngaarden et al., 2013). Only 5 of the 13 subtests of the WISC-III were used at 9 years of age (Block Design, Digit Span, Information, Coding, and Vocabulary), and there were no associations between prenatal exposure to MeHg and any of the individual subtests that were administered (Davidson et al., 2000; van Wijngaarden et al., 2009). However, when Axelrad and colleagues (2007) combined data from the Seychelles with data from the Faroe Islands and from a New Zealand cohort, they did see an association between higher prenatal exposure to MeHg and lower full-scale IQ scores at 6-9 years, measured using the WISC-R or WISC-III.

In the ALSPAC cohort, there was an association between prenatal mercury exposure and lower full-scale IQ scores at 8 years on the WISC-III; however, this effect was only seen in children of mothers from high social class (Julvez et al., 2013). No association was found between prenatal MeHg exposure and WISC-III full-scale, performance, or verbal IQ at 7-9 years in the Italian cohort or between prenatal mercury and WISC scores at 8 years in a Hong Kong cohort (Deroma et al., 2013; Lam et al., 2013).

In general, the results of studies assessing the relationship between prenatal mercury exposure and cognitive function during childhood have been mixed. However, it is noteworthy that, two larger studies with greater statistical power, the Axelrad study which combined data from three cohorts and the ALSPAC study, which included over 1,000 children, did find associations between higher prenatal mercury exposure and lower IQ scores in childhood.

4.2. Language Abilities

Language development was assessed at 5.5 years of age in all three of the Seychelles cohorts using the Preschool Language Scale (PLS; Zimmerman et al., 1979), but the results were not consistent across cohorts. In the pilot cohort, there was an association between higher prenatal MeHg exposure and lower auditory comprehension (Myers et al., 1995a), but no association between exposure and the total language or verbal abilities scales. In contrast, there was a small but significant association between early MeHg exposure and improved total PLS scores in the main cohort (Davidson et al., 1998). Further investigation into this result using non-linear models showed a negative association between MeHg and the PLS Total Language score when exposure was below 10 parts per million (ppm) in maternal hair and a positive association when MeHg levels were above 10 ppm (Axtell et al., 2000). There was no association between prenatal MeHg exposure and the age at which children first talked (Myers et al., 1997).

Unlike the pilot and main cohorts, there were no associations between prenatal MeHg exposure and PLS scores in the follow-up cohort. In both the Seychelles main and follow-up cohorts, no associations were found between maternal amalgam history and expressive or receptive language as measured by the PLS (Watson et al., 2011; Watson et al., 2013). In the follow-up cohort, there was also no association between maternal amalgam history and verbal knowledge as measured by the Kaufman Brief Intelligence Test at 5 years of age (Watson et al., 2013).

A few other studies also included direct assessments of language abilites. In the ALSPAC Study, there was no association between prenatal mercury exposure and outcomes on the MacArthur Communicative Development Inventory (Fenson et al., 1993) at 15 months (Daniels et al., 2004). In the Philippines, there was an association between prenatal exposure to mercury and lower scores on the expressive language quotient and clinical linguistic auditory milestone scale of the Cognitive Adaptive Test and Clinical Linguistic Auditory Milestone Scale (CAT/CLAMS; Watchel et al., 1994) at 2 years (Ramirez et al., 2003), but there were no associations with the receptive language quotient, cognitive adaptive test, or full-scale developmental quotient.

Although not a standard measure of language ability because it was used to assess adult language use after neurological insults, the Boston Naming Test was used to assess word knowledge in three studies. There was an association in boys but not girls between prenatal MeHg exposure and increased (better) overall scores on the Boston Naming Test at 9 years of age in the main Seychelles cohort (Davidson et al., 2000). The Boston Naming Test was also used in the Faroe Islands cohort when children were 7 and 14 years of age (Grandjean et al., 1997; Debes et al., 2006), revealing associations between prenatal exposure and poorer performance on both cued and non-cued naming at 7 years (Grandjean et al., 2014). At 14 years of age, there was an association with cued but not non-cued naming (Debes et al., 2006). Finally, in a Hong Kong cohort, there were no associations between prenatal mercury exposure and either non-cued or cued naming at 8 years (Lam et al., 2013).

School achievement tests which included measures of letter and word recognition were administered in the Seychelles main cohort. There were no associations between prenatal MeHg exposure and the Letter and Word Recognition Tests of the Woodcock-Johnson Test of Achievement at either 5.5 or 9 years (Davidson et al., 1998; Davidson et al., 2006). When boys and girls were considered separately, there was an association between maternal dental amalgam history and lower scores on the Letter and Word Recognition test of the Woodcock-Johnson Tests of Achievement at 5.5 years of age that was present in boys only. (Watson et al., 2011).

In summary, a handful of the mercury studies included direct assessments of language development, assessments of word knowledge, or school achievement tests that included measures of language comprehension. These tests were typically administered at just one or perhaps two time points, and, similar to the standardized tests of cognitive function, the results have been quite mixed, with effects on language abilities observed in some cohorts but not others. These inconsistencies may be related to the sources of mercury exposure. In the Seychelles cohorts, where relatively few negative impacts were observed, exposure occurred via consumption of ocean fish, which contains fats and nutrients that may be protective or beneficial to neurodevelopment. In contrast, in the Faroe Islands, some ocean fish was consumed, but exposure was primarily from consumption of pilot whale meat, which is not rich in those beneficial fats and nutrients.

4.3. Verbal and auditory learning and memory

Verbal learning and memory were assessed in a few of these studies. There was an association in the Seychelles main cohort between postnatal MeHg exposure and short-delay

free recall on the California Verbal Learning Test at 9 years (Palumbo et al., 2000). However, there were no associations between exposure and learning, immediate recall, or long-delay recall on the same task (Davidson et al., 1998; van Wijngaarden et al., 2009). Contrary to this, there was no association between prenatal MeHg exposure and memory at 9 years, as assessed using the memory scale of the Wide Range Assessment of Memory and Learning (Davidson et al., 2006).

In the Faroe Islands cohort, there was an association between prenatal MeHg exposure and both poorer learning and poorer short delay free recall on the California Verbal Learning Test at 7 years (Grandjean et al., 1997). However, there was no association between exposure and long delay free recall or verbal recognition memory on this task. Nor was there an association between MeHg exposure and the WISC-R Digit Span Task, another verbal working memory task (Grandjean et al., 1997). When models were adjusted to account for the positive effects of fatty acids from fish consumption, the association between MeHg exposure and both verbal learning and verbal short delay recall became stronger (Choi et al., 2014). Children from the Faroe Islands cohort were assessed again at 14 years (Debes et al., 2006), and prenatal MeHg exposure was again associated with learning, but, unlike at 7 years, there was no association with short-delay recall, nor was there an association with performance on the WISC-R Digit Span task, another verbal working memory task. Unlike the data at 7 years, it does not appear that these models were adjusted to account for the positive effects of fatty acids from fish consumption.

In contrast to the results from the Seychelles cohort, there was an association in the New Bedford cohort between higher prenatal exposure to MeHg and lower learning and verbal memory scores on the WRAML at 8 years of age (Orenstein et al., 2014). Verbal learning and memory was also assessed in children in the Hong Kong cohort at 8 years (Lam et al., 2013). There was an association between prenatal mercury exposure and both the short- and long-delay recall but not with learning on the Hong Kong List Learning Test (Chan & Kwong, 1998). Together, the results of these three studies suggest an effect of mercury exposure on verbal working memory, a functional domain that is critical to language development (Gathercole and Baddeley, 1993).

4.4. Summary

Although the results are mixed, a majority of the studies found associations between prenatal mercury exposure and at least one aspect of cognition relevant to language development. Although an association between early exposure to MeHg and overall cognition was not found when the Seychelles main cohort was considered alone, the meta-analysis by Axelrad and colleagues (2007) which combined data from the Seychelles, Faroe Islands, and New Zealand did find a significant association as did the large ALSPAC study. Findings from the Faroe Islands, Seychelles, and Hong Kong cohorts also suggest that there may be an association between prenatal mercury exposure and verbal working memory. Finally, although the results are inconsistent across studies, language assessments suggest that impairments in verbal comprehension and word knowledge might be associated with prenatal MeHg exposure.

5. Other Chemicals

A more limited amount of data are available for other contaminants. The evidence that early exposures to brominated diphenyl ether flame retardants or organophosphate insecticides negatively impact cognitive development is summarized briefly below. At this point, most studies have not followed children beyond early childhood.

5.1. Polybrominated Diphenyl Ethers

Polybrominated diphenyl ethers (PBDEs) are chemicals used as flame retardants in building materials, furniture, and electronics (Sjödin et al., 2008). The PBDEs are stable, bioaccumulative compounds that are structurally similar to the PCBs. Animals studies suggest they have similar toxic effects and similar mechanisms of action (Fonnum and Mariussen, 2009). PBDEs were used more extensively in the US; thus, exposures in America are typically about 20 times higher than in Europe (Hites, 2004). The effects of prenatal PBDE exposure have been studied in several prospective birth cohorts.

Early mental development has been assessed in three cohorts using the BSID-II and in one using the BSID-III, with mixed results. There were associations between prenatal PBDE exposure and lower MDI scores at 24 and 36 months in a New York City cohort (Herbstman et al., 2010). In contrast, there was only a marginal association between prenatal PBDE exposure and lower MDI scores at 12-18 months in a cohort in Spain, and no associations in cohorts in Cincinnati or Taiwan (Gascon et al., 2012; Chen et al., 2014; Chao et al., 2011). In a cohort in North Carolina, children were assessed using the Mullen Scales of Early Learning at 36 months (Mullen, 1995), and there was an association between prenatal PBDE exposure and higher (better) scores on the expressive language scale (Adgent et al., 2014).

In New York City, children's cognition was assessed again at 4 and 5 years using the WPPSI-R (Herbtsman et al., 2010). At 4 years, there was an association between higher prenatal PBDE exposure and lower verbal, performance, and full-scale IQ scores. At 5 years, there was an association with lower performance, but not verbal or full-scale IQ scores. Researchers in Spain found no associations between prenatal exposure to PBDEs and overall cognition or any sub-scale scores on the McCarthy Scales of Children's Abilities at 4 years (Gascon et al., 2011). In a cohort in California, there was an association between prenatal PBDE exposure and poorer verbal comprehension as well as a marginal association with lower full-scale IQ on the WISC-IV at 7 years (Wechsler, 2003; Eskenazi et al., 2013). Although the results of these early childhood assessments are mixed, two studies do suggest a possible relationship between higher prenatal PBDE exposure and poorer verbal abilities in early childhood. Thus, further studies are warranted to clarify whether prenatal exposure to PBDEs is associated with reduced verbal abilities or, more specifically, with impaired language development.

5.2. Organophosphate Insecticides

Organophosphate (OP) insecticides are a class of compounds with known neurotoxic effects at high exposure levels (Sultatos, 1994). Although most residential use of OP insecticides was banned in the United States in 2001, these chemicals are still widely used in agriculture

and mothers and children may still be chronically exposed through working in or living near agricultural fields, and via residues in food, particularly fresh fruits and vegetables (Bradman et al., 2007). The classically recognized mechanism of action for the OPs is inhibition of the activity of cholinesterase, the degradative enzyme for the neurotransmitter acetylcholine, leading to overstimulation of postsynaptic cells (Terry, 2012). However, there are also non-cholinesterase targets of OPs including cytoskeletal and motor proteins involved in axonal transport within neurons (Terry, 2012). The neurodevelopmental effects of prenatal exposure to OP insecticides have been studied in four prospective birth cohorts in the US.

In two New York and one California cohort, children were assessed at multiple ages between 6 and 36 months using the BSID-II. All three studies found at least one association between prenatal OP exposure and lower MDI scores, although the age at which an association was observed was not consistent across cohorts (Engel et al., 2011; Eskenazi et al., 2007; Rauh et al., 2006). In the California cohort, there was an association between prenatal OP exposure and lower scores on all 5 WISC-IV scales (working memory, processing speed, verbal comprehension, perceptual reasoning, and full-scale IQ) at 7 years (Bouchard et al., 2011). There was also an association in one of the two New York cohorts between prenatal OP exposure and lower working memory and full-scale IQ on WISC-IV at 7 years (Rauh et al., 2011). In contrast, there were no associations between prenatal OP exposure and scores on the WPPSI-III at 6 years or the WISC-IV at 7-9 years in the other New York cohort (Engel et al., 2011). Although the results are mixed, 3 of 3 studies found negative associations with MDI scores and 2 of 3 with IQ scores, indicating that prenatal OP exposure may negatively impact language development.

6. Conclusions

Table 7 summarizes the results across the three chemicals—PCBs, lead, and MeHg—that were the primary focus of this review, and reveals some interesting patterns. First, early cognitive assessments, most of which used the Mental Development Index (MDI) from the Bayley Scales of Infant Development (BSID) found little evidence of an association between PCB or mercury exposure and cognitive function. Only 1 of 5 PCB studies and 1 of 8 mercury studies reported negative associations. In contrast, 8 of 10 lead studies found negative associations between early lead exposure and MDI scores. The reason for this discrepancy in the sensitivity of early assessments is not clear, but late infancy and early childhood is typically the peak period for lead exposure due to the presence of lead in soil and house dust and the tendency for mouthing behaviors during this time. In contrast, prenatal exposures seem to play a more important role for PCBs and mercury. Unlike the early assessments, a majority of studies of PCBs, lead, and mercury reported associations between early exposures and reduced verbal ability or verbal IQ later in childhood. These findings highlight the fact that assessments conducted early in development do not always accurately predict risk, and demonstrate the importance of longitudinal follow-ups of children across developmental stages.

Second, very few studies of PCBs, lead or mercury included any direct assessments of language. Only 1 of 9 PCB studies included a direct assessment of language using the

Reynell Language Development Scales. Only the verbal comprehension subscale was used, and it was administered at only one age, 3.5 years (Patandin et al., 1999), so it is not clear if this PCB-related decrease in verbal comprehension is an effect that persists over the course of development. Similarly, only 1 of 12 lead studies included direct assessments of language. In this case the Sequenced Inventory of Communication Development was used to assess both receptive and expressive language at 12, 24, and 36 months and decreased expressive language scores were observed at 36 months (Ernhart and Greene, 1990), but there were no follow-up assessments to determine if this effect persisted at later ages.

Four mercury studies including three cohort studies conducted in the Seychelle Islands and one conducted in the Philippines used direct assessments of language. In the Seychelles, the Preschool Language Scale (PLS) was administered at 5 or 5.5 years of age, but the results were not consistent across the three cohorts. The study in the Philippines assessed receptive and expressive language at 2 years using the Clinical Linguistic Auditory Milestone Scale (CLAMS) and reported that higher prenatal mercury exposure was associated with lower expressive language scores (Ramirez et al., 2003). As in the PCB and lead studies, the language assessments in these mercury studies were only carried out at one age, and typically during early childhood, so it is unclear if they would persist over time. An interesting factor to consider is that all three of these contaminants have been associated with subtle deficits in hearing and/or auditory processing (e.g. Osman et al., 1999; Rice and Gilbert, 1992; Jusko et al., 2014). This suggests there could be a complex interplay whereby subtle deficits in auditory function impair language development resulting in deficits in overall cognitive function, and verbal abilities in particular. Complex interactions such as this are difficult to address in an epidemiological setting. Nonetheless, this is a potential exposure-outcome pathway that deserves careful consideration.

While there is evidence to suggest negative impacts of all three chemicals on language development, clearly the findings are mixed. Some of this is undoubtably related to differences in exposure across studies, but there are a number of other potential contributing factors. The various cohorts differ in terms of socioeconomic status, breastfeeding practices, and nutritional variables, all of which could influence outcomes. For example, data analyses in the Michigan and Dutch PCB cohorts that separated breastfed and formula-fed infants revealed that negative cognitive impacts were present only in the formula-fed infants, indicating that there could be a protective effect of breast feeding (Jacobson & Jacobson, 2002; Patandin et al., 1999). Indeed, the positive impact of breastfeeding on neurodevelopment in general, and cognitive development in particular is highlighted in this issue (Smith, this issue).

In addition, the Dutch cohort was primarily children from younger, less educated mothers that were negatively impacted by exposure, suggesting that a more advantaged rearing environment is also protective (Vreugdenhil et al., 2002). In line with this, there were no associations between PCB exposure and cognitive outcomes in the North Carolina cohort, in which the women were mostly well-educated and middle class, and the majority breast fed their infants. Studies have also found that the impact of lead exposure is more pronounced among more disadvantaged children (e.g., Dietrich et al., 1993). For mercury, nutritional factors may be especially important. When the primary source of exposure is ocean fish, as

was the case in the Seychelles studies, exposure occurs along with the intake of nutrients such as omega-3 fatty acids and selenium that may have protective effects (e.g. Smith, this issue); whereas, when mercury exposure is primarily from other sources, as was the case in the Faroe Islands, the relative absence of these protective nutrients could increase risk. In fact, Choi et al. (2014) found that adjusting for the positive impact of fatty acids in fish strengthened the negative association between mercury exposure and verbal learning.

Prospective cohort studies addressing the impact of prenatal and early postnatal exposure to some of the more contemporary environmental chemicals including the PBDEs and the organophosphate insecticides are still in the relatively early stages. However, like the studies of PCBs, lead, and mercury, most of these studies do not appear to include longitudinal assessments of language development.

Although there are still more questions than answers when it comes to the impact of chemicals on language development, uncertainty is not an excuse for inaction. Clinicians can have an important positive impact by educating families about how to limit exposure to environmental chemicals that may negatively impact language development (Hepp, 2011). There are simple common sense steps parents can take to reduce exposures to chemicals such as lead and pesticides, including removing shoes at the door, washing fruits and vegetables thoroughly, or eating organically grown food. Various resources are available online to assist with this effort (e.g. http://www.cdc.gov/nceh/lead/tips.htm; http://prhe.ucsf.edu/prhe/pdfs/pesticidesmatter_readable.pdf). The primary source of PCBs and mercury is contaminated fish and seafood, and the USEPA has easy-to-use online resources to inform pregnant women and parents about which types of fish are safe and healthy to eat and which types should be avoided (http://water.epa.gov/scitech/swguidance/fishshellfish/fishadvisories/general.cfm).

Lead is the only chemical discussed herein for which the federal government has set a threshold for action (Schnur & John, 2014). Clinicians can protect children's health by encouraging all parents to have their children screened for lead exposure, preferably between 1 and 2 years of age. The CDC provides specific guidance regarding steps that should be taken should blood lead levels above the 5 μg/dL threshold for action be detected in a child (Schnur & John, 2014). Clinicians can also inform parents that good nutrition and a positive, enriched social environment can help to protect children from the negative impacts of exposure to chemicals. In conclusion, clinicians can have an important positive impact by taking an exposure history with patients and their families to assess past and current exposures, and by providing materials or resources to families that may be at risk for certain types of exposures to guide them in how to limit exposure and reduce risk. Finally, clinicians have an important role to play in effecting change by advocating both locally and nationally for changes in policy that would reduce or prevent exposures of pregnant women and children to toxic environmental chemicals.

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Glossary

AA	arachidonic acid
ALSPAC	Avon Longitudinal Study of Parents and Children
BNT	Boston Naming Test
BSID	Bayley Scales of Infant Development
CAT/CLAMS	Cognitive Adaptive Test and Clinical Linguistic Auditory Milestone Scale
CDC	Centers for Disease Control and Prevention
CVLT	California Verbal Learning Test
DDST	Denver Developmental Screening Test
DHA	docosahexaenoic acid
fMRI	functional magnetic resonance imaging
GCI	general cognitive index
K-ABC	Kaufman Assessment Battery for Children
K-BIT	Kaufman Brief Intelligence Test
K-TEA	Kaufman Test of Educational Achievement
MCDI	MacArthur Communicative Development Index
MDI	mental development index
MeHg	methyl mercury
MLU	mean length of utterance
MSCA	McCarthy Scales of Children’s Abilities
OP	organophosphate
PBDE	polybrominated diphenyl ether
PCB	polychlorinated biphenyl
PDI	psychomotor development index
PLS	Preschool Language Scale
ppm	parts per million
SBIS	Stanford-Binet Intelligence Scale
SCAN	Screening Test for Auditory Processing Disorders
SICD	Sequenced Inventory of Communicative Development
WASI	Wechsler Abbreviated Scale of Intelligence

WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scales of Intelligence
WRAML	Wide Range Assessment of Memory and Learning

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Highlights

- Early PCB or lead exposure is associated with deficits in language-related domains.
- Results relating early mercury exposure to language development are mixed.
- Future studies should include specific tests of language development.

Learning Outcomes

The goal of this review is to summarize the evidence that prenatal and/or early postnatal exposure to certain chemicals may be associated with delays or impairments in language development. Readers will gain an understanding of the literature suggesting that early exposure to polychlorinated biphenyls (PCBs), lead, and mercury may be associated with decrements in cognitive domains that depend on language or are critical for language development. We also briefly summarize the smaller body of evidence regarding polybrominated diphenyl ether flame retardants (PBDEs) and organophosphate pesticides. Very few studies of exposure to these chemicals have used specific assessments of language development; thus, further investigation is needed before changes in clinical practice can be suggested.

Table 1

Summary of outcomes associated with early PCB exposure.

Cohort	Age at Assessment	Measure & Effect	Effect Size	Reference
		Cognition and IQ – Infants and Toddlers		
North Carolina	6, 12 mos.	BSID[a] MDI[b]: -, -		Gladen et al. 1988
North Carolina	18, 24 mos.	BSID MDI: -, -		Gladen & Rogan 1991
Netherlands	3, 7, 18 mos.	BSID MDI: -, -, -		Koopman-Esseboom et al. 1996
Duisburg	12, 24 mos.	BSID-II MDI: -, -		Wilhelm et al. 2008
Dusseldorf	7 mos.	BSID-II MDI: ↓	β = −0.69 ± 0.41 (ΣPCB (milk) vs raw score)	Winneke et al. 1998
Dusseldorf	30 mos.	BSID-II MDI: ↓	β = −4.98 (log base 2 of PCB sum vs raw score)	Walkowiak et al. 2001
Quebec	11 mos.	BSID-II MDI: -		Boucher et al., 2014
		Cognition and IQ – Early Childhood		
North Carolina	3, 4, 5 yrs.	MSCA[c] All subscales: -, -, -		Gladen & Rogan 1991
Netherlands	3.5 yrs.	K-ABC[d] Overall cognition: ↓[e]	β = −4.56 β 1.62 r = 0.65 (ln PCB sum vs raw score)	Patandin et al. 1999
Netherlands	6.5 yrs.	MSCA Overall cognition: ↓[f]	β = −147.51 ± 50.44 (adjusted for maternal age) β = −26.06 β 10.37 (adjusted for parental VIQ)	Vreugdenhil et al. 2002
Dusseldorf	3.5 yrs.	K-ABC Overall cognition: ↓	β = −4.30 (log base 2 of PCB sum vs raw score)	Walkowiak et al. 2001
Dusseldorf	6 yrs.	K-ABC Overall cognition: -		Winneke et al. 2005
Michigan	4 yrs.	MSCA GCI[g]: ↓[h]	β = −0.13 r = −0.09 (Prenatal PCB exposure vs raw score)[h]	Jacobson & Jacobson 2002
Michigan	4 yrs.	MSCA Verbal scale: ↓	β = −0.14 r = −0.12 (Prenatal PCB exposure vs raw score)	
		Memory scale: ↓	β = −0.18 r = −0.15 (Prenatal PCB exposure vs raw score)	Jacobson, Jacobson & Humphrey 1990
		Verbal memory subtest: ↓	β = −0.22 r = −0.19 (Cord serum PCB level vs raw score)	
Oswego	3 yrs. 2 mos.	MSCA GCI: ↓ Word knowledge: ↓	GCI: r = 0.20 Parameters for word knowledge not reported	Stewart et al. 2003
Oswego	4.5 yrs.	MSCA GCI: - Word knowledge: -		Stewart et al. 2003

Cohort	Age at Assessment	Measure & Effect	Effect Size	Reference
		Cognition and IQ – Later Childhood		
Michigan	11 yrs.	WISC-Ri Full-scale IQ: ↓	β = −0.17 r =-0.16 (Prenatal PCB exposure vs raw score)	Jacobson & Jacobson 1996
		Verbal IQ: ↓ Performance IQ: -	β = −0.16 r = −0.15 (Prenatal PCB exposure vs raw score)	
Oswego	9 yrs.	WISC-III Full-scale IQ: ↓	β = −0.167 R = 0.74 (Standardized β; placental PCB levels vs raw score)	Stewart et al. 2008
		Verbal IQ: ↓	β = −0.213 R = 0.72 (Standardized β; placental PCB levels vs raw score)	
		Language Abilities		
Netherlands	3.5 yrs.	Reynell Language Development Scales Verbal comprehension: ↓	β = −3.36 ± 1.91 R = 0.63 (lnΣPCBmaternal plasma vs raw score)	Patandin et al. 1999
Michigan	11 yrs.	WISC-R Verbal comprehension: ↓	β = −0.16 r = −0.15 (Prenatal PCB exposure vs raw score)	Jacobson & Jacobson 1996
Michigan	11 yrs.	Woodcock Reading Mastery Tests – Revised Word comprehension: ↓	β = −0.17 r = −0.18 (Prenatal PCB exposure vs raw score)	Jacobson & Jacobson 1996
		Reading comprehension: ↓	β = −0.13 r = −0.14 (Prenatal PCB exposure vs raw score)	
Faroe Islands	7 yrs.	BNT[j] Reaction time: ↑	β = −1.56 (LogΣPCBcord – wet weight vs raw score)	Grandjean et al. 2001
		Verbal and Auditory Learning and Memory		
Netherlands	9 yrs.	Auditory-Verbal Learning Task (Dutch Version) Short-term memory: – Long-term memory: -		Vreugdenhil et al. 2004
Michigan	4 yrs.	MSCA Verbal memory subtest: ↓	β = −0.22 r = −0.19 (Cord serum PCB level vs raw score)	Jacobson, Jacobson & Humphrey 1990
Michigan	11 yrs.	Digit Span task Verbal working memory: ↓[h]	β = −0.31 r = −0.22 (Standardized regression coefficient; prenatal PCB exposure vs raw score)	Jacobson & Jacobson 2003
		Seashore Rhythm Test Auditory working memory: ↓	β = −0.15 r = −0.14 (Standardized regression coefficient; prenatal PCB exposure vs raw score)	
Faroe Islands	7 yrs.	CVLT[k] Learning: -		Grandjean et al. 2001

Cohort	Age at Assessment	Measure & Effect	Effect Size	Reference
		Short delay recall: - Long delay recall: - Long delay recognition: -		
New Bedford	8 years	WRAML[l] Learning: - Verbal memory: -		Orenstein et al., 2014

Note: A direct comparison of effect sizes may be inappropriate due to differences in statistical analyses, including differences in how exposure is measured, the transformation of independent variables, and adjustment for confounders.

i WISC: Wechsler Intelligence Scale for Children.

[a] BSID: Bayley Scales of Infant Development.

[b] MDI: mental development index.

[c] MSCA: McCarthy Scales of Children's Abilities

[d] K-ABC: Kaufman Assessment Battery for Children.

[e] Only in formula-fed children.

[f] Only in children born to younger mothers or to parents with lower verbal IQ scores.

[g] GCI: general cognitive index.

[h] Only in children breast-fed less than 6 weeks.

[j] BNT: Boston Naming Test.

[k] CVLT: California Verbal Learning Test.

Table 2

Comparison across cohorts of median PCB 153 levels in maternal serum[a]

Cohort	Median PCB 153 serum levels (ng/g lipid)	Measured in
North Carolina	80	Maternal serum
Netherlands	100	Maternal plasma
Duisburg[b]	70	Milk
Dusseldorf	140	Milk
Quebec	100	Maternal plasma
Michigan	120	Maternal serum
Oswego	40	Milk
Faroe Islands	450	Maternal serum
New Bedford	30	Milk

[a]Data taken from Longnecker et al., 2003, unless otherwise noted. Some data has been transformed from measures in other biological samples for ease of comparison.

[b]This cohort was not presented in Longnecker et al., 2003. Median values for PCB 153 were published only for milk collected 2 weeks after birth. This value was transformed using the methods found in Longnecker et al., 2003. The median value of 85 ng/g lipid was multiplied by 1.05 to account for lower levels of PCBs in milk at 2 weeks after birth as compared to at birth. This value was then divided by 1.34, as the ratio of the median PCB concentration in milk to serum was found to have an unweighted median value of 1.34 across 5 studies. This value was then rounded to the nearest 10.

Table 3

Summary of outcomes associated with early lead exposure.

Cohort/Location	Age at Assessment	Measure & Effect	Effect Size	Reference
		Cognition and IQ – Infants and Toddlers		
Boston	6, 12, 18, 24 mos.	BSID[a] MDI[b]: ↓[c], ↓, ↓, ↓	Longitudinal analysis: High exposure group vs low exposure group: −4.8 points High exposure group vs medium exposure group: −3.8 points	Bellinger et al., 1987
China	6, 12, 24, 36 mos.	BSID-II MDI: ↓, ↓, ↓, ↓	High exposure group vs. low exposure group: −5.0 points, −5.1 points, −5.8 points, −5.5 points	Liu et al., 2014
Poland	12, 24, 36 mos.	BSID MDI: ↓[c], ↓, ↓	Highest quintile vs lowest quintile: −3.7 points, −2.1 points, −2.2 points	Jedrychowski et al., 2009
Mexico City	24 mos.	BSID MDI: ↓	β = −3.54 R^2 = 0.22 (standardized beta; ln plasma lead vs raw score)	Hu et al., 2006; Tellez-Rojo et al., 2006
Port Pirie	24 mos.	BSID MDI: ↓	β = −0.26 (BPb vs. raw score) r = −0.12	Vimpani et al., 1988
Yugoslavia	24 mos.	BSID MDI: ↓	β = −5.307 (BPb vs. raw score) R^2 = 1.0	Wasserman et al., 1992
Taiwan	24-36 mos.	BSID-II MDI: ↓	r = −0.164	Huang et al., 2012
Cincinnati	3, 6, 24 mos.	BSID MDI: ↓, ↓, -	β = −0.60 (Cord blood Pb vs. raw score) β = −0.76 (Maternal BPb vs. raw score)	Dietrich et al., 1987; Dietrich et al., 1990
Cleveland	6, 12, 24 mos.	BSID MDI: -, -, -		Ernhart & Greene, 1990; Ernhart et al., 1989
Quebec	11 mos.	BSID-II MDI: -		Boucher et al., 2014
		Cognition and IQ – Early Childhood		
Boston	4 yrs. 9 mos.	MSCA[d] GCI[e]: ↓	β = −2.95 (Ln BPb vs raw score)	Bellinger et al., 1991
Rochester	3 yrs., 5 yrs.	SBIS[f] Full-scale IQ: ↓, ↓	β = −0.31 β = −0.61 (BPb vs. score)	Canfield et al., 2003
Mexico City	4 yrs.	MSCA GCI: ↓	β = −6.5 (BPb vs. score)	Braun et al., 2012
Port Pirie	4 yrs.	MSCA GCI: ↓	High exposure group vs. low exposure group: −8.9 points	Tong et al., 1998
Yugoslavia	3 yrs.	MSCA GCI: -		Wasserman et al., 2000
Yugoslavia	4 yrs.	MSCA GCI: ↓ Perceptual performance: ↓ Verbal: ↓	β = −10.44 (Log BPb vs. score) β = −6.76 (Log BPb vs. score)	Wasserman et al., 1994

Cohort/Location	Age at Assessment	Measure & Effect	Effect Size	Reference
		Quantitative: ↓ Memory: ↓ Motor: ↓	β = −3.73 (Log BPb vs. score) β = −6.19 (Log BPb vs. score) β = −3.82 (Log BPb vs. score) β = −4.88 (Log BPb vs. score)	
Yugoslavia	5 yrs.	WPPSI-R[g] Full-scale IQ: ↓	β = −6.05 (Maternal BPb vs. score)	Wasserman et al., 1997
Taiwan	5-6 yrs.	WPPSI-R Full-scale IQ: ↓ Performance IQ: ↓ Verbal IQ: ↓	r = −0.240 r = −0.197 r = −0.229	Huang et al., 2012
Cincinnati	4 yrs.	K-ABC[h] Mental processing: ↓ [i] Sequential processing: ↓ [i] Simultaneous processing: ↓ Nonverbal: ↓ Achievement: ↓ [i]	β = −0.63 (BPb vs. score) β = −0.68 (BPb vs. score) β = −0.50 (BPb vs. score) β = −0.63 (BPb vs. score) β = −0.28 (BPb vs. score)	Dietrich et al., 1991
Cincinnati	5 yrs.	K-ABC Mental processing: - Sequential processing: - Simultaneous processing: ↓ Nonverbal: ↓ Achievement: -	β = −0.20 (BPb vs. score) β = −0.15 (BPb vs. score)	Dietrich et al., 1992
Cleveland	3 yrs.	SBIS: -		Ernhart & Greene, 1990; Ernhart et al., 1989
Cleveland	4 yrs. 10 mos.	WPPSI: -		Ernhart & Greene, 1990; Ernhart et al., 1989
		Cognition and IQ – Later Childhood & Adulthood		
Boston	10 yrs.	WISC-R[j] Full-scale IQ: ↓ Performance IQ: ↓[c] Verbal IQ: ↓	β = −0.58 (BPb vs. score) β = −0.39 (BPb vs. score) β = −0.63 (BPb vs. score)	Bellinger, Stiles, & Needleman, 1992
Boston	Adulthood (mean age = 29 yrs.)	WASI[k] Full-scale IQ: ↓ Performance IQ: ↓ Verbal IQ: ↓[c]	β = −1.66 (BPb vs. score) R^2 = 0.117 β = −0.81 (BPb vs. score) R^2 = 0.115 β = −0.80 (BPb vs. score) R^2 = 0.080	Mazumdar et al., 2011
Port Pirie	7 yrs.	WISC-R Full-scale IQ: ↓ Performance IQ: – Verbal IQ: ↓	β = −5.8 (log BPb vs score) β = −4.6 (log BPb vs score)	Baghurst et al., 1992
Port Pirie	11-13 yrs.	WISC-R Full-scale IQ: ↓ Performance IQ: ↓ Verbal IQ: ↓	β = −3.7 (Log BPb vs. score) β = −3.7 (Log BPb vs. score) β = −4.0 (Log BPb vs. score)	Tong et al., 1996
Yugoslavia	7 yrs.	WISC-III Full-scale IQ: ↓ Performance IQ: ↓ Verbal IQ: ↓ Perceptual organization: ↓ Freedom from distractability: ↓ Verbal comprehension: ↓	β = −8.5864 (cumulative lead exposure vs. score) β = −9.1669 (cumulative lead exposure vs. score) β = −6.5931 (cumulative lead exposure vs. score) β = −10.1340 (cumulative lead exposure vs. score) β = −8.7952 (cumulative	Wasserman et al., 1997

Cohort/Location	Age at Assessment	Measure & Effect	Effect Size	Reference
			lead exposure vs. score) β = −4.4100 (cumulative lead exposure vs. score)	
Taiwan	8-9 yrs.	WISC-III Full-scale IQ: ↓ Performance IQ: - Verbal IQ: -	β = −0.220 (Ln BPb vs score)	Huang et al., 2012
Cincinnati	6.5 yrs.	WISC-R Full-scale IQ: ↓ Performance IQ: ↓ Verbal IQ: -	β = −0.23 (Ln BPb vs score) β = −0.38 (Ln BPb vs score)	Dietrich et al., 1993
		Language Abilities		
Boston	10 yrs.	K-TEA[l] Composite score: ↓ Mathematics: ↓ Reading: ↓[c] Spelling: ↓	β = −0.89 (BPb vs score) β = −0.91 (BPb vs score) β = −0.38 (BPb vs score) β = −0.97 (BPb vs score)	Bellinger, Stiles, & Needleman, 1992
Yugoslavia	7 yrs.	WISC-III Verbal comprehension: ↓	β = −4.4100 (cumulative lead exposure vs. score)	Wasserman et al., 1997
Cincinnati	5 yrs.	SCAN[m] Filtered word subtest: ↓ Figure-ground subtest: -	β = −0.26 (BPb vs. score)	Dietrich et al., 1992
Cleveland	12 mos.	SICD[n] Receptive language: - Expressive language: -		Ernhart & Greene, 1990
Cleveland	24 mos.	SICD Receptive language: - Expressive language: -		Ernhart & Greene, 1990
Cleveland	36 mos.	SICD Receptive language: - Expressive language: ↓	r = −0.21	Ernhart & Greene, 1990
Cleveland	24 mos.	Recorded sample of spontaneous speech MLU[o]: ↓	r = −0.24	Ernhart & Greene, 1990
North Carolina	4th grade	End of Grade standardized state testing Reading: ↓ Mathematics: ↓	β = −0.20 (BPb vs. score) β = −0.16 (BPb vs. score)	Miranda et al., 2007

Note: A direct comparison of effect sizes may be inappropriate due to differences in statistical analyses, including differences in how exposure is measured, the transformation of independent variables, and adjustment for confounders.

[p] fMRI: functional magnetic resonance imaging.

[a] BSID: Bayley Scales of Infant Development.

[b] MDI: mental development index.

[c] Marginal association.

[d] MSCA: McCarthy Scales of Children's Abilities.

[e] GCI: general cognitive index.

[f] SBIS: Stanford Binet Intelligence Scale.

[g] WPPSI: Wechsler Preschool and Primary Scales of Intelligence.

[h] K-ABC: Kaufman Assessment Battery for Children.

[i] Only in poorest children.

[j] WISC: Wechsler Intelligence Scales for Children.

[k] WASI: Wechsler Abbreviated Scales of Intelligence.

[l] K-TEA: Kaufman Tests of Educational Achievement.

[m] SCAN: Screening Test for Auditory Processing Disorders.

[n] SICD: Sequenced Inventory of Communication Development.

[o] MLU: mean length of utterance.

Table 4

Comparison of lead exposure levels across cohorts

Cohort	BPb (μg/dL)[a]	Measured in[b]
Boston	6.5	Child blood
China	Low exposure group: 3.31 High exposure group: 4.39	Child blood
Poland	Median: 1.23	Cord blood[c]
Mexico City	Median: 4.6	Child blood
Port Pirie	Geometric mean: 21.3	Child blood
Yugoslavia	Geometric means: Low exposure group: 8.4 High exposure group: 35.5	Child blood
Taiwan	Geometric mean: 2.48	Child blood
Cincinnati	17.45	Child blood
Cleveland	16.70	Child blood
Quebec	Median: 3.5	Cord blood
Rochester	9.7	Child blood
North Carolina	4.52	Child blood between 1 and 2 years

[a] Reported as a mean value unless otherwise noted.

[b] Measured at approximately 2 years of age unless otherwise noted.

[c] Cord blood levels are reported for cohorts that did not measure or report blood levels in children at 2 years of age.

Table 5

Summary of outcomes associated with early mercury exposure.

Cohort/Location	Age at Assessment	Measure & Effect	Effect Size	Reference
		Cognition and IQ – Infants and Toddlers		
Seychelles – Main	6.5 mos.	DDST-R[a] Overall cognition: -		Myers et al., 1995b
Seychelles – Main	19, 29 mos.	BSID-II[b] MDI[c]: -, -		Davidson et al., 2006
Seychelles - Follow-up	9, 30 mos.	BSID-II MDI: -, -		Davidson et al., 2008; Stokes-Riner et al., 2011; Strain et al., 2008
Seychelles - Follow-up (Amalgam)	9, 30 mos.	BSID-II MDI: -, -		Watson et al., 2012
New York City	36 mos.	BSID-II MDI: -		Lederman et al., 2008
Spain	14 mos.	BSID MDI: -		Llop et al., 2012
Quebec	11 mos.	BSID-II MDI: -		Boucher et al., 2014
Taiwan	36 mos.	BSID-III Cognitive: - Receptive language: - Expressive language: ↓ Fine motor: - Gross motor: -	β = −1.19 (Child nail Hg vs. score)	Hsi et al., 2014
Italy	18 mos.	BSID-III Cognitive: - Language: - Social-emotional: - Adaptive behavior: -		Valent et al., 2013
United Kingdom	18 mos.	DDST: -		Daniels et al., 2004
		Cognition and IQ – Early Childhood		
Seychelles – Main	5.5 yrs.	MSCA[d] GCI[e]: -		Davidson et al., 2006
Seychelles – Main (Amalgam)	5.5 yrs.	MSCA GCI: -		Watson et al., 2011
Seychelles – Main	5.5 yrs.	MSCA Memory sub-scale: -		Davidson et al., 2006
New York City	4 yrs.	WPPSI-R[f] Full-scale IQ: ↓ Performance IQ: ↓ Verbal IQ: ↓	β = −3.8 (Log cord blood Hg vs. score) β = −3.4 (Log cord blood Hg vs. score) β = −2.9 (Log cord blood Hg vs. score)	Lederman et al., 2008
Spain	4 yrs.	MSCA General cognitive: ↓ Quantitative: - Memory: ↓ Verbal: ↓ Perceptual-performance: - Motor: -	β = −6.60 (Fish intake vs. score) β = −7.19 (Hair Hg vs. score) β = −6.54 (Hair Hg vs. score)	Freire et al., 2010

Cohort/Location	Age at Assessment	Measure & Effect	Effect Size	Reference
		Cognition and IQ – Later Childhood & Adulthood		
Seychelles – Main	9 yrs.	WISC-III[g] Global cognition: -		Davidson et al., 2006
Seychelles – Main	9 yrs.	WISC-III Block Design: - Digit Span: - Information: - Coding: - Vocabulary: -		Davidson et al., 2000; van Wijngaarden et al., 2009
Seychelles – Main	19 yrs.	K-BIT[h]: -		van Wijngaarden et al., 2013
Seychelles – Main	9 yrs.	WRAML[i] Overall memory: -		Davidson et al., 2006
Faroe Islands, New Zealand, Seychelles	6-9 yrs.	WISC-R & WISC-III Full-scale IQ: ↓	β = −0.18 (Hair Hg vs. score)	Axelrad et al., 2007
Italy	7-9 yrs.	WISC-III Full-scale IQ: – Performance IQ: – Verbal IQ: -		Deroma et al., 2013
United Kingdom	8 yrs.	WISC-III Full-scale IQ: ↓[j]	β = −4.9 (Log cord blood Hg vs. score)	Julvez et al., 2013
Hong Kong	8 yrs.	WISC Full-scale IQ: -		Lam et al., 2013
		Language Abilities		
Seychelles – Pilot	5.5 yrs.	PLS[k] Total language: - Verbal ability: - Auditory comprehension: ↓		Myers et al., 1995a
Seychelles – Main	5.5 yrs.	PLS Total language: ↑	β = 0.13 (Maternal MeHg vs. score)	Davidson et al., 1998
Seychelles – Main	5.5 yrs.	PLS Total language: ↓ (< 10 ppm[l] MeHg) ↑ (> 10 ppm MeHg)	β = −0.089 (Maternal hair Hg vs. score) β = 1.3 (Maternal hair Hg vs. score)	Axtell et al., 2000
Seychelles – Main (Amalgam)	5.5 yrs.	PLS Expressive language: - Receptive language: -		Watson et al., 2011
Seychelles – Follow-up (Amalgam)	5 yrs.	PLS Total language: – Verbal ability: – Auditory comprehension: -		Watson et al., 2013
Seychelles – Follow-up	5 yrs.	PLS Total language: ↑ with DHA ↓ with AA - with mercury Verbal ability: ↑ with DHA ↓ with AA - with mercury Auditory Comprehension: ↓ with AA -with DHA -with mercury	β = 41.3 (Maternal DHA vs. score) β = −15.8 (Maternal DHA vs. score) β = 24.6 (Maternal DHA vs. score) β = −8.3 (Maternal DHA vs. score) β = 16.7 (Maternal DHA vs. score)	Strain et al., 2012

Cohort/Location	Age at Assessment	Measure & Effect	Effect Size	Reference
Seychelles – Main	19 mos.	Age at which child talked: -		Myers et al., 1997
Seychelles – Follow-up (Amalgam)	5 yrs.	K-BIT Verbal knowledge: -		Watson et al., 2013
Seychelles – Main	5.5 yrs.	Woodcock-Johnson Letter and Word Recognition Tests of Achievement: -		Davidson et al., 1998
Seychelles – Main	9 yrs.	Woodcock-Johnson Letter and Word Recognition Tests of Achievement: -		Davidson et al., 2006
Seychelles – Main (Amalgam)	5.5 yrs.	Woodcock-Johnson Letter and Word Recognition Tests of Achievement : ↓[m]	β = −0.16 (Maternal dental amalgam occlusal sites vs. score)	Watson et al., 2011
Seychelles – Main	9 yrs.	BNT[n] Total score: ↑[m]	β = 0.42 (Maternal hair MeHg vs. score)	Davidson et al., 2000; van Wijngaarden et al., 2009
Faroe Islands	7 yrs.	BNT Non-cued naming: ↓ Cued naming: ↓	β = −1.72 (Log maternal hair MeHg vs. score) β = −1.91 (Log maternal hair MeHg vs. score)	Grandjean et al., 2014
Faroe Islands	14 yrs.	BNT Non-cued naming: - Cued naming: ↓	β = −5.90 (Log_2 cord blood MeHg vs. score)	Debes et al., 2006
United Kingdom	15 mos.	MCDI[o]: -		Daniels et al., 2004
Hong Kong	8 yrs.	BNT Non-cued naming: - Cued naming: -		Lam et al., 2013
Phillipines	24 mos.	CAT/CLAMS[p] Receptive language quotient: – Expressive language quotient: ↓ CLAMS: ↓ CAT: – Full-scale developmental quotient: -	r = −0.284 r = −0.171	Ramirez et al., 2003
		Verbal and Auditory Learning and Memory		
Seychelles – Main	9 yrs.	CVLT[q] Learning: - Immediate recall: - Short delay recall: ↓ Long delay recall: -	β = −0.37 (Maternal hair Hg vs. score)	Davidson et al., 2000; van Wijngaarden et al., 2009
Faroe Islands	7 yrs.	CVLT Learning: ↓ (marginal) Short delay free recall: ↓ Long delay free recall: - Long delay recognition: - WISC-R Digit Span: -	β = −14.3 (Log_2 cord blood Hg vs. score) β = −18.9 (Log_2 cord blood Hg vs. score)	Choi et al., 2014; Grandjean et al., 1997; Grandjean et al., 1998; Grandjean et al., 2014
Faroe Islands	14 yrs.	CVLT Learning: ↓ Short delay free recall: - Long delay free recall: - Long delay recognition: - WISC-R Digit Span: -	β = −9.01 (Log_2 cord blood Hg vs. score)	Debes et al., 2006
Hong Kong	8 yrs.	Hong Kong List Learning Test	β = −1.087 (Cord blood Hg vs. score)	Lam et al., 2013

Cohort/Location	Age at Assessment	Measure & Effect	Effect Size	Reference
		Learning: – Short delay recall: ↓ Long delay recall: ↓	β = −1.161 (Cord blood Hg vs. score)	
New Bedford	8 years	WRAML Learning: ↓ Verbal memory: ↓	β = −2.4 (Maternal hair Hg vs. score) β = −1.9 (Maternal hair Hg vs. score)	Orenstein et al., 2014

Note: A direct comparison of effect sizes may be inappropriate due to differences in statistical analyses, including differences in how exposure is measured, the transformation of independent variables, and adjustment for confounders.

[a] DDST: Denver Developmental Screening Test.

[b] BSID: Bayley Scales of Infant Development.

[c] MDI: mental development index.

[d] MSCA: McCarthy Scales of Children's Abilities.

[e] GCI: general cognitive index.

[f] WPPSI: Wechsler Preschool and Primary Scales of Intelligence.

[g] WISC: Wechsler Intelligence Scales for Children.

[h] K-BIT: Kaufman Brief Intelligence Test.

[i] WRAML: Wide Range Assessment of Memory and Learning.

[j] Only in children of mothers from high social class.

[k] PLS: Preschool Language Scale.

[l] ppm: parts per million.

[m] In boys only.

[n] BNT: Boston Naming Test.

[o] MCDI: MacArthur Communicative Development Index.

[p] CAT/CLAMS: Cognitive Adaptive Test and Clinical Linguistic Auditory Milestone Scale.

[q] CVLT: California Verbal Learning Test.

Table 6

Comparison across cohorts of total mercury levels in cord blood

Cohort	Total cord blood Hg (μg/L)[a]	Measured in
Seychelles – Pilot	Median: 48.28	Maternal hair[b]
Seychelles – Main	46.24	Maternal hair
Seychelles – Follow-up	50.15	Maternal hair
New York City	7.82	Cord blood
Spain	Geometric mean: 8.4	Cord blood
Quebec	22.5	Cord blood
Taiwan	Geometric means:	
	1.96 μg/g MeHg[c]	Child hair
	0.64 μg/g MeHg[c]	Child fingernail
	0.55 μg/g MeHg[c]	Child toenail
Italy	5.54	Cord blood
United Kingdom	Geometric mean: 0.01	Cord blood
Faroe Islands	Geometric mean: 29.125	Cord blood
Hong Kong	Median: 9.18	Cord blood
Phillipines	53.3[d]	Cord blood
New Bedford	4.08	Maternal hair

[a] Reported as a mean value unless otherwise noted. Some values have been transformed from methylmercury to total mercury using ratio for methylmercury to total mercury of 0.8 (WHO, 1990).

[b] For cohorts that did not report cord blood mercury levels, maternal hair levels were transformed to cord blood levels for ease of comparison. This transformation was done based on information from WHO (1990). First, values were transformed using a ratio for hair mercury to maternal blood mercury of 250:1. That value was then transformed using a ratio for cord blood to maternal blood of 1.7 to give an approximate value for cord blood total mercury.

[c] Neither cord blood nor maternal hair nor blood levels were reported for this cohort; thus, a transformation to cord blood levels cannot be performed. Values reported here are for reference and should not be directly compared to values reported for other cohorts.

[d] Only among those with mercury detected (detection limit = 20 μg/L).

Table 7

Number of cohorts showing detrimental effects in specific cognitive domain as a proportion of cohorts assessed.

Contaminant	Cognition and IQ – Infants and Toddlers	Cognition and IQ – Early Childhood	Cognition and IQ – Later Childhood	Language Abilities	Verbal and Auditory Learning and Memory
PCBs	1/5	4/5	2/2	3/3	1/4
Lead	8/10	7/8	5/5	5/5	
Mercury	1/8	2/3	2/5	4/7	4/4