The Impact of Prenatal Exposure to Environmental Contaminants on Cognitive and Brain Development in Childhood and Adolescence

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Abstract

The Impact of Prenatal Exposure to Environmental Contaminants on Cognitive and Brain Development in Childhood and Adolescence

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Exposure to environmental contaminants is ubiquitous. Studies increasingly suggest that these chemicals pose a risk for human health, including neurodevelopment in children. Prenatal exposure to environmental contaminants warrants particular concern given the fragility of fetal development and the foundational nature of this period for the rest of the lifespan. However, little is known about potential mechanisms. Furthermore, researchers and practitioners in psychology and child development are generally unaware of such toxicological research.

The objective of the present thesis is to examine the impact of prenatal contaminant exposure on neurodevelopment in children, explore avenues for future research on potential mechanisms, improve dissemination of toxicology studies to psychology researchers and practitioners, and advocate for a larger role of psychologists in prevention, intervention, and public policies. To do so, the thesis contains three manuscripts.

The first manuscript is a PRISMA-guided scoping review of studies on prenatal exposure to a wide range of environmental contaminants and various neurodevelopmental outcomes in children. This chapter provides an overview of neurotoxicology research from birth to age 17 inclusively and aims to make these findings more accessible to clinicians and researchers in fields relevant for child development.

The second manuscript is an empirical study within a pan-Canadian pregnancy cohort examining the association between prenatal exposure to a flame-retardant chemical and IQ at age 3 years. This chapter provides a typical example of a developmental neurotoxicology study in terms of its method, results, and effect sizes.

The third manuscript is an empirical study with an American community cohort composed of participants aged 6 to 20 years old. Participants underwent executive function testing and structural brain imaging at baseline and up to two follow-up sessions scheduled 15 months apart. This chapter aims to inform the design of future research into the mechanisms of neurotoxicity following contaminant exposure.

Overall, prenatal contaminant exposure is associated with small adverse effects on cognition for individuals, but has significant societal implications. Future studies should aim to better characterize potential mechanisms like cortical morphology to inform prevention and intervention efforts. Lastly, the thesis highlights the benefits of disseminating neurotoxicology findings to psychologists and child development experts.

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Contributions of Authors

The present thesis contains three manuscripts. While I wrote each of them in their entirety, I received support in other aspects of the research. All authors reviewed the final manuscripts and approved the contents.

The conceptualization of the scoping review in Chapter 2 was done collaboratively between Dr. Linda Booij and I in the wake of the COVID-19 pandemic, which had disrupted my original doctoral research plans. My committee members Dr. Natalie Phillips and Dr. Diane Poulin-Dubois provided feedback on the design of the review and advised that we follow PRISMA guidelines. I conducted the literature search, initial article screening, and article selection. I received invaluable help from Dr. Carola Tuerk to extract the data and build detailed tables summarizing the results. I drafted the manuscript and created the figures. I received feedback from Dr. Tuerk and Dr. Booij. Micaël Thériault was tremendously helpful in proofreading the article and its supplemental materials. This scoping review is a manuscript in preparation.

The empirical study in Chapter 3 was conducted in the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort. Drs. Gina Muckle, Tye E. Arbuckle, and William D. Fraser were responsible for funding acquisition for the MIREC cohort. Drs. Muckle and Arbuckle, along with Drs. William D. Fraser and Bruce P. Lanphear were involved in data collection. Drs. Linda Booij and Maryse Bouchard, along with Drs. Muckle, Arbuckle, Fraser, and Lanphear were responsible for project administration. The study was conceptualized by Dr. Booij, Dr. Bouchard, and I. Dr. Bouchard and I collaborated on the statistical analyses. I wrote the original draft with detailed feedback from Drs. Booij and Bouchard. Feedback was also provided by Dr. Jean R. Séguin and Dr. Elizabeth Asztalos along with Drs. Muckle, Arbuckle, Fraser, and Lanphear. This article is published in Environment International.

The empirical study in Chapter 4 was conducted in the Nathan Kline Institute Rockland Sample (NKI-RS) cohort. Data are available upon request. I conceptualized the project with support from Dr. Linda Booij and Dr. Carola Tuerk. Dr. Budhachandra Khundrakpam accessed the NKI-RS data and was responsible for data cleaning and quality control procedures. Statistical analyses were conducted by Dr. Khundrakpam, Mr. Sean Spinney, and Dr. Kevin F. Casey. I conducted the literature review and drafted the manuscript. Drs. Booij and Casey provided feedback on the initial draft and interpretation of findings. I edited and revised the manuscript with more detailed feedback from Dr. Booij. This study is a manuscript in preparation.

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Chapter 1: General Introduction

General Introduction

Environmental contaminants are naturally-occurring or industrially-manufactured chemicals that can be found in nearly everything in our environments. These contaminants are in indoor and outdoor air, food, water, and several consumer goods such as furniture, electronics, clothing, and personal care products (Grandjean & Landrigan, 2006, 2014; Schantz et al., 2020; Vrijheid et al., 2016). The public is generally aware of a few key contaminants – such as mercury (Hg), bisphenol A (BPA), and pesticides – through media coverage (Mello, 2015). In recent months, it has been the turn of per- and polyfluoroalkyl substances (PFAS) to receive greater media coverage and receive the title of "forever chemical" due to their persistent nature. (e.g., Khandaker, 2023, July 19; Singh, 2023, June 1; Thurnton, 2023, May 20). Further details about key contaminants are provided later in this chapter under the heading "Relevant Background Information on Selected Contaminants". Although a handful of contaminants are relatively well-known by the general population, regulatory and government agencies monitor many more. For example, the Centers for Disease Control and Prevention (CDC) in the United States periodically monitors over 400 chemicals and their by-products to examine their impact on human health and the environment (CDC, 2021a).

Exposure to various contaminants has been associated with adverse human health outcomes across the lifespan, including mental, physical, reproductive, and neurological health issues (Kahn et al., 2020; Landrigan et al., 2020; Rivollier et al., 2019; Vrijheid et al., 2016; Wigle et al., 2008; Zeliger, 2013). In the present thesis, the focus is on associations between prenatal contaminant exposure and neurocognitive outcomes in youth, including symptoms and diagnoses of attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and intellectual disability (ID) (Bellinger, 2013; Grandjean & Landrigan, 2006, 2014; Vrijheid et

al., 2016; Wigle et al., 2008). Chemicals that impact neuropsychological and cognitive functioning are said to be "neurotoxic" (Grandjean & Landrigan, 2014). As such, throughout the thesis, the word "neurodevelopment" is used to describe functions related to neurodevelopmental disorders (e.g., intellectual functioning, attention, executive function, symptoms of autism spectrum disorder) and the word "neurotoxic" is used to describe decrements in neurodevelopment following contaminant exposure (e.g., Barbone et al., 2019; Barkoski et al., 2021; Braun, 2017; Grandjean & Landrigan, 2006, 2014; Hyland et al., 2019; Jankowska et al., 2021).

In this introductory chapter, I will review some fundamental information on human brain development and the reasons why the prenatal period is of critical importance above and beyond postnatal life when it comes to neurotoxicity related to contaminant exposure. This discussion will be followed by a review of the Developmental Origins of Health and Disease (DOHaD) hypothesis and the issue of how adverse neurodevelopmental outcomes may progress (or cascade) over time. Next, some background information on contaminants that are known to be or strongly suspected of being neurotoxic will be presented. Neurotoxicity itself will then be discussed in terms of the mechanisms of action of the contaminants reviewed in the previous section as well as the types of evidence that lead to the identification of neurotoxicity. This introductory chapter will then conclude with a brief discussion of the importance of psychology expertise in neurotoxicology research and a presentation of the thesis objectives.

Importance and Vulnerability of Prenatal Brain Development

Human Brain Development

Human brain development is a protracted process that remains ongoing until the mid-twenties (Fiske & Holmboe, 2019; Johnson et al., 2009; Sowell et al., 1999). Nonetheless,

several brain development milestones take place during the prenatal period (Rice & Barone, 2000; Schepanski et al., 2018). For typical development, everything must happen in a specific sequence and within specific time windows. Brain development starts early in the first trimester of pregnancy with neurulation, followed by neurogenesis (Schepanski et al., 2018; Silbereis et al., 2016). These neurons then start to migrate to form distinct brains regions. The bulk of the brain is formed by the end of the second trimester of pregnancy. The fine-tuning of brain structures and connectivity (e.g., synaptogenesis, gliogenesis, myelination) starts late in the second trimester and continues until birth, with some development continuing into infancy and childhood (Schepanski et al., 2018; Silbereis et al., 2016). Given this clearly defined sequence of events, the timing of prenatal events may create distinct, lasting impacts depending on the developmental process taking place at that time.

In addition, comparatively to other organs and systems, the development of the nervous system in the prenatal period is extremely rapid, making it particularly vulnerable to changes in the uterine environment (Davis & Pfaff, 2014). Maternal hormones, exposure to viral, bacterial, or parasitic infections, and exposure to teratogens (i.e., toxic substances, including drugs and medications) all impact the homeostasis of the mother's endocrine and immune system and in turn, the balance of the prenatal milieu, which may then create a lasting impact on the offspring (Davis & Pfaff, 2014; Schepanski et al., 2018).

Lastly, some of the processes involved in prenatal brain development may unfold in a sexually dimorphic way. While more research is needed to fully characterize these potential sex differences, it is important to note that male and female fetuses may be impacted differently depending on the type and timing of a given prenatal stressor, resulting in different phenotypes in

later development (Davis & Pfaff, 2014; Glover & Hill, 2012; Sandman et al., 2013; Vasileiadis et al., 2009).

Significance of Prenatal Contaminant Exposure Beyond Postnatal Exposure

While contaminant exposure can occur throughout the lifespan, prenatal exposure may be of particular concern for neurodevelopment given the vulnerability of the developing fetal brain (Heindel et al., 2015; Lanphear, 2015). Developing neurons may sustain damage from exposure at lower doses than mature neurons (Lanphear, 2015; Rice & Barone, 2000). Furthermore, several critical and sensitive periods occur *in utero* (Kenner, 2019; Rice & Barone, 2000; Schepanski et al., 2018; Silbereis et al., 2016). Organ systems and critical structures are developed during gestation and disruptions to normal developmental events or sequences may therefore interfere with future functioning.

Developmental Cascades and the DOHaD Hypothesis

The impact of prenatal contaminant exposure on health is consistent with the Developmental Origins of Health and Disease (DOHaD) hypothesis. Specifically, the DOHaD framework suggests that adverse health outcomes and functional impairments throughout the lifespan may originate from various early life adversities and stressors (Barker, 1990, 2007). Initial evidence for this framework came from the observation that low birth weight was associated with infant mortality and ischemic heart disease in adulthood. In turn, evidence emerged that maternal nutrition during gestation was associated with morphological measurements at birth and in turn metabolic health in adulthood (Barker, 2007; Barker & Osmond, 1986; Wadhwa et al., 2009). Since then, studies have examined a range of different types of early life adversities and documented their impact on lifespan health and development. It has come to be accepted that prenatal and early life contaminant exposures were one form of

stressors that impacted future physical and psychological health (Almeida et al., 2019; Demeneix, 2019; Haugen et al., 2015; Heindel et al., 2015; Heindel et al., 2017; Lucock, 2021).

It might appear evident that a developmental approach is crucial when examining the association of prenatal contaminant exposure and development. However, due to practical limitations, studies generally focus on a limited subset of outcomes over a limited developmental period. The issue with such a narrow scope is that alterations in early development can lead to a cascade of adverse impacts across multiple areas of functioning, potentially throughout the lifespan (Bellinger, Matthews-Bellinger, et al., 2016). Indeed, given the interrelation of many developmental domains, an adverse outcome in adulthood may bear little resemblance to an impairment that appeared earlier in life (Bellinger, Matthews-Bellinger, et al., 2016). For example, poor occupational functioning in adulthood may be due to poor social skills and inhibitory control, which may have manifested as hyperactivity and impulsivity in childhood. In addition, the association between contaminant exposure and a given developmental outcome may be moderated by factors such as sex, socioeconomic status, genetic, and epigenetic factors (Bellinger, 2009). Moreover, developmental alterations taking place in early life may appear differently as an individual progresses through their lifespan as a function of the interplay of protective factors, risk factors, and increasing demands (Bellinger, Matthews-Bellinger, et al., 2016; Dietrich et al., 2005). Hypothetically, an alteration in the structure and function of a specific brain network *in utero* may manifest as impaired reflexes in infancy, poorer attentional abilities in childhood, weaker impulse control in adolescence, and increased risk-taking behaviour in adulthood. Relatedly, poor impulse control may only become a concern in adolescence as environmental demands increase and compensation for this deficit becomes more difficult. Conversely, low cognitive ability in early childhood may correct itself later in

childhood and adolescence in the presence of adequate remedial support and increased environmental stimulation. It is therefore important to consider how prenatal contaminant exposure alters early development and in turn, how these alterations evolve over time.

Relevant Background Information on Selected Contaminants

Before delving deeper into the association of prenatal contaminant exposure and neurodevelopment in children, some important background information on contaminants themselves is necessary. The focus of this thesis is on contaminants that are confirmed or strongly suspected of being neurotoxic (Grandjean & Landrigan, 2006, 2014). As such, this section describes the nature of each contaminant as natural or man-made, common sources of exposure, and the biological matrices used to determine exposure levels. This section was written as a Supplement to the scoping review manuscript found in Chapter 3. Mechanisms of neurotoxicity and the types of studies used to determine whether a contaminant is neurotoxic are discussed in the next section of this introductory chapter.

Metals and Minerals

Lead (Pb)

Lead is a naturally occurring metal originating from the Earth's crust that can be found across our environments due to human activities such as mining and manufacturing (Sanders et al., 2009; World Health Organization [WHO], 2021). While many lead-containing products have been banned in Western countries (e.g., lead-based paint, leaded gasoline), exposure continues as lead is a persistent element that does not degrade over time. Most human lead exposure occurs through ingestion of contaminated food/water, soil, or dust (Sanders et al., 2009; WHO, 2021). For example, exposure may occur through lead-based paint still present in older homes and lead leaching into drinking water from lead pipes or lead solder (Sanders et al., 2009; WHO, 2021).

Human lead exposure is most commonly measured in whole blood (Sanders et al., 2009). Lead can accumulate in teeth and bone and may be released in the bloodstream during certain metabolic processes, some of which naturally occur during pregnancy, thus resulting in fetal lead exposure (Risova, 2019). Young children are at particular risk from lead exposure as they absorb four to five times more lead than adults (WHO, 2021). There is evidence suggesting that calcium and iron may inhibit absorption of lead in the digestive tract, raising some possibilities for lead toxicity prevention (Fullmer, 1992; Kwong et al., 2004; Wright et al., 1999). Importantly, current scientific consensus is that there is no safe dose of lead exposure, which means that lead is neurotoxic even in very small doses (Budtz-Jørgensen et al., 2013; Grandjean, 2010; Lanphear et al., 2005).

Mercury (Hg) and Methylmercury (MeHg)

Mercury is a metal that is released in the environment from natural sources such as volcanic activities, but also from human industrial and mining activities (Bellinger, O'Leary, et al., 2016; Clarkson & Strain, 2020). When mercury eventually finds its way into bodies of water, it is transformed into methylmercury (an organic form of mercury) by aquatic micro-organisms (Bellinger, O'Leary, et al., 2016; Clarkson & Strain, 2020; Grandjean et al., 2010). It then makes its way up the food chain and accumulates more at each level as it is absorbed by smaller organisms, that are eaten by increasingly larger fish and sea mammals and eventually, by humans (Karagas et al., 2012). While mercury exposure usually occurs through consumption of contaminated rice in certain regions, the primary source of methylmercury exposure in most countries is contaminated fish and seafood (where predatory species or those that are higher in the food chain tend to have a higher mercury content) (Bellinger, O'Leary, et al., 2016; Zhang, Feng, Larssen, Qiu, et al., 2010; Zhang, Feng, Larssen, Shang, et al., 2010). Importantly, there is

evidence that certain nutrients that are commonly found in fish, like long-chain polyunsaturated fatty acids (PUFAs) and selenium, have a positive impact on fetal brain development. As such, there is debate in the literature as to whether these key nutrients confound or counterbalance the negative impact of methylmercury exposure in fish eating populations (Choi et al., 2014; Clarkson & Strain, 2003; Oken & Bellinger, 2008; Oken et al., 2016). Hair is the most sensitive and widely used biological matrix to quantify mercury exposure (80-90% of which is methylmercury), though blood, fingernail, and toenail are commonly used as well (Bellinger et al., 2019; Bellinger, O'Leary, et al., 2016; Clarkson & Magos, 2006).

Manganese (Mn)

In low doses, manganese is an essential element obtained from the diet which contributes to the healthy functioning and development of many bodily systems. However, at higher exposure levels, manganese is a toxic metal (Boyes, 2010; Santamaria & Sulsky, 2010). Manganese naturally occurs in the environment and is found in soil, plants, and rocks. Manganese is also used in a variety of industrial settings (e.g., steel manufacturing, welding, as an additive in gasoline and in certain fungicides), thus resulting in further release in the environment. However, manganese from natural sources and human activity eventually finds itself in the water supply, especially ground water (O'Neal & Zheng, 2015). In certain localized areas, manganese in drinking water significantly exceeds safety recommendations, thus exposing the general population to toxicity risks (Bouchard et al., 2007; Frisbie et al., 2012; Wasserman et al., 2006). Dentine in deciduous teeth is one of the most well-supported matrices for prenatal exposure (Arora et al., 2012; Cigan et al., 2018). Alternatively, hair and nail/toenail may be other helpful matrices (Cigan et al., 2018; Coetzee et al., 2016).

Arsenic (As)

Arsenic is a metalloid naturally present in the Earth's crust (Grandjean & Landrigan, 2006; Yager et al., 2015). Arsenic is present in groundwater in many countries across the world, such that most exposure occurs by drinking contaminated water. Airborne arsenic is also produced by human industrial activity, leading to exposure through inhalation (Grandjean & Landrigan, 2006; Yager et al., 2015). Arsenic is a confirmed carcinogen and is also known to be neurotoxic (Grandjean & Landrigan, 2006; Landrigan, 1981). The most used matrix to measure exposure is urine (Hughes, 2006; Marchiset-Ferlay et al., 2012). Research suggests hair, fingernail, and toenail are also appropriate matrices to measure arsenic (Hughes, 2006; Marchiset-Ferlay et al., 2012; Normandin et al., 2014). While urine represents short-term exposure (i.e., a few days), hair and nail represent longer-term exposure (i.e., a few months) (Hughes, 2006; Marchiset-Ferlay et al., 2012; Normandin et al., 2014).

Fluoride (F^-)

Fluoride is an ionized form of the element fluorine (Adkins & Brunst, 2021). Fluoride occurs naturally in the environment and is commonly found in water. While fluoride is naturally found in low doses in drinking water in many parts of the world, certain regions (including areas of China, India, Iran, and Mexico) have "endemic fluorosis", meaning that fluoride is regularly found in excessive quantities in the water supply (Saeed et al., 2020). In other places (e.g., parts of the United States and Canada), fluoride is added to drinking water to contribute to dental caries prevention (Aoun et al., 2018; Grandjean, 2019). There is increasing recognition of the developmental neurotoxicity of fluoride, primarily from cross-sectional studies (Choi et al., 2012; Grandjean, 2019; Grandjean & Landrigan, 2014). Depending on the timing of developmental fluoride exposure, some children exposed to higher levels of fluoride develop

dental fluorosis whereby white discoloration forms on teeth (Grandjean, 2019; Hong et al., 2006). While generally considered a cosmetic effect, emerging evidence suggests that dental fluorosis correlates with neurotoxicity (Grandjean, 2019). Lastly, fluoride exposure can be measured in a variety of matrices, including blood (serum and plasma), urine, fingernail, toenail, hair, and dentine (Ahmed et al., 2012; dela Cruz et al., 2008; Elekdag-Turk et al., 2019; Opydo-Szymaczek & Borysewicz-Lewicka, 2005; Rango et al., 2017; Till et al., 2018).

Polychlorinated Biphenyls (PCBs)

PCBs are a group of human-made (or synthetic) organochlorine compounds (that is, chemicals composed of carbon, hydrogen, and chlorine) (Environmental Protection Agency [EPA], 2022b). While there are 209 different forms (or congeners) of PCBs depending on the number and position of chlorine atoms in the molecule, all PCBs are highly stable and heat-resistant, making them well-suited as an additive in a variety of products, including electrical equipment, paints/dyes, and plastic/rubber objects (EPA, 2022b; Health Canada, 2006, 2010a). PCBs are known as a persistent organic pollutant (POP) as they do not degrade in the environment over time. While PCB concentrations in ecosystems and human tissue are decreasing in recent years due to laws banning or limiting their use in North America since the 1970s, they are still detected to this day, largely due to improper disposal or poor management of hazardous waste sites (Bartalini et al., 2020; EPA, 2022b; Health Canada, 2010a; Sun et al., 2007). Following release in the environment, PCBs can accumulate in ecosystems and organisms, such that human exposure now occurs primarily through diet. Since PCBs are accumulative, they are found in higher concentrations in organisms at the upper levels of the food chain (e.g., predatory fish, marine mammals, wild game) (EPA, 2022b; Health Canada, 2006). PCBs are most commonly measured in blood (Smolders et al., 2009).

Pesticides

Pesticides are an extremely broad chemical category, including several thousands of different chemicals used across the world (Pascale & Laborde, 2020). Pesticides refer to chemicals that are used to remove or repel various pests, such as rodents (rodenticides), insects (insecticides), fungi (fungicides), and plants/weeds (herbicides) (Mostafalou & Abdollahi, 2017; Pascale & Laborde, 2020). Such pesticides can be used for a variety of residential, industrial, and populational purposes. For example, pesticides can be used in homes and gardens, in fields used for agriculture, or to prevent the spread of infections and diseases (e.g., malaria transmitted through mosquitoes) (Mostafalou & Abdollahi, 2017; Pascale & Laborde, 2020). Pesticides belonging to four categories (i.e., organochlorines, organophosphates, carbamates, and pyrethroids, which are all used as insecticides) known to be neurotoxic in children (Grandjean & Landrigan, 2006, 2014) will be reviewed in this paper. Interestingly, insecticides function by attacking the nervous system, making them neurotoxic by design. Because they are not species-specific, they place many species beyond insects (including humans) at risk for neurotoxicity (Costa et al., 2008).

Organochlorine Pesticides

Organochlorine pesticides belong to the same broad class of chemicals as PCBs discussed earlier, whereby they are largely composed of carbon, hydrogen, and chlorine. Like other organochlorinated compounds, these pesticides are highly persistent and accumulate in the environment and within living organisms (Grandjean & Landrigan, 2014). The most researched organochlorine pesticide is called dichloro-diphenyl-trichloroethane (DDT) while its primary metabolite is called dichloro-diphenyl-dichloroethylene (DDE) (Grandjean & Landrigan, 2014). DDT was used to successfully control insect-borne diseases like malaria and typhus before

concerns about its toxicity resulted in bans in many countries starting in the 1970s (EPA, 2022a; Grandjean & Landrigan, 2014; Jayaraj et al., 2016). Today, DDT's only recommended use is called 'indoor residual spraying', whereby the pesticide is sprayed in small amounts on the indoor walls and ceilings of homes to kill and repel mosquitoes in regions dealing with endemic malaria (Jayaraj et al., 2016; WHO, 2006). The small DDT amounts used for this purpose are thought to have little to no adverse impact on human health and the benefits of its use to control malaria are far greater than the risks (WHO, 2006). Prior to its ban in the 1970s, exposure to DDT could occur through inhalation or dermal absorption during pesticide application. Residues can still be found due to DDT's high persistence. Exposure to DDT now largely occurs through diet (Agency for Toxic Substances and Disease Registry, 2002; EPA, 2022a; Richardson et al., 2019). Urine is the best biomarker to measure DDT and its metabolite DDE (Agency for Toxic Substances and Disease Registry, 2002).

Organophosphate Pesticides

Organophosphate pesticides are far less persistent than the organochlorines, with half-lives ranging from hours to weeks (CDC, 2017a). They gained popularity after the organochlorines were banned in the 1970s and several compounds are still used today in various agricultural applications (CDC, 2017a; Health Canada, 2019). Exposure to these pesticides primarily occurs in occupational settings and through ingestion of food containing pesticide residues (CDC, 2017a; Health Canada, 2019). Organophosphate pesticides all breakdown into dialkyl phosphate (DAP) metabolites which can be easily measured in urine (CDC, 2017a; Kapka-Skrzypczak et al., 2011). However, given their short half-lives, it is difficult to assess chronic exposure and the timing of measurement significantly impacts the result (Grandjean & Landrigan, 2014; Kapka-Skrzypczak et al., 2011).

Carbamates

Like organophosphates, pesticides in the carbamate class function by inhibiting the acetylcholinesterase enzyme (Costa et al., 2008). However, unlike organophosphates, the acetylcholinesterase inhibition lasts from minutes to hours, such that acute carbamate poisoning symptoms resolve (Bjørling-Poulsen et al., 2008; Costa et al., 2008). Routes of exposure to carbamate pesticides vary based on the specific compound, though exposure in occupational settings (e.g., pesticide applicators and handlers) is most common, followed by ingestion of contaminated food (CDC, 2017b, 2017c). Exposure is assessed by measuring the presence of metabolites in urine (CDC, 2017b, 2017c).

Pyrethroids

Pyrethroid pesticides are derived from a compound in the chrysanthemum flower. They are commonly used in agriculture as well as households, such as in treatment for head lice (Costa et al., 2008; Morgan, 2012). Exposure typically occurs through accidental ingestion or inhalation in residential and occupational settings as well as ingestion of food contaminated with trace residues (CDC, 2017d; Costa et al., 2008). Pyrethroids typically have low to moderate acute toxicity in humans (Costa et al., 2008; He et al., 1989). These pesticides are considered non-persistent, with half-lives of just a few hours (Fortin et al., 2008; Ratelle et al., 2015; Rodzaj et al., 2021). Exposure to pyrethroids is typically assessed by measuring amounts/concentrations of their metabolites in urine samples (Fortin et al., 2008; Ratelle et al., 2015; Rodzaj et al., 2021). As with other non-persistent chemicals, the measurement of pyrethroid exposure is subject to great variation within and between individuals (Bradman & Whyatt, 2005; Ferland et al., 2015).

Flame Retardants: Polybrominated Diphenyl Ethers (PBDEs)

PBDEs are a class of chemicals used as flame retardants (i.e., delaying or preventing something from catching fire). As such, they were added to household items like furniture, upholstery and textiles, appliances, and electronics (CDC, 2017f; Costa & Giordano, 2007). PBDEs are not chemically bound to the consumer goods they are added to, which allows them to leach out into the environment (Costa & Giordano, 2007; Linares et al., 2015). Certain features of PBDEs brought cause for concern. For instance, PBDEs are persistent, with half-lives up to 12 years depending on the congener (Geyer et al., 2004; Trudel et al., 2011). They are also lipophilic, which means they can accumulate in the environment and especially in fatty tissue (Darnerud et al., 2001; Linares et al., 2015). PBDEs were designated as persistent organic pollutants in the Stockholm Convention in 2004, which marks the beginning of restrictions on the use and production of PBDEs in several countries across the world. Given the long half-lives of PBDEs, exposure may persist despite the bans (Health Canada, 2022b; Sharkey et al., 2020). Exposure in humans occurs primarily due to ingestion, inhalation, and dermal absorption of contaminated house dust, though it may also occur through diet with foods that are high in fat (e.g., fish, meat, dairy) (CDC, 2017f; Frederiksen et al., 2009; Klinčić et al., 2020). PBDE exposure is typically measured in serum (a component of blood), which is believed to reflect exposure over the last few months or years depending on the congener (CDC, 2017g).

Organic Solvents

Solvents have many possible applications and are commonly found in paints, degreasants, and household cleaning products (Dick, 2006). One subcategory within solvents is glycol ethers, which are helpful in a variety of applications as they have both hydrophilic and hydrophobic properties (Multigner et al., 2005). Solvents have been related to a wide range of

adverse health effects following acute and chronic exposure, though identifying the specific compound responsible is complex (Dick, 2006; Grandjean & Landrigan, 2014; Multigner et al., 2005). Exposure most often occurs in occupational settings. The pathways of exposure are typically inhalation or dermal absorption depending on the specific compound and the industry in which it is used (Dick, 2006; Multigner et al., 2005). Lastly, urine is the preferred biological matrix to measure solvent metabolites as an index of exposure (Multigner et al., 2005).

Phenols: Bisphenol A

Bisphenol A (BPA) belongs to the broader category of chemicals called phenols. It was most notably found in plastic containers, bottles, and other forms of plastic packaging as well as can coatings (CDC, 2017e; Geens et al., 2011). The most common route of exposure is ingestion of food and water stored in containers that have BPA in them (CDC, 2017e; Michałowicz, 2014), though studies increasingly recognize the significance of routes like dermal absorption (Geens et al., 2011; Liu & Martin, 2017; Mustieles et al., 2020; von Goetz et al., 2017). BPA has been related to a wide variety of adverse health outcomes and is known to impact the function of hormones like estrogen and thyroid hormones, making it an "endocrine-disrupting chemical" (Ma et al., 2019; Rubin, 2011). Importantly, BPA is a nonpersistent chemical, with a half-life of a few hours or a few days at most (Stahlhut et al., 2009; Vandenberg et al., 2010). As with most non-persistent chemicals, the most commonly used biological matrix is urine (Bousoumah et al., 2021; Calafat et al., 2015).

Phthalates

Phthalates can be used either as plasticizers, where they are added to plastics to make them softer, more flexible, and more durable, or as solvents, where they help dissolve other materials in household products (CDC, 2021b; Health Canada, 2020). Phthalates are used in a

wide variety of goods including polyvinyl chloride (PVC) and other plastics, food production materials and packaging, medical supplies, construction products (e.g., paint, lubricants, flooring), personal care products (e.g., shampoos, soaps, cosmetics), and textiles (CDC, 2021b; Engel et al., 2021; Health Canada, 2020). Exposure to phthalates occurs through diet, inhalation, and dermal absorption (Heudorf et al., 2007). Phthalates are non-persistent chemicals, with half-lives under 24 hours (Hoppin et al., 2002; Wang et al., 2019), and are typically measured in urine (Calafat et al., 2015; National Research Council Committee on the Health Risks of Phthalates, 2008). Like BPA, phthalates are endocrine-disrupting chemicals as they interfere with the function of glucocorticoid, androgen, and thyroid hormones (Benjamin et al., 2017; Braun, 2017; Radke et al., 2020; Sree et al., 2023).

PFAS

Per- and polyfluoroalkyl substances (PFAS) is a large group of chemicals. Some of the most commonly known PFAS are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) (CDC, 2022a; Health Canada, 2021b). PFAS are persistent chemicals that can accumulate in the environment, with half-lives of several years (Braun, 2017). PFAS are commonly found in heat-, water, or grease-resistant products or coatings (Braun, 2017; CDC, 2022a; Health Canada, 2021b). For example, PFAS are used in non-stick cookware, food packaging and container coatings, certain types of textiles and clothing, firefighting foams, and personal care products (Braun, 2017; CDC, 2022a; Health Canada, 2021b). PFAS exposure occurs mainly through diet, though it may also occur by inhalation of PFAS particles in the air or ingestion of house dust (Haug et al., 2011; Trudel et al., 2008). PFAS are considered endocrine-disrupting chemicals as they interfere with glucocorticoid and thyroid hormone pathways (Braun,

2017). The most common biological matrices for PFAS measurement are serum and plasma (Braun, 2017; Da Silva et al., 2020).

Neurotoxicity

The previous section presented a vast range of neurotoxic chemicals, with a variety of different sources and uses in modern human life. Nonetheless, they all share an association with neurotoxicity in humans. The following section introduces the mechanisms through which these diverse contaminants affect neurocognitive function and the types of studies that have led to this conclusion.

Mechanisms

Many contaminants appear to share similar mechanisms of neurotoxicity. For example, oxidative stress, apoptosis, and alterations in neurotransmitter function are hypothesized mechanisms of neurotoxicity for metals and minerals like lead, mercury, manganese, arsenic, and fluoride (Barbier et al., 2010; Farina et al., 2011; Mochizuki, 2019; Neal & Guilarte, 2013; Novo et al., 2021; Sanders et al., 2009; Thakur et al., 2021). Oxidative stress also appears to play a role in the neurotoxicity of synthetic chemicals like polychlorinated biphenyls PCBs (Pessah et al., 2019) and polybrominated diphenyl ethers (PBDEs) (Costa & Giordano, 2007). Several other contaminants are referred to as “endocrine-disrupting chemicals” or EDCs because they alter the functioning of hormones like estrogens, androgens, and thyroid hormones. This is the case for chemicals like bisphenol A (BPA) (Ma et al., 2019; Rubin, 2011), phthalates (Benjamin et al., 2017; Braun, 2017; Radke et al., 2020; Sree et al., 2023), PFAS (Braun, 2017), polybrominated diphenyl ethers (PBDEs) (Costa & Giordano, 2007; Gibson et al., 2018), polychlorinated biphenyls (PCBs) (Pessah et al., 2019), and fluoride (Grandjean, 2019).

The mechanisms listed in the previous paragraph suggest that alterations in brain structure and function are likely involved in the causal pathway of neurotoxicity. By definition, mechanisms like oxidative stress (Salim, 2017), apoptosis, and alterations in neurotransmitter function affect the brain and its structures. Maternal endocrine function is also essential for fetal brain development. As such, maternal chemical exposure may alter maternal endocrine function, which in turn may impact fetal brain development (Miranda & Sousa, 2018; Schepanski et al., 2018). Emerging evidence supports the presence of an association between prenatal contaminant exposure and brain structure/function (e.g., Binter et al., 2020; Binter et al., 2019; England-Mason et al., 2020; Nisevic et al., 2019; Sussman et al., 2022). Nonetheless, more studies are needed to reliably document these associations across a wide range of contaminants. Importantly, while early alterations in brain structure or activity may affect current functioning, some researchers hypothesize that they may also reduce cognitive reserve, which in turn negatively impacts the brain's ability to withstand neurodegeneration in later adulthood (Bellinger, Matthews-Bellinger, et al., 2016).

Types of Evidence

Acute Toxicity

Environmental chemicals often begin attracting scrutiny after some form of critical acute neurotoxicity incident happens. Usually, these incidents involve workers in an industrial or other occupational setting who accidentally become exposed to a very large dose of the chemical and suffer immediate neurological symptoms of chemical poisoning (Grandjean & Landrigan, 2006, 2014). For example, manganese was suspected of neurotoxicity after workers exposed to very high doses in occupational settings developed "manganism", a condition characterized by neurological symptoms similar to those of Parkinson's Disease, which is hypothesized to be due

to a dysregulation of dopamine function (Andruska & Racette, 2015; Lin et al., 2020; Neal & Guilarte, 2013).

In certain cases, developmental neurotoxicity was also identified from chemical poisoning. For PCBs, developmental neurotoxicity was identified following accidents leading to PCB-contaminated cooking oil in the late 1970s and 80s in Asia (Chen et al., 1992; Grandjean & Landrigan, 2006; Guo et al., 2004). As for methylmercury, large-scale methylmercury poisoning accidents from contaminated fish in Japan in the 1950s and 60s and from contaminated grains in Iraq in the 1970s (Clarkson & Strain, 2020; Grandjean & Landrigan, 2006; Grandjean et al., 2010; Harada, 1995), resulted in the discovery that methylmercury is particularly neurotoxic for the developing fetus as infants with severe neurological damage were born to women who demonstrated minimal toxicity symptoms (Clarkson & Strain, 2020).

In Vitro and Animal Studies

Many of the questions investigators have had about contaminants could not be answered in human research for practical and ethical reasons. As such, *in vitro* and animal studies provide critical insights which have in turn informed human research studies and policies. They may provide a rationale for conducting large-scale community studies or even allow deeper investigation into the mechanisms of neurotoxicity.

For the purpose of toxicology research on environmental contaminants, *in vitro* studies allow researchers to study the impact of chemicals on cells and their processes in a highly controlled environment. They can be conducted quickly and inexpensively relative to animal and human studies. By exposing cell cultures to a given chemical or chemical mixture, researchers can examine outcomes such as synaptogenesis, neurogenesis, gliogenesis, neuronal differentiation, protein expression, apoptosis, and oxidative stress (e.g., Davidsen et al., 2021;

Franco et al., 2009; Gao et al., 2009; Garcia et al., 2005; Huang et al., 2010; Kodavanti & Ward, 2005; Parent et al., 2016; Pistollato et al., 2021; Wilson et al., 2014). These findings can justify the need for larger-scale epidemiological studies, but also supplement the results of human studies by providing mechanistic evidence. However, *in vitro* studies extract cells to consider them in isolation from the tissues and organs they interact with *in vivo*, thus limiting the interpretation and real-world significance of these results (Devlin et al., 2005).

Meanwhile, animal studies examining the impact of environmental contaminants on neurodevelopment are most often conducted on mice and rats, though certain studies use other species such as guinea pigs and zebrafish (Mamczarz et al., 2016; Sun et al., 2016). In the context of neurotoxicology research, rodent studies can examine behavioural outcomes as well as structural changes in the brain. For example, studies can expose a female mouse or rat to a given chemical and examine the offspring's behaviour (e.g., memory, social behaviour, repetitive behaviour, locomotor activity) and post-mortem brain (e.g., Fagundes et al., 2022; Hawkey et al., 2020; Zhang et al., 2022; Zhao et al., 2020). Animal studies have several advantages as they are more rapid and less expensive than human studies and can include manipulations that would be highly invasive and otherwise unethical in humans. They also have the ability to suggest causality as exposure can be manipulated in a controlled setting. However, even though there are similarities between the human and rodent nervous system, it is often difficult to establish whether results from these rodent studies could be replicated in humans. Nonetheless, studies in rodents are often an important precursor to human community studies (Devlin et al., 2005).

Community-Based Cohorts

Certain community cohorts serve primarily to characterize contaminant exposure in representative population samples and evaluate the association with population health. Examples

of such studies are the Canadian Health Measures Survey (CHMS) (Health Canada, 2010b, 2021c, 2023a, 2023b) and the National Health and Nutrition Examination Survey (NHANES) in the United States (CDC, 2023). These studies are conducted in cycles and repeated in new representative samples every few years to track overall population exposures to various contaminants and health. Published results are therefore cross-sectional (e.g., Arbuckle et al., 2016; Cakmak et al., 2022; Hendryx & Luo, 2018; Woodruff et al., 2011).

Meanwhile, pregnancy cohorts recruit pregnant persons to estimate their contaminant exposure and eventually follow their children. By design, these studies are therefore prospective and longitudinal. They accomplish a different, complementary purpose to the representative surveys discussed in the previous paragraph. The pregnancy cohort samples are often compared to the population survey samples to determine whether they are representative of the general population in terms of demographic characteristics as well as exposure levels. Some influential cohorts in the United States are the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort (Center for Environmental Research and Community Health, 2023) and the Health Outcomes and Measures of the Environment (HOME) cohort (Braun, Kalloo, et al., 2017; Cincinatti Children's Hospital Medical Center, 2023). There are similar cohorts across the world, including the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort in Canada (Arbuckle et al., 2013; Health Canada, 2022a; MIREC, 2022), the INfancia y Medio Ambiente (INMA) cohort in Spain (Guxens et al., 2011), the Mothers and Children’s Environmental Health (MOCEH) cohort in Korea (Kim et al., 2009), the Seychelles Child Development Study (SCDS) in the Republic of Seychelles (Shamlaye et al., 1995), and the Rio Birth Cohort Study (PIPA) in Brazil (Asmus et al., 2020). The major contributions of these

studies are the characterization of exposure during pregnancy and its association with various aspects of child development over time.

These prospective community-based studies are the subject of the scoping review included in Chapter 2 of the present thesis. In addition, Chapter 3 is an example of such a study conducted in the MIREC cohort. Thus, further details on the methodology and the strengths and limitations of these community studies are discussed in these chapters.

Several recent studies in the MIREC cohort have provided further evidence that a variety of individual contaminants and chemical mixtures are associated with child neurodevelopment (e.g., Goodman, Till, et al., 2023; Packull-McCormick et al., 2023; Yonkman et al., 2023). Importantly, while neurodevelopment is the focus of the present dissertation, it is not the only endpoint of interest in these cohort studies. It is important to keep in mind that prenatal contaminant exposure can have system-wide effects on development. For example, birth outcomes (Goodman et al., 2022), birth weight (Johnson et al., 2022), anthropometric features (e.g., adiposity, weight, height, head/waist/hip circumferences, body mass index) (Ashley-Martin et al., 2021; Patti et al., 2022), endocrine and reproductive health markers (e.g., anogenital distance, penile length) (Arbuckle et al., 2018; Romao et al., 2020), and inflammation markers (Palaniyandi et al., 2023) are some of the many endpoints examined in the MIREC study.

Case-Control and Clinical Studies

Though they are not the focus of the present dissertation, it is also important to acknowledge the contributions of clinical epidemiological studies. These studies often adopt a case-control design to evaluate the association between prenatal contaminant exposure and a confirmed clinical diagnosis. For example, in the Norwegian Mother and Child Cohort (MoBA), pregnant women were recruited to assess prenatal contaminant exposure. Childhood diagnoses of

Attention Deficit/Hyperactivity Disorder (ADHD) were then ascertained from public health records (e.g., Engel et al., 2018). Other studies collect biological specimens in pregnancy and later match these data to the individual after they are diagnosed and referred to the study program. This is the case of the Early Markers for Autism (EMA) study in California where biological specimens are collected as part of expanded prenatal screening programs and diagnoses of autism spectrum disorder (ASD) or intellectual disability are made through community services for children with developmental delays (e.g., Lyall et al., 2018). Lastly, another model is the high-risk design, such as in the Markers of Autism Risk in Babies − Learning Early Signs (MARBLES) cohort in California. This study invites pregnant persons who already have a child diagnosed with ASD as they present higher risk of having another child with a neurodevelopmental disorder. These families are identified through community organizations that provide services for children with developmental delays (e.g., Philippat et al., 2018). This type of study adds to the understanding of the association between prenatal contaminant exposure and neurodevelopment by providing complementary information to the studies conducted in the general population.

Importance of Psychology Expertise in Toxicology

While there is increasing awareness among public health researchers and policymakers about the possible impact of environmental contaminants on behaviour and cognition, there is relatively less awareness of the possible impacts among health professionals, and even less so in the pediatric mental health field. Researchers and practitioners in mental health would benefit from a better awareness of the impact of prenatal chemical exposure, as it could be an important element to consider in a biopsychosocial conceptualization of neurodevelopment.

In addition, psychologists and allied health professionals can play a role in reducing the burden of exposure through prevention/intervention strategies that directly target neuropsychological outcomes of contaminant exposure. Current policy is inadequate as a chemical can be marketed and utilized widely before it undergoes stringent testing for toxicity risks (Bennett et al., 2016; Lanphear, 2015). While policy changes are ultimately necessary for long-term exposure reduction, they will not reduce short-term harm because many contaminants have half-lives of months or even years, such that they will remain in the environment long after they have been banned. In the meantime, psychologists and healthcare professionals are ideally positioned to reduce the impact of contaminant exposure from a prevention and intervention perspective. Specifically, they can design prevention and intervention programs that target the likely consequences of contaminant exposure, thereby reducing harm. The role of psychologists in research, clinical settings, policy, and advocacy is further discussed in Chapter 6.

Thesis Objectives

The objective of the present thesis is to examine the impact of prenatal contaminant exposure on neurodevelopment in children, improve dissemination of toxicology research findings to healthcare professionals, and advocate for a larger role of psychologists in prevention, intervention, and policy. To do so, the thesis contains three manuscripts accompanied by an overarching discussion of key issues.

The first manuscript in this thesis is a scoping review examining the relation between prenatal exposure to various environmental contaminants and neurocognitive development from birth to adolescence, with a focus on contaminants that have been identified as or are strongly suspected of being neurotoxic (Grandjean & Landrigan, 2006, 2014). It aims to provide a broad

overview of developmental neurotoxicology research in a way that is accessible to clinicians and researchers in fields relevant for child development.

The second manuscript is an empirical study in a pan-Canadian birth cohort examining the association between prenatal exposure to a specific contaminant (PBDEs) and IQ in 3-year-old children. This study provides a specific example of empirical research in the field of developmental neurotoxicology.

The third and last manuscript in this thesis is an empirical study in an American community cohort examining the association between executive function and cortical thickness across childhood and adolescence. While this study does not include environmental contaminants, it is intended as a proof-of-concept for the use of executive function as a marker of brain morphology and for the appropriateness of cortical thickness as a measure of brain structure in relation to executive function. The results of this study can therefore be used to assist in the design of future studies on the potential mechanistic role of brain structure in the association between contaminant exposure and neurocognitive functioning.

Together, these three manuscripts demonstrate the association between prenatal contaminant exposure and cognitive function in children and the likely underlying alterations in brain structure. A discussion of the implications of these findings for research, clinical work, and policy then concludes the thesis.

Chapter 2: Prenatal Exposure to Environmental Contaminants and Child Cognitive Development – A Scoping Review for Researchers and Practitioners in Mental Health

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Manuscript in preparation

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Abstract

Background: Contaminant exposures are ubiquitous. Mounting evidence suggests that exposure to contaminants is associated with adverse health outcomes, including children's neurodevelopment. Prenatal exposure warrants particular attention given the fragility of fetal development and possible lifespan implications.

Objective: Conduct a scoping review of the literature on prenatal contaminant exposure and neurodevelopment in children for researchers and practitioners in mental health-related fields.

Method: Literature search conducted on PubMed to identify population studies where prenatal exposure to selected neurotoxic contaminants was measured in a biological sample and age-appropriate neurodevelopmental outcomes were measured between birth and age 17 inclusively. Overall, 338 studies were retained.

Results: Studies report adverse neurodevelopmental outcomes or null results following prenatal contaminant exposure. Results varied by age group and neurodevelopmental domain. Results on sex differences were inconsistent.

Conclusions: Prenatal contaminant exposure is associated with adverse neurodevelopmental outcomes or no change in neurodevelopment, depending on age and specific neurodevelopmental domain. While effect sizes are generally small at an individual level, the effect of contaminants may be comparable to that of other well-characterized perinatal risk factors and may interact with other developmental risk factors (e.g., genetics, postnatal adversity). Moreover, given the ubiquitous nature of exposures, the neurodevelopmental impact is significant at a population scale. Clinicians should assess for potential contaminant exposures during the intake process for (neuro)psychological assessments. Psychologists and other mental health professionals are ideally positioned to develop prevention strategies and clinical interventions to mitigate the widespread subclinical neurodevelopmental consequences of contaminant exposures. Policy changes are needed for long-term exposure reduction.

Keywords: Children; Development; Neurodevelopment; Contaminant; Neurotoxic; Psychology

Introduction and Rationale

Exposure to environmental contaminants is ubiquitous. Naturally-occurring or industrially-manufactured chemicals are found in nearly everything: from the air we breathe, to our food and water, and even consumer goods such as furniture, electronics, and clothing (Grandjean & Landrigan, 2006, 2014; Schantz et al., 2020; Vrijheid et al., 2016). The public generally knows of a few key contaminants – such as mercury (Hg), bisphenol A (BPA), and pesticides – through media coverage (Mello, 2015). However, regulatory and government agencies monitor many more. For example, the Centers for Disease Control and Prevention (CDC) in the United States examines over 400 chemicals and their by-products to monitor their impact on human health and the environment (CDC, 2021a).

Exposure to various contaminants has been associated with adverse human health outcomes across the lifespan, including mental, physical, reproductive, and neurological health issues (Kahn et al., 2020; Landrigan et al., 2020; Rivollier et al., 2019; Vrijheid et al., 2016; Wigle et al., 2008; Zeliger, 2013). Neurocognitive associations have also been documented in youth, including symptoms and diagnoses of attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and intellectual disability (ID) (Bellinger, 2013; Grandjean & Landrigan, 2006, 2014; Vrijheid et al., 2016; Wigle et al., 2008). Chemicals that impact neurocognitive functioning are said to be “neurotoxic” (Grandjean & Landrigan, 2014). Importantly, the association between contaminant exposure and neurodevelopment may be moderated by factors such as sex, socioeconomic status, genetic, and epigenetic factors (Bellinger, 2009).

Contaminant exposure can occur throughout the lifespan. However, when it comes to neurodevelopment, prenatal exposure is of particular concern given the vulnerability of the

developing fetal brain (Heindel et al., 2015; Lanphear, 2015). In turn, alterations in early neurodevelopment can lead to a cascade of adverse impacts across multiple areas of functioning, potentially throughout the lifespan (Bellinger, Matthews-Bellinger, et al., 2016). This concept is consistent with the Developmental Origins of Health and Disease (DOHaD) hypothesis, whereby adverse health outcomes and functional impairments may originate from various early life stressors, including contaminant exposures (Heindel et al., 2015). In addition, neurodevelopmental alterations taking place *in utero* may shift and result in different phenotypes as an individual progresses through infancy, childhood, and adolescence as a function of the interplay of protective factors and increasing cognitive demands (Bellinger, Matthews-Bellinger, et al., 2016; Dietrich et al., 2005).

Whereas there is increasing awareness among public health researchers and policymakers about the possible impact of environmental contaminants on behaviour and cognition, there is relatively less awareness of the possible impacts among health professionals, and even less so in the pediatric mental health field. Researchers and practitioners in mental health would benefit from a better awareness of the impact of prenatal chemical exposure, as it could be an important element to consider in a biopsychosocial conceptualization of neurodevelopment. Given the breadth and heterogeneity of neurotoxicology research, a scoping review approach was selected to synthesize the body of evidence and make it accessible for researchers and practitioners in fields related to mental health and child development.

Objective

The primary aim of this review is to describe the relation between prenatal exposure to various environmental contaminants and neurocognitive development from birth to adolescence, thus providing a portrait of the epidemiological situation across child development. We

specifically focus on contaminants that have been identified as or are strongly suspected of being neurotoxic (Grandjean & Landrigan, 2006, 2014). Following an overview of the literature relevant for mental health professionals, we will discuss key issues at the intersection of mental health and developmental neurotoxicology, including the significance of the prenatal period above and beyond early postnatal life, the importance of following a developmental approach, the difference between individual and population effects, and the relation of both cognitive outcomes and contaminant exposures with social factors.

Common Contaminants: Relevant Background Information

In 2014, Grandjean and Landrigan published an update to their seminal 2006 review article, in which they list contaminants that are known neurotoxicants or are strongly suspected of being neurotoxic (Grandjean & Landrigan, 2006, 2014). The majority of these contaminants are briefly reviewed in Table 1. Note that contaminants belonging to the air pollution category (e.g., nitrogen dioxide [NO2], polycyclic aromatase [PAH]) are not included in this review (please refer to the Method section for inclusion/exclusion criteria).

Table 1

Chemical background information summary[1]

Contaminant	Origin	Common exposure sources and routes	Persistence	Matrices
Metal and minerals				
Lead (Pb)	Natural	Despite bans in Western countries, lead is still found in lead-based paint in older homes and can leach into drinking water from lead pipes or lead solder. Exposure occurs through ingestion of contaminated food, water, soil, or dust.	Persistent	Blood
Mercury (Hg)	Natural	Released from volcanic activity and from industrial/mining activities, mercury eventually finds its way into bodies of water and contaminates fish and seafood (and grains/rice in certain regions). Exposure occurs through diet fish, seafood, and in certain regions, rice).	Persistent	Hair and cord blood
Manganese (Mn)	Natural	Manganese naturally occurs in soil, plants, and rocks. It is also used in industrial settings (e.g., steel manufacturing, welding, as an additive in gasoline and in certain fungicides), where exposure can occur through inhalation. Manganese from natural and industrial sources can also contaminate drinking water.	Depends on tissue	Blood, urine, and saliva (short-term); Hair, teeth, and nail (long-term)
Arsenic (As)	Natural	Naturally present in the Earth's crust, arsenic can leach into drinking water. Airborne arsenic is also produced by human industrial activity, leading to exposure through inhalation.	Depends on tissue	Blood and urine (short-term); Hair and nail (long-term)

[1] Table based on references such as Bellinger, O'Leary, et al. (2016), Braun (2017), Costa & Giordano (2007), Costa et al. (2008), Engel et al. (2021), Environmental Protection Agency [EPA] (2022), Geens et al. (2011), Grandjean (2019), Jayaraj et al. (2016), Kapka-Skrzypczak et al. (2011), Multigner et al. (2005), O'Neal & Zheng (2015), Sanders et al. (2009), Yager et al. (2015). Please see Chapter 1 for complete details.

Contaminant	Origin	Common exposure sources and routes	Persistence	Matrices
Metal and minerals				
Fluoride (F^-)	Natural	Fluoride occurs naturally in the environment and is commonly found in water (usually in low doses, but found in excess in certain regions). Fluoride is added to drinking water to contribute to dental caries prevention in certain regions (e.g., parts of the United States and Canada).	Depends on tissue	Blood (serum and plasma), urine, nail, hair, and teeth
Polychlorinated biphenyls (PCBs)	Synthetic	Before bans in the 1970s in North America, PCBs were used as additives in electrical equipment, paints/dyes, and plastic/rubber objects. PCBs are found in the environment due to improper disposal or management of hazardous waste sites. PCBs then accumulate in ecosystems and organisms, such that exposure now occurs primarily through diet.	Persistent	Blood
Pesticides				
Organochlorine (OC) pesticides	Synthetic	The most researched organochlorine pesticide is called dichloro-diphenyl-trichloroethane (DDT). Prior to its ban in the 1970s, exposure to DDT could occur through inhalation or dermal absorption during pesticide application. Residues can still be found due to its high persistence, such that human exposure now largely occurs through diet.	Persistent	Urine
Organophosphate (OP) pesticides	Synthetic	Exposure primarily occurs in occupational settings (e.g., pesticide applicators and handlers) as well as through ingestion of pesticide residues in food.	Non-persistent	Urine
Carbamates	Synthetic	Routes of exposure vary based on the specific compound, though exposure in occupational settings (e.g., pesticide applicators and handlers) is most common, followed by ingestion of contaminated food.	Non-persistent	Urine

Contaminant	Origin	Common exposure sources and routes	Persistence	Matrices
Pesticides				
Pyrethroids	Synthetic	Commonly used in agriculture and in households, pyrethroids are often found in treatment for head lice. Exposure occurs through accidental ingestion or inhalation in residential and occupational settings as well as ingestion of food contaminated with trace residues.	Non-persistent	Urine
Polybrominated diphenyl ethers (PBDEs)	Synthetic	PBDEs are flame retardants (i.e., delaying or preventing something from catching fire) and are added to household items like furniture, upholstery and textiles, appliances, and electronics. Exposure in humans occurs primarily due to ingestion, inhalation, and dermal absorption of contaminated house dust, though it may also occur through diet with foods that are high in fat (e.g., fish, meat, dairy).	Persistent	Blood (serum)
Organic solvents (glycol ethers)	Synthetic	Solvents have many possible applications and are commonly found in paints, degreasants, and household cleaning products. Exposure occurs by inhalation or dermal absorption depending on the specific compound.	Depends on the specific compound	Urine
Bisphenol A (BPA)	Synthetic	BPA was most notably found in plastic containers, bottles, and other forms of plastic packaging as well as can coatings. The most common route of exposure is ingestion of food and water stored in containers that have BPA in them.	Non-persistent	Urine
Phthalates	Synthetic	Phthalates can be used as plasticizers (i.e., making plastics softer, more flexible, and more durable) or as solvents. They are used in a wide variety of goods including polyvinyl chloride (PVC) and other plastics, food production materials and packaging, medical supplies, construction products (e.g., paint, lubricants, flooring), personal care products (e.g., shampoos, soaps, cosmetics), and textiles. Exposure to occurs through diet, inhalation, and dermal absorption.	Non-persistent	Urine

Contaminant	Origin	Common exposure sources and routes	Persistence	Matrices
Per- and polyfluoroalkyl substances (PFAS)	Synthetic	PFAS are commonly found in heat-, water, or grease-resistant products or coatings (e.g., non-stick cookware, food packaging and container coatings, certain types of textiles and clothing, firefighting foams, and personal care products. PFAS exposure occurs mainly through diet, though it may also occur by inhalation of PFAS particles in the air or ingestion of house dust.	Persistent	Blood serum and plasma

Methods

Protocol

This scoping review was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018). The protocol was created by N.A. and reviewed and edited by C.T. and L.B.

Eligibility Criteria and Information Sources

We searched for empirical studies published in English in peer-reviewed journals between 2000 and December 2023. The last search was conducted on December 19, 2023. Only human epidemiological studies were selected.

We focused our search on 11 chemicals for which there is sufficient evidence of neurotoxicity as outlined in the seminal review by Grandjean and Landrigan (2014). Specifically, we searched for studies examining exposure to the following chemicals (or groups of chemicals): lead (Pb), methylmercury (MeHg), manganese (Mn), arsenic (As), fluoride, polychlorinated biphenyls (PCBs), pesticides (specifically the organochlorine pesticide dichloro-diphenyl-trichloroethane [DDT] and its metabolite dichloro-diphenyl-dichloroethylene [DDE], organophosphate pesticides, pyrethroids, and carbamates), polybrominated diphenyl ethers (PBDEs), solvents (specifically, glycol ether, toluene, tetrachloroethylene, or perchloroethylene), bisphenol A (BPA), phthalates, and per- and polyfluoroalkyl substances (PFAS). Importantly, studies must have measured chemical exposure using a biological sample that reflects exposure in the prenatal period (i.e., conception to birth) (Till et al., 2002). For this reason, we did not include studies focusing on air pollutants as exposure is often measured via environmental

concentrations, which may not correlate with concentrations in biological samples (Sagiv et al., 2018).

Next, we targeted child neurodevelopmental outcomes from birth to age 17 inclusively. As such, the specific outcome constructs were selected based on developmentally appropriate measures of neurocognitive functioning. This includes neonatal reflexes, infant mental and psychomotor development, and child and adolescent cognition (e.g., IQ, executive function, memory, attention, hyperactivity and other externalizing behaviours, and symptoms of autism like impaired social functioning, repetitive behaviours, and restricted interests). Importantly, the present review focused on outcomes in the general population, not clinical populations. As such, studies in which the main outcome is a diagnosis of a neurodevelopmental disorder (e.g., ADHD, ASD) were not included. Studies focusing on clinical outcomes (e.g., Hertz-Picciotto et al., 2011; Oh et al., 2021) typically have a different research design (i.e., case-control) and potentially different risk factors (e.g., genetic susceptibilities) than community cohort studies, making them more difficult to compare. Furthermore, language development, communication skills, academic achievement, learning disabilities, vision/visual acuity, and motor skills were not targeted outcomes, unless they were examined as part of a cognitive battery.

Studies must report results adjusted for common covariates that have been shown to impact the association between contaminants and developmental outcome (e.g., maternal education, socioeconomic status). The results reported in this review are the adjusted results only. In addition, as the present review targets prenatal exposure, we did not include findings if postnatal exposure was part of the statistical model. In addition, we excluded articles that presented a re-analysis of results that were part of another article that was already included in the review. Studies that examined exposure to multiple contaminants were included, though only

results on the chemicals targeted by this review were included in our analyses. Studies were excluded from the review if they grouped chemicals together, thus not allowing a distinction between the included and excluded chemicals.

Search and Selection of Sources of Evidence

The search process was conducted for each chemical (or group of chemicals) individually. The full search terms for each chemical are outlined in Table 2 along with the number of records it returned.

Table 2

Search Strategy

Chemical	Search terms	# of results
Arsenic	(prenatal) AND ("arsenic" OR "As") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	116
BPA	(prenatal) AND ("BPA" OR "bisphenol a") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	137
Fluoride	(prenatal) AND ("fluorid*") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	33

Chemical	Search terms	# of results
Lead (Pb)	(prenatal) AND ("Pb") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	153
Manganese	(prenatal) AND ("manganese" OR "Mn") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	247
Methylmercury (MeHg)	(prenatal) AND ("methylmercury" OR "meHg") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	245
Per- and polyfluoroalkyl substances (PFAS)	(prenatal) AND ("PFAS" OR "PFOA" OR "PFOS" OR "PFC" OR "polyfluoroalkyl*" OR "perfluoroalkyl*" OR "perfluorinated") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	260
Pesticides	(prenatal) AND ("pesticid*" OR "insecticid*" OR "fungicid*" OR "organochlorin*" OR "organophosph*" OR "dde" or "ddt" OR "chlorpyrifos" OR "pyrethroid*" OR "carbamate*") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	481

Chemical	Search terms	# of results
Phthalates	(prenatal) AND ("phthalate" OR "phthalates") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	201
Polybrominated diphenyl ethers (PBDEs)	(prenatal) AND ("PBDE" OR "PBDEs" OR "polybrominated diphenyl ether*" OR "BDE" OR "brominated") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	88
Polychlorinated biphenyls (PCBs)	(prenatal) AND ("PCB" OR "PCBs" OR "polychlorinated biphenyl*") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	272
Solvents	(prenatal) AND ("solvent*" OR"glycol ether*" OR "toluene" OR "tetrachloroethylene" OR "perchloroethylene" OR "ethanol" NOT "alcohol") AND ("executive function" OR "EF" OR "working memory" OR "inhibit*" OR "shift*" OR "intelligence" OR "IQ" OR "cogniti*" OR "neurodevelopment*" OR "neurocogniti*" OR "neuropsycholog*" OR "attention" OR "adhd" OR "memory" OR "asd" OR "autism" OR "behavior*" OR "behaviour*") AND ("child*" OR "adolescen*" OR "youth")	86

Data Items and Charting Process

Data charting was conducted by two authors (N.A. and C.T.) in a structured spreadsheet in MS Excel. Specific data items to extract were the cohort in which the study was conducted (or the geographical region when a specific cohort name was not provided), the sample size and the proportion of female participants, the contaminant(s) of interest, the biological matrix(ces) in

which the contaminant was measured and the time at which the sample was collected, the age at which neurodevelopment was assessed and the specific measure used, and the main results of the study. Importantly, as this review targets a specific readership (mental health researchers and practitioners), our aim was to provide a broad overview of the developmental neurotoxicology literature. As such, we extracted results for chemical categories and did not differentiate between different formulations within a chemical group (e.g., we do not differentiate between PBDE congeners BDE-47 and BDE-153 and will rather report results as 'PBDEs' more broadly). Similarly, while some studies specifically measured methylmercury, other studies measured total mercury as a proxy for methylmercury. For the purpose of this review, we refer to both simply as "mercury". In addition, we did not differentiate whether the contaminant exposure was based on a measurement of the contaminant itself or one of its metabolites.

Regarding the main findings, we extracted results on the association between prenatal exposure to the targeted chemical and the neurodevelopmental outcome (positive, negative, or null). We considered statistically significant findings those with a *p*-value below .05. In addition, we extracted marginally significant results with *p*-values above .05 but below .10 to avoid bias caused by over-reliance on *p*-values (CDC, 2022b; Wasserstein & Lazar, 2016). Lastly, we documented when the association was examined separately in boys and girls or when an interaction term was included to examine the effect of sex.

Process for the Synthesis of Results

Based on the data we charted in the previous step, we divided the studies based on the mean age group during which the neurodevelopmental outcome was assessed. Specifically, we categorized studies as taking place during infancy (birth to 11 months), toddlerhood and preschool age (12 months to 5 years), school-age (6 to 12 years), and adolescence (13 to 17

years). Studies in which the mean participant age range did not neatly fit our categories were placed in the most appropriate category (e.g., a hypothetical sample age range of 8-13 years would be placed in the school-age category while a range of 11-16 years would be placed in the adolescence category). Some studies examined neurodevelopment at multiple timepoints across multiple age groups. When the results of each age group were presented separately, they were each placed in the corresponding table, such that a given study may be found in multiple tables. When data were analyzed using longitudinal analyses and the results spanned multiple age groups, the study was placed in a separate table for longitudinal/repeated measures and were therefore considered separately. We created a summary table for each age category in which the results of each study were summarized in 1-3 sentences. These tables (Tables A1 to A5) are available in Appendix A.

To create a global overview of results, associations between contaminants and neurodevelopment were categorized as being null, protective, or detrimental. For the sake of conciseness, this synthesis did not differentiate between statistically significant and marginally significant results (i.e., p-values <.10 are interpreted the same as p-values <.05). Neurodevelopmental data were then aggregated into broad categories (e.g., cognition encompasses all IQ-related results, psychomotor includes fine motor skills, gross motor skills, and visual-motor integration). When studies had multiple findings, each finding was documented separately (e.g., in a study examining full scale IQ [FSIQ] and its related five index scores, the results for each of these six scores were documented). As such, the results section refers to ‘findings’ as opposed to ‘studies’ to account for most studies reporting multiple findings and to avoid bias by giving null associations the same weight as statistically significant ones.

Percentages were calculated to display the proportion of findings that were null, protective, and detrimental for each chemical category and neurodevelopmental outcome.

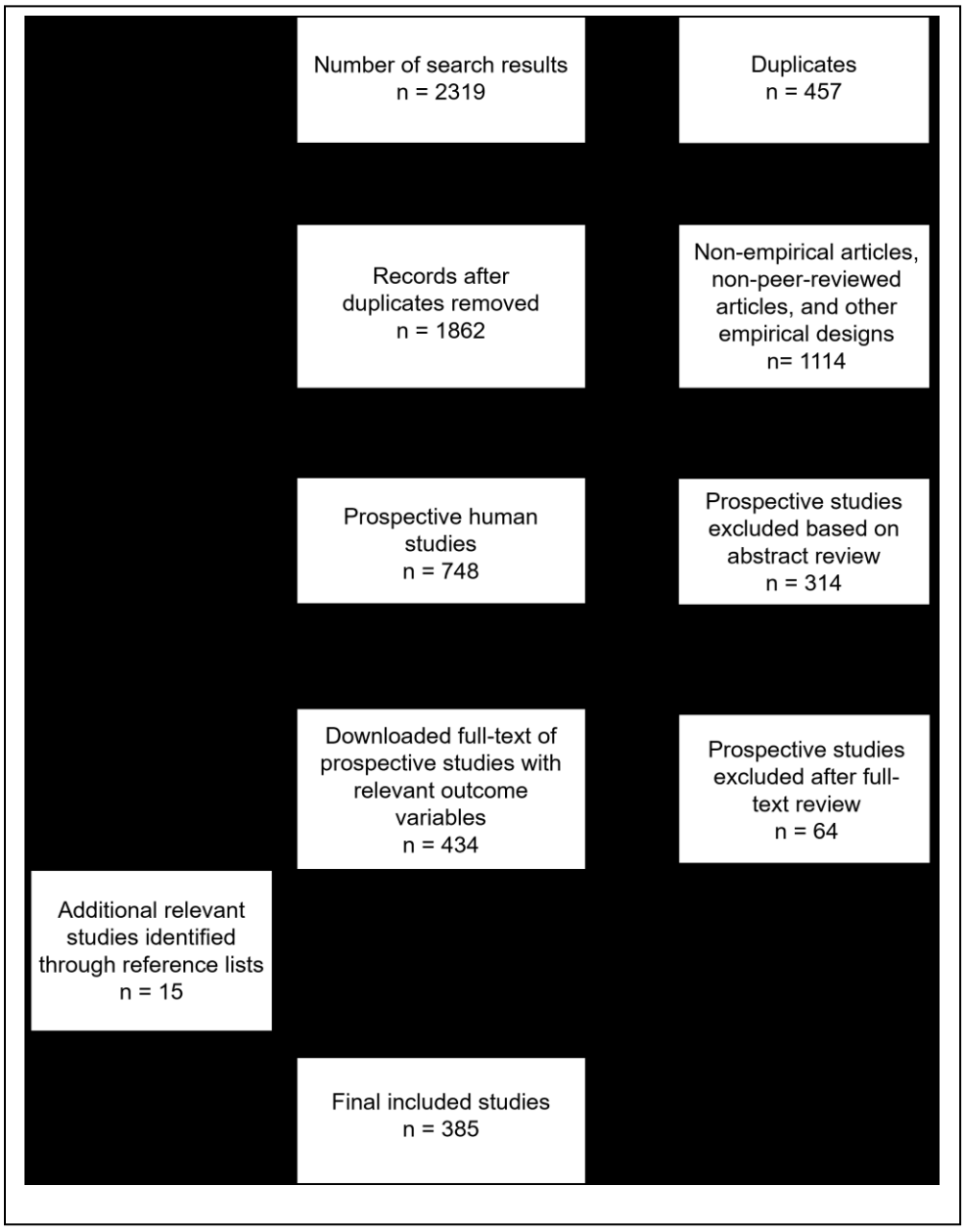
Results

Selected Sources of Evidence

The initial search returned 2319 records. After eliminating duplicates (*n*=457), titles and abstracts of the remaining 1862 articles were scanned to identify studies that fit our inclusion criteria. This resulted in 450 studies for which the full text was reviewed. During this step, another 65 studies were excluded due to unmet inclusion criteria. Fifteen additional relevant studies were identified by examining reference lists. In total, 385 studies were selected for review. The full flowchart representing the search process is found in Figure 1.

Figure 1

Flowchart of the search process



Characteristics and Results of Individual Sources of Evidence

Please refer to Tables A1 to A5 for a detailed report of cohort, sample size, proportion of female participants, chemical exposure matrix and timing of measurement, outcome measures, main findings, and possible sex differences. Studies are categorized by age group and listed alphabetically by first-author.

Synthesis of Results

Overall, few findings indicated that contaminants have a beneficial impact on child development. Rather, most studies reported a detrimental association or no impact. In addition, studies did not systematically account for sex as a potential moderator and reports of sex differences were often inconsistent. The most studied outcome in each age group was cognition and its components (e.g., verbal comprehension, visual-spatial understanding, working memory, processing speed).

Infancy

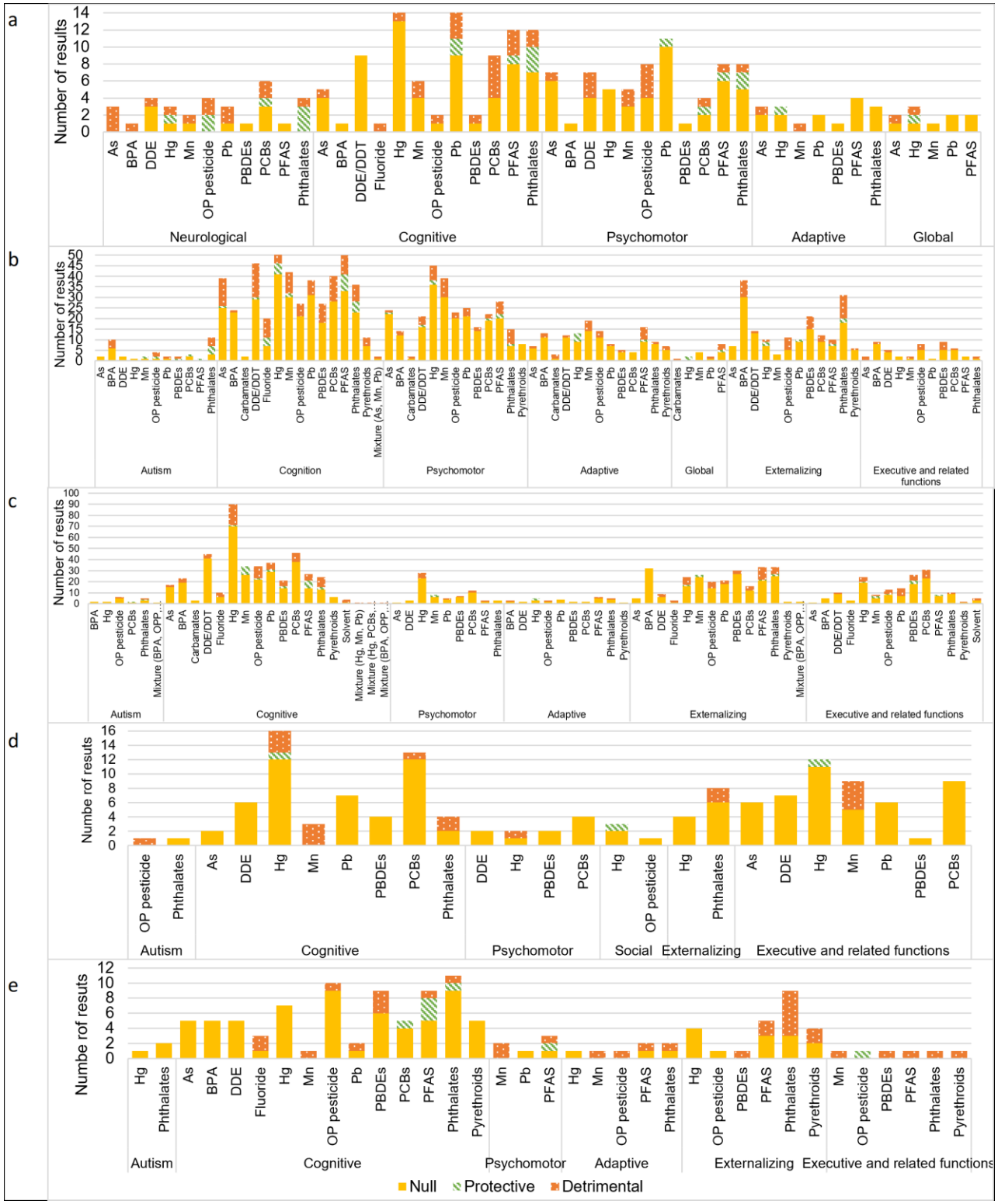
Sixty-three studies reported neurodevelopmental findings from birth to approximately 11 months of age. Of those 63 studies, 29 included an examination of sex-specific associations. The developmental domains examined at this age include cognition (e.g., global cognition, verbal development, memory, attention), psychomotor development (e.g., fine and gross motor skills), social and adaptive functioning, and neurological functioning (i.e., reflexes).

The majority of findings (65.4%) indicated that contaminants were not associated with neurodevelopment at this age (see Figure 2a). Approximately one quarter of results (25.2%) indicated a detrimental association, while a minority (9.4%) suggested an (unexpected) protective association with neurodevelopment. The proportions were approximately the same across all neurodevelopmental domains, except for the neurological functioning domain, where

there were more detrimental associations (43.8%) than null results (34.4%) or protective associations (21.9%). Regarding the chemicals, lead, mercury, PFAS, and phthalates were the most studied, but only organophosphate pesticides were associated with detrimental outcomes at least 50% of the time.

Figure 2

Association Between Neurodevelopment and Contaminants in Each Age Group

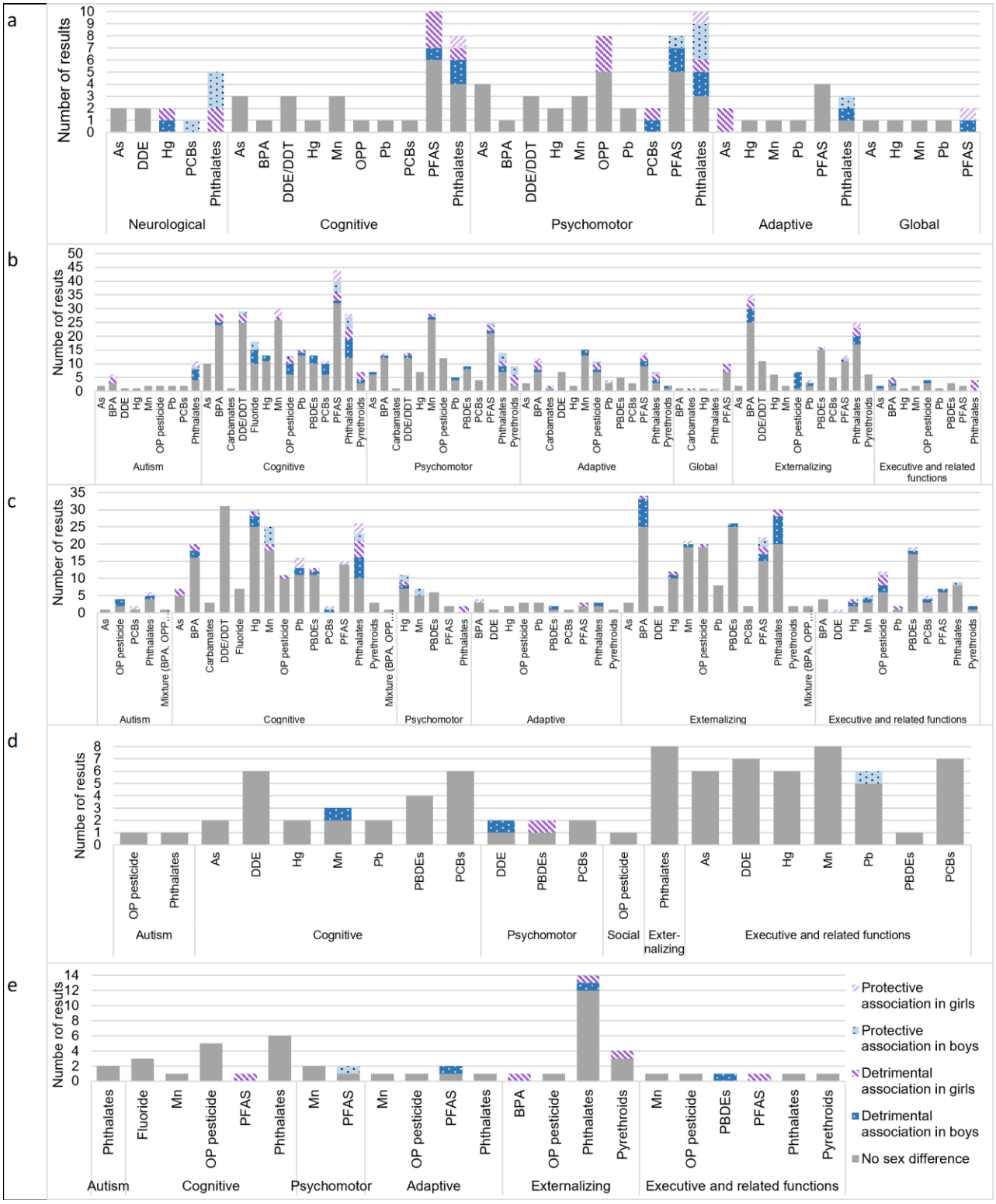


Note. a) Infancy; b) Toddlerhood and Preschool-Age; c) School-Age; d) Adolescence; e) Longitudinal

As for sex differences, the majority of findings (63.6%) indicated no significant difference between boys and girls (see Figure 3a). Girls were more often found to be disadvantaged by contaminant exposure compared to boys (girls: 14.0%; boys: 10.3%). More protective associations were reported in boys than in girls (girls: 3.7%; boys: 8.4%). There was more variability in the neurological functioning domain, where only one third of findings (33.3%) suggested no sex differences. There was also more variability for phthalates, where only one third (30.8%) of the results indicated there were no sex differences. For this contaminant, there were more sex-specific associations in boys (protective: 26.9%, detrimental: 19.2%) than in girls (protective: 7.7%, detrimental: 15.4%). Similarly, one quarter (25.0%) of results on PCBs suggested there were no sex differences, though this finding should be cautiously interpreted as there were only four data points on PCBs at this age.

Figure 3

Overview of Sex Differences in Each Age Group as A Function of Contaminants



Note. a) Infancy; b) Toddlerhood and Preschool-Age; c) School-Age; d) Adolescence; e) Longitudinal

Toddlerhood and Preschool-age

There were 193 studies reporting neurodevelopmental findings from ages 12 months to 5 years. Of those 193 studies, 120 included an examination of sex-specific associations. Domains of interest included symptoms of autism (e.g., parent-report questionnaires, affect recognition tasks), cognition (e.g., full-scale IQ and its components, namely verbal IQ, non-verbal IQ, memory, and processing speed), psychomotor development (e.g., fine and gross motor skills, visual-motor integration), social and adaptive skills, global development (including cognitive, motor, and social development), externalizing behaviours (e.g., informant reports of conduct problems, aggression, hyperactivity/impulsivity, and inattention), and executive function (e.g., informant reports of executive functioning and tasks measuring executive function, attention, and impulsivity).

The majority of results (72.9%) indicated that contaminants were not associated with neurodevelopment at this age (see Figure 2b). Approximately one fifth (22.1%) of results indicated that contaminants were associated with detrimental outcomes while a minority (5.0%) found a protective association between contaminants and neurodevelopment. This pattern of results held true across most domains, with a few exceptions. Results were more variable in the neurological functioning and the global development domains, with approximately half of the findings being null (47.5% and 52.9%, respectively), one third were detrimental associations (30.0% and 29.1%, respectively), and one fifth were protective associations (22.5% and 17.7%, respectively). In the executive function domain, one third (29.2%) of findings were detrimental outcomes while the remaining two thirds (70.8%) were null. Regarding the chemicals, mercury, PFAS, manganese, BPA, and phthalates were the most studied chemicals, though only carbamates were associated with detrimental outcomes 50% of the time.

As for sex differences, the majority of findings (75.0%) suggested no significant difference between boys and girls (see Figure 3b). There were more sex-specific detrimental associations than protective associations. In both cases, there were somewhat more sex-specific associations in boys (detrimental: 9.8%; protective 3.6%) than in girls (detrimental: 8.5%; protective 3.2%). While there was some variation in directionality of sex differences across domains, the majority of findings in all domains suggested there were no sex differences. Regarding specific chemicals, girls were more negatively impacted by carbamates and pyrethroids (40.0% and 29.2% of results on each chemical, respectively) while boys were more negatively impacted by fluoride and organophosphate pesticides (27.8% and 24.5% of results on each chemical, respectively).

School-age

There were 142 studies that included results spanning the ages of 6 to 12 years. Of those 142 studies, 82 included an examination of sex-specific associations. These studies examined the same neurodevelopmental outcomes as those in the toddlerhood/preschool-age category.

The pattern of results was the same as in the previous age group. Specifically, the majority of findings (76.9%) were null results (see Figure 2c), one fifth of findings (18.6%) were detrimental associations between contaminants and neurodevelopment, and a minority (4.5%) of findings were protective associations. The cognition and executive function domains had similar proportions, with approximately 75% of results (specifically, 74.8% and 73.8% respectively) being null and 20% (specifically, 19.8% and 21.3% respectively) being detrimental outcomes. For the psychomotor, social, and externalizing domains, there were slightly fewer detrimental outcomes (approximately 15%) and proportionally more null results (approximately 80%). The only domain with a significantly different pattern was the autism domain, where the same

proportion of findings suggested protective and detrimental associations (11.1% each), with the remainder (77.8%) being null results. Regarding the chemicals, mercury was the most studied, while only solvents were associated with detrimental outcomes at least 50% of the time.

In terms of sex differences, the majority of findings (78.6%) once again suggested no significant difference between boys and girls (see Figure 3c). As with the preschool-age results, there were more sex-specific detrimental associations than protective associations. There were more detrimental associations in boys (9.5%) than in girls (5.7%), but somewhat more protective associations in girls (3.2%) than in boys (3.0%). The pattern was reversed for the psychomotor domain, where there were more detrimental associations in girls (10.7%) than in boys (3.6%), but more protective associations in boys (14.3%) and in girls (0%). Nonetheless, most findings on psychomotor development suggest no sex differences (71.4%). PCBs were associated with protective outcomes in girls 25.0% of the time while phthalates were associated with negative outcomes in boys 21.1% of the time.

Adolescence

Thirteen studies reported findings between the ages of 13 and 17 years inclusively. Of those 13 studies, 7 included an examination of sex-specific associations. The examined outcomes were the same as those of the two previous age groups. Similarly, the broad results were consistent with those found in studies of younger children. Specifically, the majority of findings (84.3%) were null results, one tenth of findings (13.4%) were detrimental outcomes, and very few findings (2.2%) were protective associations between contaminants and neurodevelopment (see Figure 2d). Regarding the chemicals, mercury was once again the most studied and only manganese and organophosphate pesticides were associated with detrimental outcomes more than 50% of the time.

Regarding sex differences, the results in adolescence were consistent with those of younger age groups where majority of findings (95.2%) suggested no significant difference between boys and girls (see Figure 3d). Similar to the results in preschool-age, there were more sex-specific detrimental associations than protective associations. In both cases, there were slightly more sex-specific associations in boys (detrimental: 2.4%; protective 1.2%) than in girls (detrimental: 1.2%; protective 0.0%). The only exception to this pattern was the psychomotor development domain, where 66.7% of findings indicated there were no sex differences while 16.7% of findings indicated a detrimental effect for each sex. There were no notable patterns of sex differences for any specific contaminants in this age group.

Longitudinal Studies

This category included 24 studies that spanned multiple age groups. Of those 24 studies, 17 included an examination of sex-specific associations. Similar to results from individual age groups, the majority of findings were null (67.5%), one quarter (26.8%) of findings indicated detrimental associations, and a minority (5.7%) indicated a protective association between contaminants and neurodevelopment (see Figure 2e). Three domains (social development, psychomotor development, and executive function) had more detrimental associations (60.0%, 50.0%, and 83.3% respectively) than null results (42.9%, 33.3%, and nil, respectively), but should be interpreted with caution given the relatively small number of studies included in this section. Regarding the chemicals, phthalates and PFAS were studied most often while only fluoride and manganese were associated with detrimental outcomes more than 50% of the time.

Once more, most studies (83.0%) suggested no significant difference between boys and girls (see Figure 3e). While none of the studies reported protective associations in girls and only one finding indicated a protective association in boys (1.9%), there were more detrimental

associations in girls (9.4%) than in boys (5.7%), though this should be interpreted with caution given the small number of studies included in this section. Results for PFAS were mixed in terms of sex differences. Specifically, an equal number of findings indicated no sex differences and detrimental associations in girls (33.3% each) while half as many findings supported either detrimental or protective associations in boys (16.7% each) and no findings supported a protective association in girls. There were no other notable patterns of sex differences for any specific contaminants in this category of studies.

Discussion

Summary of Evidence

The aim of this review was to examine the literature on prenatal contaminant exposure and neurodevelopment in community cohorts from birth to the end of adolescence. Importantly, the focus of the review was on the neurodevelopmental outcomes rather than the specific contaminants. This angle was chosen as humans are constantly exposed to co-occurring chemicals and disentangling the impact of each substance is impossible (Dorea, 2019; Mitro et al., 2015; Padula et al., 2020).

Overall, we found that approximately 10 to 25% of results across age groups indicated that prenatal contaminant exposure was associated with a detrimental neurodevelopmental outcome. Notably, the proportion of detrimental outcomes to null results varied based on age group. The largest proportions of detrimental outcomes were in the infancy (25.2%) and longitudinal (26.8%) categories. The preschool and school-age groups were similar to each other and had a somewhat smaller proportion of detrimental outcomes (22.1% and 18.6%) than infancy, but more than adolescence (13.4%). Importantly, there are markedly fewer studies of adolescents (13) than of younger children (63 in infants, 193 of toddlers/preschoolers, and 143 of

school-age children), which may explain why the pattern of results was different than that of younger age groups. These results highlight the importance of following a developmental approach. Specifically, the impact of contaminant exposure may vary with time and therefore requires follow-up over time to be best understood. For instance, it is possible that a deficit appearing early in life will improve over time with factors like environmental stimulation, parental nurturance, and education (Bellinger, Matthews-Bellinger, et al., 2016; Horton et al., 2012). Conversely, an early adverse outcome may worsen in the absence of these protective environmental factors. Certain deficits may also appear later in development, long after the initial exposure, either because measures used in early life are not sensitive enough, the affected ability is one that only emerges later, or the deficit is the result of a cascade of events over time (Bellinger, Matthews-Bellinger, et al., 2016; Rice & Barone, 2000). For example, some researchers suggest that alterations in cognitive function in early life may play a role in neurodegenerative diseases in late adulthood (Bellinger, O'Leary, et al., 2016; Mostafalou & Abdollahi, 2018; Saeedi Saravi & Dehpour, 2016). Thus, more studies examining developmental trajectories, such as those included in the longitudinal section of this review, are needed (Schantz et al., 2020).

In addition, the proportion of detrimental outcomes to null results varied based on specific neurodevelopmental domain. Indeed, from infancy to school-age, the neurocognitive, cognitive, and executive function domains had greater proportions of detrimental outcomes than the social, externalizing, and psychomotor domains. Importantly, the social and externalizing domains are most often assessed by informant report while neurocognition (e.g., neurological function evidence by reflexes in infants), cognition, and executive function are most often assessed using standardized tests. The variation in results across neurodevelopmental domains

may therefore reflect differences in measurement or indicate that cognitive domains are more vulnerable to contaminant exposure than more behavioural domains.

It is difficult to establish whether any of the contaminants examined in this review is more detrimental than others. This scoping review was designed to outline the overall relevance of prenatal exposures to contaminants for (neuro)psychological functioning, rather than examining the impact of specific contaminants. Different contaminants have different mechanisms of action and may have different critical windows during which they impact neurodevelopment. Beyond the timing of exposure, the association with neurodevelopment may also vary based on the biological matrix in which the contaminant was measured (e.g., maternal blood vs. cord blood) as well as the extent of the exposure (i.e., dosage). These aspects were beyond the scope of this review as the focus was rather on the neurodevelopmental domains.

Across age groups, our review found inconsistent evidence of sex differences in these associations, with most studies reporting no significant differences between boys and girls. In preschool-age, school-age, and adolescence, there were generally more adverse associations in boys than in girls, though the gap was not very large.

Important Issues

Significance of the Prenatal Period

Even though brain development is a highly protracted process that continues into early adulthood, several critical and sensitive periods take place during fetal development (Knudsen, 2004; Rice & Barone, 2000). Contaminants can impact *in utero* development as they can cross the placenta (Aylward et al., 2014; Vizcaino et al., 2014). Importantly, developing neurons are more vulnerable than mature neurons and may sustain damage from exposure at lower doses (Lanphear, 2015; Rice & Barone, 2000). In addition, alterations in development at this early

stage can shift future trajectories and impact functioning down the line (Bellinger, Matthews-Bellinger, et al., 2016). Although postnatal exposure in early life likely plays a role as well, exposure in the prenatal period may be more impactful (Sapbamrer & Hongsibsong, 2019; Verner et al., 2015).

Effect Sizes in Context: Individuals, Populations, Known Risk Factors, and Health Endpoints

Most detrimental outcomes reported in population studies have quite small effect sizes and some studies may have been underpowered to find significant associations due to sample size. For example, several studies examining prenatal PBDE exposure and IQ in children report a decrease of 2 to 5 points in FSIQ (Azar et al., 2021; Chen et al., 2014; Eskenazi et al., 2013; Lam et al., 2017; Zhang et al., 2017b). Given that the standard deviation of most IQ scores is 15 points, an IQ decrease of 2-5 points is not clinically significant for a given individual. However, at a population level, a 5-point decrease in the average IQ could substantially increase the proportion of children who have an IQ below 70 (Lanphear, 2015). Moreover, given how ubiquitous exposures are, these small decrements are widespread, therefore playing a sizeable role in overall societal burden (Bellinger, 2012a; Bellinger et al., 2019; Bellinger, O'Leary, et al., 2016). For instance, the cost of contaminant-related IQ loss in the European Union has been estimated to approximately 160 billion euros (for example, due to increased healthcare costs and lost productivity) (Trasande et al., 2015; Trasande et al., 2016).

Even though effect sizes of contaminant exposure on neurodevelopment may not be clinically significant, (Goodman, Green, et al., 2023; Lam et al., 2017) they may nonetheless be similar to those of known perinatal risk factors for neurodevelopment, such as low birth weight, prematurity, low maternal thyroid hormones, and maternal tobacco, alcohol, or opioid consumption (Corrêa et al., 2021; Gu et al., 2017; Jacobson et al., 2021; Lee et al., 2020; Levie et

al., 2018; Twilhaar et al., 2018). Importantly, as with any other perinatal risk factor for behavioural and cognitive problems, it could be speculated that perinatal exposure to certain contaminants could interact with other risk factors known to be associated with child development, such as genetic susceptibility and other environmental adversities/stressors (e.g., Engel et al., 2011; Julvez et al., 2019; Snoj Tratnik et al., 2017; Stein et al., 2016; Yu et al., 2022). Future studies are needed in this regard.

Lastly, while our review concludes that prenatal contaminant exposure is either associated with adverse neurodevelopmental outcomes or having no significant impact, it is important to note that the same contaminants have been reported to have adverse effects on a variety of other health endpoints. Though they were beyond the scope of this review, many studies reported impacts on fetal growth, respiratory and immune health, endocrine function, obesity, and reproductive health (Vrijheid et al., 2016). Therefore, when considering whether contaminants have an adverse effect on health, it is important to consider a variety of health outcomes.

Socioeconomic Factors Are Independently Associated With Both Exposure and Neurodevelopment

Evidence demonstrates that socioeconomic status (SES) is associated with contaminant exposure, though the direction of the association varies depending on the chemical. For example, while high SES groups may have greater exposure to contaminants like mercury, arsenic, and PFAS (Montazeri et al., 2019; Nelson et al., 2012; Tyrrell et al., 2013; Vrijheid et al., 2012), low SES groups have greater exposure to like lead and BPA (Nelson et al., 2012; Tyrrell et al., 2013).

Low SES and greater socioeconomic adversity are associated with poorer neurodevelopment in children (Farah, 2017; Hanscombe et al., 2012; Ming et al., 2021; Noble &

Farah, 2013; Noble et al., 2007; Piccolo et al., 2016; Stein et al., 2016; Turkheimer et al., 2003; von Stumm & Plomin, 2015). In combination with the evidence that socioeconomically vulnerable groups have higher exposures for certain contaminants, they may be at greater risk of contaminant-related adverse neurodevelopmental outcomes (Engel et al., 2021; Zota & Shamasunder, 2017). In addition, there is evidence that socioeconomic adversity potentiates the association between contaminants and neurodevelopment, therefore further increasing the vulnerability of already marginalized groups (Elliott et al., 2004; Fernandez-Bou et al., 2021; Weiss & Bellinger, 2006).

There are several pathways through which lower SES groups may have increased risk and/or exposure. For example, blue-collar workers are more likely than their white-collar counterparts to have greater occupational exposure to contaminants (e.g., agricultural workers and pesticides, factory workers and toxic fumes) (Evans & Kantrowitz, 2002; Pampel et al., 2010). Occupational exposure in pregnant workers can in turn have transgenerational consequences through fetal exposure and transmission of altered epigenetic markers (Aylward et al., 2014; Haimbaugh et al., 2022; Risova, 2019; Svoboda et al., 2022). Families in lower SES are also more likely to live in older, lower quality housing, which may contain more hazardous chemicals (e.g., lead-based paint) and therefore increase both pre- and postnatal exposure (Bellinger, 2008; Dunn, 2020; Evans & Kantrowitz, 2002; Moody et al., 2016; Pampel et al., 2010). Another noteworthy pathway is nutrition. Nutritional factors like iron and calcium can be protective against exposure to contaminants like lead and manganese (Kupsco et al., 2020; Lanphear et al., 2002; Liu et al., 2014; Shah-Kulkarni et al., 2016). Similarly, polyunsaturated fatty acids in fish appear to mitigate the impact of mercury on neurodevelopment (Choi et al., 2014; van Wijngaarden et al., 2017). Lower SES families often have less access to healthy food

options, thus resulting in suboptimal consumption of essential nutrients and relatedly, the loss of their potential protective impact (Evans & Kantrowitz, 2002; Kordas et al., 2007; McCullough et al., 2022). Meanwhile, fast food and processed food may be more accessible for various reasons (e.g., lower price, reduced time needed to prepared food) (Baraldi et al., 2018; French et al., 2019). However, these foods often have greater concentrations of contaminants like BPA or PFAS due to their packaging or the manufacturing process (Nelson et al., 2012; Susmann et al., 2019). Lastly, lower SES families have less access to educational resources, which could have helped mitigate the negative impact of other risk factors (Evans & Kantrowitz, 2002; Farah, 2017; Rosen et al., 2020; Sanrey et al., 2021).

Policy Issues

Societal and political approaches to chemical use and policy are part of the broader issue. Contaminants are treated as innocent until proven guilty, meaning that they can be marketed and utilized widely before they are stringently tested for toxicity risks (Bennett et al., 2016; Lanphear, 2015). For example, PBDEs were designated as persistent organic pollutants in the Stockholm Convention in 2004, which marks the beginning of restrictions on the use and production of PBDEs in several countries across the world (Sharkey et al., 2020). However, the need for flame retardant chemicals remained, such that they were eventually replaced by organophosphate esters. Emerging research now suggests that organophosphate esters may pose similar concerns for neurodevelopment (Doherty, Hammel, et al., 2019; Doherty, Hoffman, et al., 2019a, 2019b; Liu et al., 2021; Percy et al., 2021). As evidence of toxicity accumulates, organophosphate esters may become restricted as well, only to be replaced by another contaminant, which in turn will be suspected of toxicity a few years later (Bennett et al., 2016).

While banning harmful environmental contaminants is a key long-term strategy, it is not effective for short-term harm reduction. Given that some chemicals can linger in the environment for many years, exposure will persist for some time after the contaminant is banned (Grandjean & Landrigan, 2014). In addition, exposure is widespread and originates from so many sources that individual behaviour changes to reduce exposure would likely be ineffective (Dorea, 2019; Mitro et al., 2015; Sears & Braun, 2020). Rather, harm reduction plans should target the adverse health outcomes directly through prevention, intervention, and disability-reduction strategies (Atli & Baran, 2022; Bann et al., 2016; Bigorra et al., 2016; Blauw-Hospers et al., 2007; Burger, 2010; Chen et al., 2021; Kitzman et al., 2010; Obradović et al., 2016; Ramey & Ramey, 1998; Reyno & McGrath, 2006; Rosen et al., 2020; Watanabe et al., 2005). Prenatal screenings may also be a useful and cost-effective strategy to assist pregnant persons in limiting their exposure, in turn reducing prenatal exposure for the fetus and future developmental consequences (Gaskin et al., 2015).

Significance in Mental Health Research and Clinical Practice

Understanding the landscape of neurotoxicology research is an asset for researchers in Psychology and allied mental health fields. They are ideally trained to collaborate with epidemiologists and public health experts to ensure that 1) neuropsychological measures are used and interpreted appropriately in population studies, and 2) SES and marginalized identities are given due consideration (Fernandez-Bou et al., 2021).

Furthermore, knowledge of the potential effects of contaminant exposures is also key in clinical practice as it contributes to biopsychosocial conceptualizations of neurodevelopment in children. Contaminant exposure as a sole risk factor may not result in clinically significant cognitive impairment and is generally not being assessed for individual children in the context of

a neuropsychological assessment. Nonetheless, practitioners should be aware of contaminant exposure as an additional risk factor for poor neurodevelopmental outcomes and that certain groups are disproportionately affected. Just as clinicians routinely assess lifestyle factors and pregnancy/birth complications during their initial evaluation process, it would be important to consider potential pre- and postnatal contaminant exposures. Knowledge of potential significant exposures (e.g., parental occupational exposure during pregnancy resulting in prenatal exposure for the child, living in housing with confirmed lead-soldered pipes) may further inform the case conceptualization and allow the clinician to make specific recommendations to mitigate individual risk and decrease exposure accordingly.

Limitations

While our literature search was broad and comprehensive, it is possible that we have missed certain studies by our choice of search terms. In addition, we may have left out important studies based on our exclusion criteria. For example, we did not include studies of academic achievement and communication/language development because we chose to focus on neurocognitive functions (e.g., intelligence, executive function, attention). Similarly, we did not examine all relevant chemicals. We chose to focus on contaminants that are known or strongly suspected to be neurotoxic to help focus the scope of the review. We did not include studies on air pollution despite evidence of neurotoxicity (Grandjean & Landrigan, 2014) because exposure to air pollutants is not usually measured using biological samples. Rather, exposure is most often assessed using atmospheric measurements and residential proximity to sources of air pollution (e.g., highways). Further, given our focus on specific contaminants, few studies on multiple exposures were included. Simultaneous exposure to multiple contaminants is inevitable given how widely used they are. Importantly, these co-exposures may have additive, multiplicative, or

synergistic effects, or otherwise modify the impact of other exposures (Bellinger, 2009; Maffini & Neltner, 2015; Vrijheid, 2014; Yorifuji et al., 2011). While there is an increasing number of studies on co-exposures and 'exposomes' (i.e., the sum of all exposures), there is still insufficient data to fully understand the role of individual chemicals in relation to each other as well as how cumulative exposure affects health and wellbeing (e.g., Jedynak et al., 2021; Julvez et al., 2021; Kalloo et al., 2021; Maitre et al., 2021).

Nonetheless, we included a wide range of contaminants and outcomes to provide a broad overview. As a result, we could not fully explore all the interpretive nuances of the included studies. For example, we did not discuss mediation or moderation effects, the role of sociodemographic variables, or the impact of nutritional variables (e.g., how polyunsaturated fatty acids in fish may modify the association between mercury and neurodevelopment).

Lastly, most studies included in this review are conducted in populations located in North America, Europe, and East Asia. As such, there is little information on the association between prenatal contaminant exposure and neurodevelopment in other regions. More studies are needed in developing countries, where exposure may be higher (e.g., due to rapid economic growth, poor waste management practices, lack of efficient water treatment infrastructure) and regulations may be less stringent or less reliably enforced (Anyanwu et al., 2018; Bellinger, O'Leary, et al., 2016; Dai et al., 2020; Ostrosky-Wegman & Gonsebatt, 1996; Selwe et al., 2022; Sharma et al., 2014).

Conclusions

Contaminant exposure is associated with detrimental neurodevelopmental outcomes at worst or no change at best. Associations vary based on the outcomes and age group, reinforcing the importance of adopting a developmental approach. More longitudinal studies are needed to

track potential changes across development and to account for multiple co-exposures. In addition, more studies are needed in developing countries to better understand the consequences of exposure in the local context. Importantly, while effect sizes are generally small, they remain significant at a population scale. Policy changes are needed to improve safety testing standards prior to large scale use and marketing of contaminants. From a clinical perspective, practitioners should be trained to assess for potential toxic exposures in the intake process, and prevention and intervention strategies should be developed to address the widespread subclinical consequences of developmental contaminant exposure.

Chapter 3: Prenatal Exposure to Polybrominated Diphenyl Ethers (PBDEs) and Cognitive Ability in Early Childhood

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Abstract

Background: Prenatal exposure to polybrominated diphenyl ethers (PBDEs) has been associated with adverse neurodevelopmental outcomes in children, but evidence remains mixed regarding sex differences in this association.

Objective: To examine the prospective association between prenatal PBDE exposure and cognitive ability in young children, as well as potential sex differences.

Methods: The study was conducted in a multi-site Canadian pregnancy cohort recruited in 2008-11. PBDEs were measured in maternal plasma samples collected early in pregnancy. Cognitive ability was assessed using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) in children at age 3 years (mean = 3.4). Multiple linear regression was used to analyze the association between maternal PBDE plasma concentrations (lipid-standardized and log10-transformed) and Verbal, Performance, and Full Scale IQ scores on the whole sample and stratified by sex, adjusting for confounders.

Results: The sample was composed of 592 children (291 boys and 301 girls). A tenfold increase in maternal blood PBDE concentration (sum of BDE-47, -99, -100, and -153) was associated with lower Full Scale scores in boys (-3.4 points; 95% CI: -7.0, 0.1), after adjusting for confounders. BDE-47 was the congener with the highest concentrations in maternal blood and a tenfold increase in exposure was associated with significantly lower Full Scale IQ scores in boys (-4.4 points; 95% CI: -7.9, -0.9), after adjusting for confounders. Verbal and Performance IQ scores were similarly associated with PBDE exposure. Maternal blood PBDEs concentrations were not associated with IQ scores in girls.

Conclusions: Prenatal exposure to background levels of PBDEs, especially BDE-47, was associated with lower IQ scores in boys, but not in girls. Our results support that exposure to PBDEs during early development may be sex-dependent and detrimental to a child's neurodevelopmental trajectory.

Keywords: Polybrominated diphenyl ethers; Neurodevelopment; Cognitive ability; Pregnancy cohort

Introduction

Polybrominated diphenyl ethers (PBDEs) are chemicals used as flame retardants in many household items, including textiles, furniture, appliances, and electronics. PBDEs, which are semi-volatile compounds added during the polymer manufacturing process, are not chemically-bound to substrates and can leach into the environment (Costa & Giordano, 2007; Linares et al., 2015). There are 209 different congeners of PBDEs based on the number of bromine atoms in the molecule (Darnerud et al., 2001; Klinčić et al., 2020). Importantly, PBDEs are lipophilic persistent organic pollutants (POPs) that bioaccumulate and biomagnify in the food chain (Darnerud et al., 2001; Linares et al., 2015). PBDEs are highly resistant to degradation, with biological half-lives ranging from 2 to 12 years in humans (Geyer et al., 2004; Trudel et al., 2011).

Levels of PBDEs have decreased over the last two decades due to reductions in their use, driven by regulations limiting their utilization (Guo et al., 2016; Health Canada, 2019b; Ma et al., 2013). Still, populations continue to be exposed to PBDEs since these chemicals are persistent and PBDE-containing products are still in use. Blood concentrations of PBDEs are higher in North American than European populations by approximately one order of magnitude (Frederiksen et al., 2009). Primary exposure routes for PBDEs include ingestion, inhalation, and dermal absorption of house dust (Frederiksen et al., 2009; Klinčić et al., 2020). Exposure is also linked to diet, with high lipid-content foods (e.g., fish, meat, dairy products) often containing higher concentrations of PBDEs than low lipid-content foods (Frederiksen et al., 2009; Klinčić et al., 2020). Furthermore, exposure can occur *in utero* because PBDEs readily cross the placenta (Doucet et al., 2009; Mazdai et al., 2003; Vizcaino et al., 2014). This finding is particularly concerning given that the prenatal stage is a vulnerable period in human life and that prenatal

development can set the stage for future development (Grandjean & Landrigan, 2014; Vizcaino et al., 2014).

Findings from animal studies indicate that prenatal exposure to PBDEs adversely impacts neurodevelopment. Indeed, prenatal exposure to the deca-BDE congener BDE-209 has been related to disruptions in the response of cholinergic receptors, which are closely linked to behavioural and cognitive functioning, as well as decreased habituation, and impaired learning and memory (Buratovic et al., 2014; Viberg et al., 2007). Similar results were found for exposure to BDE-153 (Viberg et al., 2003), BDE-99 (Branchi et al., 2002), and BDE-47 (Eriksson et al., 2001; Gee & Moser, 2008). Importantly, these rodent studies identified a sensitive period characterized by a brain growth spurt during which exposure can be particularly detrimental to neurodevelopment. In rats, this period corresponds to the first four weeks of life, with a peak occurring at postnatal day 10 (Viberg et al., 2007). In humans, that period is equivalent to that extending from the beginning of the third trimester of pregnancy to the first two years of life (Viberg et al., 2007).

Epidemiological human studies conducted with prospective birth cohorts around the world have also found that prenatal exposure to PBDEs is associated with adverse effects on various developmental domains. In infancy and toddlerhood, prenatal exposure to PBDEs has been linked to slower psychomotor and cognitive development (Herbstman et al., 2010) and to lower levels of social and language development (Ding et al., 2015). At preschool- and school-age, prenatal exposure to PBDEs has been related to poorer fine motor skills (Eskenazi et al., 2013; Roze et al., 2009), consistent with previously discussed results suggesting psychomotor alterations in studies of rodents and infants. At a behavioural and socioemotional level, prenatal PBDE exposure has been related to greater hyperactivity (Chen et al., 2014) and externalizing

problems (Roze et al., 2009; Zhang et al., 2017a), suggesting potential alterations in self-regulation and neurodevelopment. Lastly, at a cognitive level, prenatal PBDE exposure has been linked to lower intelligence quotients (IQ) (Chen et al., 2014; Eskenazi et al., 2013; Herbstman et al., 2010; Zhang et al., 2017a), readings skills (Zhang et al., 2017a), executive function (Vuong et al., 2016), and attentional abilities (Cowell et al., 2015; Eskenazi et al., 2013; Roze et al., 2009), which are also consistent with disruptions of neurodevelopment.

Some evidence suggests potential sex differences in the association between PBDE exposure and various developmental domains. For instance, Vuong and colleagues (2016) examined executive function in school-age children and reported a significant interaction between maternal PBDE concentrations and sex. Further sex-stratified analyses revealed that adverse associations were present in boys, but not in girls (Vuong et al., 2016). Some studies of prenatal PBDE exposure and child development either did not control for sex (Braun, Yolton, et al., 2017) or included sex as a covariate without examining its interaction with exposure or conducting a sex-stratified analysis (Herbstman et al., 2010; Zhang et al., 2017a). Other studies included an interaction term and/or conducted a sex-stratified analysis, but did not find an effect modification by sex for outcomes like IQ, externalizing problems, attention, and hyperactivity (Chen et al., 2014; Cowell et al., 2015; Eskenazi et al., 2013; Sagiv et al., 2015). These inconsistent findings suggest that child sex should be further investigated in relation to potential PBDE-related neurodevelopmental outcomes.

The effect of prenatal exposure to PBDEs on neurodevelopment in preschool and school age children has primarily been studied in the United States (Gibson et al., 2018), where exposure levels are higher than in Canada (Gravel et al., 2018). In addition, the birth cohorts used in these American studies conducted their sample recruitment between 1999 and 2006

(Eskenazi et al., 2013; Herbstman et al., 2010; Vuong et al., 2016). This is particularly relevant given that two of the main commercial PBDE mixtures (i.e, PentaBDE and OctaBDE) were eliminated from world-wide manufacturing in 2006 (Health Canada, 2019a). As such, the first goal of the present study is to examine whether prenatal exposure to PBDEs is associated with cognitive development in a sample of Canadian children whose mothers had lower exposure and were recruited from 2008 to 2011. A second goal of the study is to examine the association between prenatal PBDE exposure and child cognitive development separately in boys and girls in order to observe any potential sex differences.

Methods

Study Participants

Participants were 3-year-old children (range = 3.0 – 4.1, mean = 3.4, standard deviation = 0.3) born to mothers who were enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort. MIREC is a prospective pregnancy cohort of 2000 women recruited during the first trimester of pregnancy from obstetric and prenatal clinics across 10 Canadian cities. Recruitment took place between 2008 and 2011. Eligibility criteria at maternal enrolment included (a) the ability to consent; (b) speaking English or French; (c) being aged 18 years or older; (d) being between 6 and 13 weeks pregnant; and (e) intending to receive prenatal care and deliver at the local study site (please see Arbuckle et al., 2013 for full information regarding recruitment, eligibility, and study follow-ups). Exclusion criteria included congenital malformations or abnormalities of the fetus as well as maternal medical complications, history of major chronic illness, history of illicit drug use, and threatened abortion.

Participants from the six largest study sites were invited to participate in a follow-up study to assess child neurodevelopment around age 3 years. These sites, which are located across

the country, were prioritized due to practical reasons in order to maximize the number of participants that could be recruited. At the time of initial recruitment, there were 1537 participants (i.e., singleton, live births) across these six study sites. Of those, 610 children (39.7%) participated in the neurodevelopmental assessment follow-up visit. The cognitive testing took place during a home visit.

Informed consent was obtained in writing for both the prenatal biomonitoring and neurodevelopmental assessment phases of the study. The studies were approved by the Research Ethics Boards of Health Canada, Centre hospitalier universitaire (CHU) de Québec Research Center and each local study site. The study coordinating centre is at CHU Sainte-Justine's Research Center in Montreal.

Maternal Blood Concentration of PBDEs

PBDEs were measured in maternal blood samples collected during the first trimester of pregnancy. Laboratory analyses were conducted by the Centre de Toxicologie du Québec of the Institut National de Santé Publique du Québec (please see Fisher et al., 2016 for full report of PBDE exposure in the MIREC cohort). Nine PBDE congeners were measured, namely BDE-15, -17, -25, -28, -33, -47, -99, -100, and -153 using an Agilent 6890 Network or 7890A gas chromatograph (GC) coupled to an Agilent 5973 Network or 5975C mass spectrometer (Agilent Technologies; Mississauga, Ontario, Canada). The limits of detection (LOD) were 0.03 μg/L for BDE-15, -17, -25, -28, -33, -47; and 0.02 μg/L for BDE-99, -100, and -153. Blood PBDE concentrations were standardized for total lipid concentrations. Total cholesterol (TC), free cholesterol (FC), triglycerides (TG) and phospholipids (PL) levels were measured (in g/L) using enzymatic methods and colorimetry at the laboratory of Centre Hospitalier de l'Université Laval.

Total lipid concentration was calculated using the following formula:

$1.677 * (TC - FC) + FC + TG + PL$ (Patterson et al., 1991).

Child Cognitive Ability

Child cognitive ability was measured during the home visit, through the administration of the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III), a valid and reliable instrument providing scores of verbal, nonverbal and global intellectual function in young children (Wechsler, 2002). Children completed five subtests, namely Receptive Vocabulary, Information, Block Design, Object Assembly, and Picture Naming. The scores obtained from these five subtests result in three composite scores with a mean of 100 and a standard deviation of 15, namely the Verbal IQ (VIQ), Performance IQ (PIQ), and the Full Scale IQ (FSIQ).

Covariates

We carefully considered the selection of covariates for inclusion in the models to limit confusion bias. Potential confounding variables were identified based on previous studies on developmental neurotoxicity of PBDE (reviewed in Gibson et al., 2018). The variables considered as potential confounders were: maternal age during the first trimester of pregnancy, pre-pregnancy body mass index (BMI), birth weight, gestational age, race/ethnicity, maternal birth country, maternal education, household annual income, marital status, parity, self-reported smoking during pregnancy assessed in the third trimester, self-reported alcohol consumption during pregnancy, child sex, and study site. Then, we only retained variables that could be causally-related to prenatal exposure and IQ. For instance, we ensured that the timing of variables was logical for a causal association: variables used as potential confounders had all been assessed during pregnancy or at birth. Furthermore, we did not include variables that could

be on the causal pathway (i.e., gestational age). In order to build a more parsimonious model and maintain statistical power for sex-stratified analyses, we conducted ANOVAs between each of these variables and a) the sum of maternal blood PBDE concentration (BDE-47, -99, -100, and -153) and b) FSIQ. The variables that were related to both maternal PBDEs and FSIQ ($p < 0.20$) were included as covariates: maternal education, maternal birth country, maternal smoking during pregnancy, study site, and child sex.

Statistical Analyses

We transformed lipid-adjusted PBDE concentrations using log10 to normalize the distribution and reduce the influence of outliers. We conducted our analyses using the four congeners with a detection rate ≥ 20%, namely BDE-47 (detection frequency 66%), BDE-99 (19%), BDE-100 (21%), and BDE-153 (42%). The other PBDE congeners, namely BDE-15, -17, -23, 25, and -33, were not included in analyses as their respective detection rates were below 2%. Values below the LOD for the four analyzed congeners were imputed with regression on order statistics (Helsel, 2005). We considered three cognitive outcome variables (i.e, FSIQ, VIQ, and PIQ scores on the WPPSI-III), and conducted multiple linear regression models to assess the association with maternal blood PBDE concentrations. Separate regression models were built for log10-transformed lipid-standardized maternal blood concentrations of i) sum of those four congeners (Σ_4PBDEs), ii) BDE-47, and iii) BDE-153 (only these two congeners were analyzed individually given their relatively high detection rate). We first examined the raw, unadjusted model followed by the adjusted models. Each adjusted model included the same set of covariates, as outlined in the previous section (e.g., maternal education, maternal birth country, smoking during pregnancy, study site, and child sex). An interaction term between maternal PBDEs and child sex was included to test effect modification by sex. Lastly, we conducted sex-

stratified multiple regression analyses, adjusting for the same set of covariates, to examine potential differences in association between boys and girls (as decided *a priori* for the second study objective). Statistical analyses were conducted using SPSS version 25. A threshold of $p < 0.05$ was used for statistical significance.

Results

Sample Characteristics

While 610 children participated in the neurodevelopmental follow-up, the following analyses are based on the 592 children with measures of maternal blood PBDEs and to whom all WPPSI-III subtests were administered. Table 1 presents the characteristics of the study population, including median concentrations of PBDEs in maternal blood. The sample was approximately evenly distributed in terms of child sex (50.8% female) and comprised a majority of children whose mothers were born in Canada (82.4%), university-educated (66.6%), aged under 35 years during pregnancy (65.7%), and non-smokers (87.7%). Household annual income was $80,000 CAD or more for 58% of the sample. In terms of parity, 43.9% of mothers were nulliparous and 41.6% were primiparous. Most mothers were in the normal BMI range before pregnancy (56.1%). Boys and girls were comparable in terms of maternal and family characteristics. We observed higher median blood concentrations of Σ_4PBDEs in women born in Canada, those who quit smoking during pregnancy, and in those bearing boys.

The characteristics of the mother-child pairs included in the present study were comparable to those of the initial MIREC cohort, both across all ten sites and within the six study sites involved in the neurodevelopmental follow-up study (Ntantu Nkinsa et al., 2020) (Table B1). The median blood concentrations of Σ_4PBDEs was 12.9 ng/g lipid among women who participated in this follow-up study (n = 592; Table 2), while it was 13.1 ng/g lipid for those who

did not (n = 1335). Thus, prenatal exposure to the Σ_4PBDEs was not significantly different between children who completed this follow-up study and those who did not ($t(1925) = 0.50$, p = 0.614).The mean FSIQ score for the overall sample of children was 106.9. Scores were lower for boys than for girls (104.1 and 109.9, respectively; Table 3). Similarly, VIQ and PIQ mean scores were also slightly lower among boys (106.5 and 112.1 for VIQ; 101.2 and 104.9 for PIQ, respectively for boys and girls).The mean IQ score was in the "average" range of cognitive ability (which spans scores of 85 to 115) for the FSIQ, VIQ, and PIQ, and all scores were normally distributed.

Table 1

Characteristics of study participants and median maternal blood PBDE concentrations for the sum of BDE-47, -99 and -100 and -153 (Σ_4PBDE in ng/g lipid)

	Overall sample		Boys		Girls	
	n	Median Σ_4PBDEs	n	Median Σ_4PBDEs	n	Median Σ_4PBDEs
Overall	592	12.9	291	13.6	301	12.3
Study site[1]						
Site A	55	11.3	30	12.4	25	7.2
Site B	66	9.5	32	8.1	34	10.8
Site C	81	14.7	43	16.4	38	11.5
Site D	130	14.8	53	16.8	77	14.1
Site E	150	13.4	76	13.5	74	13.3
Site F	110	13.0	57	14.7	53	11.5
Maternal education[2]						
High school or less	30	17.1	19	17.6	11	14.8
College or trade school	166	14.3	86	15.5	80	13.9
Undergraduate diploma	234	11.9	109	12.0	125	11.6
Graduate diploma	160	12.2	76	13.0	84	10.7
Missing	2	9.8	1	9.9	1	9.8
Maternal age[2]						
18-29 years	146	14.0	78	16.9	68	11.9
30-34 years	243	13.6	114	12.5	129	13.9
35-39 years	170	12.0	82	12.4	88	11.8
40+ years	33	9.0	17	9.0	16	9.0
Household annual income[2] (Canadian dollars)						
< 50k	90	13.6	55	13.6	35	10.8
50 – 80k	137	12.8	64	15.3	73	11.0
80 – 100k	117	12.9	58	12.6	59	14.1
> 100k	229	12.6	107	13.2	122	12.4
Missing	19	12.5	7	16.8	12	10.8

Table 1 (continued)

Characteristics of study participants and median maternal blood PBDE concentrations for the sum of BDE-47, 99 and 100 and 153 (Σ_4PBDE in ng/g lipid)

	Overall sample		Boys		Girls	
	n	Median Σ_4PBDEs	n	Median Σ_4PBDEs	n	Median Σ_4PBDEs
Maternal birth country[2]						
Canada	488	13.9	239	14.9	249	13.0
Other	104	9.4	52	10.8	52	8.6
Parity[2]						
Nulliparous	260	13.5	126	14.8	134	12.2
1	246	12.5	118	12.5	128	12.0
2 or more	86	13.0	47	12.8	39	13.2
Smoking during pregnancy[3]						
Non smoker	519	12.3	255	12.5	264	12.2
Quit during pregnancy	34	24.9	20	26.7	14	24.5
Current smoker	15	12.6	5	18.8	10	11.5
Missing	24	12.5	11	15.4	13	11.1
Maternal pre-pregnancy BMI[2]						
Underweight (< 18.5)	14	13.1	8	9.1	6	39.3
Normal (18.51 - 25)	332	12.9	150	13.5	182	12.7
Overweight (25.1 - 30)	115	12.5	59	16.0	56	11.1
Obese (>=30)	90	14.6	50	13.9	40	15.3
Missing	41	10.2	24	12.6	17	6.8

[1] As participants from each site were not representative samples from each city, the cities have not been identified; [2] Variables assessed in the first trimester of pregnancy; [3] Variable assessed in the third trimester of pregnancy.

Table 2

Distribution of lipid-standardized maternal blood PBDE concentrations (ng/g lipid) for the overall sample and by child sex

	BDE-47	BDE-99	BDE-100	BDE-153	Σ_4PBDEs
Study overall sample (n = 592)					
Detection frequency	66%	19%	21%	42%	n/a
5th percentile	0.9	0.1	0.1	0.1	1.8
25th percentile	3.3	0.3	0.3	0.7	7.1
50th percentile	7.0	0.8	0.8	2.1	12.9
75th percentile	12.2	2.3	2.4	5.9	23.0
95th percentile	39.5	8.8	12.4	40.0	103.2
Maximum	727.3	169.1	327.3	527.3	1750.9
Boys (n = 291)					
Detection frequency	70%	22%	24%	45%	n/a
5th percentile	1.3	0.1	0.1	0.2	2.8
25th percentile	3.7	0.4	0.3	0.8	8.0
50th percentile	7.3	1.0	0.9	2.4	13.6
75th percentile	14.0	2.6	3.0	6.6	25.7
95th percentile	38.2	10.9	13.8	40.5	116.6
Maximum	727.3	127.3	213.6	211.4	1279.6
Girls (n = 301)					
Detection frequency	65%	20%	20%	40%	n/a
5th percentile	0.8	0.2	0.1	0.1	1.3
25th percentile	3.0	0.3	0.2	0.6	6.5
50th percentile	6.7	0.7	0.7	2.0	12.3
75th percentile	11.1	2.0	2.1	5.5	21.4
95th percentile	43.9	7.7	11.6	39.7	96.0
Maximum	727.3	169.1	327.3	527.3	1750.9

Note. n/a: non applicable

Table 3

Distribution of IQ scores from the WPPSI-III in the overall sample and by child sex

	Overall	Boys	Girls
FSIQ			
n	589	289	300
Minimum	51	51	77
Maximum	143	139	143
Mean	106.9	104.1	109.6
Standard deviation	13.6	14.5	12.0
VIQ			
n	586	287	299
Minimum	58	58	77
Maximum	144	141	144
Mean	109.4	106.5	112.1
Standard deviation	13.2	14.0	11.9
PIQ			
n	584	285	299
Minimum	55	55	61
Maximum	144	141	144
Mean	103.1	101.2	104.9
Standard deviation	14.9	15.5	14.1

Association between Maternal Blood Concentrations of PBDEs and IQ Scores

We first examined the unadjusted association between IQ and maternal concentrations of PBDE (Table B2). There was a statistically significant decrease of 2.2 points (95% CI: -4.4, -0.1) on FSIQ per tenfold increase in maternal Σ_4PBDEs (see Table B2). The association was slightly larger for BDE-47, whereby a tenfold increase in maternal BDE-47 concentrations was associated with significantly lower VIQ (-2.7 points; 95% CI: -4.8, -0.5) and FSIQ (-2.8 points; 95% CI: -5.0, -0.6) scores. Maternal concentrations of Σ_4PBDEs and BDE-47 were associated with lower PIQ scores (-2.1; 95% CI: -4.5, 0.2 and -2.3, 95% CI: -4.7, 0.2, respectively), although the associations did not reach significance. The associations of BDE-153 with VIQ, PIQ, and FSIQ were all negative, but were not statistically significant.

After adjusting for covariates, the association estimates for maternal PBDE concentrations and IQ scores were smaller and no longer significant, except for the association between Σ_4PBDEs and PIQ, whereby a tenfold increase in Σ_4PBDEs was associated with significantly lower PIQ scores (-2.4 points; 95% CI: -4.8, -0.1) (Table 4). Several interaction terms between sex and maternal PBDE concentrations were suggestive of a diffential association between boys and girls, especially for Σ_4PBDEs and BDE-47 for which p-values hovered around 0.1.

Table 4

Differences in IQ scores (95% CIs) for a tenfold increase in maternal PBDE concentrations, adjusting for covariates, along with p-values for the interactions between maternal PBDE concentrations and child sex

	FSIQ	VIQ	PIQ
Σ_4PBDEs	-0.9 (-3.0, 1.3)	0.0 (-2.1, 2.2)	-1.5 (-3.8, 0.9)
p-value for Σ_4PBDEs × sex	0.112	0.116	0.323
BDE-47	-1.9 (-4.1, 0.3)	-1.0 (-3.1, 1.1)	-2.4 (-4.8, -0.1)
p-value for BDE-47 × sex	0.106	0.070	0.362
BDE-153	0.3 (-1.2, 1.8)	0.6 (-0.8, 2.0)	-0.1 (-1.7, 1.5)
p-value for BDE-153 × sex	0.373	0.376	0.684

Note. Models adjusted for maternal birth country, maternal smoking at the third trimester of pregnancy, maternal education, study site, and child sex

Sex-Stratified Analysis

Once again, we first examined the unadjusted sex-stratified association between IQ and maternal PBDE concentrations (Table B3). There was a statistically significant decrease of 3.7 points (95% CI: -7.2, -0.3) on FSIQ per tenfold increase in Σ_4PBDEs for boys, whereas there was no association for girls. The associations for both cognitive domains approached significance for boys, with decreases of 3.3 VIQ points (95% CI: -6.6, 0.1) and 3.2 PIQ points (95% CI: -6.9, 0.5) per tenfold increase in Σ_4PBDEs; there were no statistically significant associations for girls. The association estimate was slightly larger for BDE-47 concentrations, with a statistically significant decrease of 4.4 VIQ points (95% CI: -7.7, -1.0) and 4.0 FSIQ points (95% CI: -7.5, -0.6) per tenfold increase in BDE-47 for boys; there were no statistically significant associations for girls. Meanwhile, the association estimates between BDE-153 and IQ scores were small and not statistically significant for either sex.

The pattern of results was similar for the models adjusted for confounders, with maternal PBDE concentrations being associated with lower IQ scores in boys but not in girls (Table 5). Specifically, there was a marginally significant decrease of 3.4 (95% CI: -7.0, 0.1) FSIQ points per tenfold increase in maternal Σ_4PBDEs for boys. The associations for BDE-47 were significant, whereby a tenfold increase in BDE-47 concentrations was associated with lower VIQ (-3.7 points; 95% CI: -7.1, -0.3), PIQ (-4.0 points; -7.8, -0.3), and FSIQ (-4.4 points; 95% CI: -7.9, -0.9) scores in boys. BDE-153 was not associated with IQ scores in either sex.

Table 5

Sex-stratified analyses for the differences in IQ scores (95% CIs) for a tenfold increase in maternal blood concentrations of PBDEs, adjusting for covariates

	FSIQ	VIQ	PIQ
Σ_4PBDEs			
Boys	-3.4 (-7.0, 0.1)	-2.6 (-6.0, 0.9)	-3.2 (-7.0, 0.7)
Girls	0.9 (-1.7, 3.4)	1.8 (-0.7, 4.3)	-0.6 (-3.6, 2.4)
BDE-47			
Boys	-4.4 (-7.9, -0.9)	-3.7 (-7.1, -0.3)	-4.0 (-7.8, -0.3)
Girls	0.0 (-2.7, 2.7)	1.3 (-1.4, 3.9)	-1.5 (-4.6, 1.6)
BDE-153			
Boys	-0.7 (-3.1, 1.7)	-0.4 (-2.7, 2.0)	-0.6 (-3.2, 2.0)
Girls	1.0 (-0.8, 2.8)	1.5 (-0.3, 3.2)	0.1 (-2.0, 2.2)

Note. Models adjusted for maternal birth country, maternal smoking at the third trimester of pregnancy, maternal education, and study site.

Discussion and Conclusions

The objective of this study was to examine the association between prenatal exposure to PBDEs and cognitive ability at the age of 3 years in the MIREC cohort. A secondary objective of the study was to explore the potential differential association between prenatal exposure to PBDEs and cognitive ability for boys and girls, given mixed evidence of sex differences in the literature. We observed that maternal concentrations of PBDEs were not associated with IQ scores in the overall group of children, but different results emerged when analyzing boys and girls separately. Among boys, higher maternal concentrations for the sum of BDE-47, -99, -100, and -153 were associated with lower IQ scores, although the association did not reach statistical significance. The congener BDE-47 had the highest concentration in mothers' blood, and increases in its concentration were significantly associated with poorer cognitive ability in boys, even after controlling for confounders. Specifically, a tenfold increase in maternal blood concentrations of BDE-47 was associated with a decrease of 4.4 FSIQ points in boys. The verbal and non-verbal cognitive domains (i.e., verbal and performance IQs, respectively) were similarly associated with prenatal PBDEs exposure. Thus, there was no evidence suggesting that association is domain-specific. Among girls, there was no evidence of association between maternal concentrations of PBDE and IQ scores. These results support the hypothesis that prenatal exposure to PBDEs may be detrimental to neurodevelopment among boys.

Our estimates are smaller in magnitude compared to those found in cohorts in the United States. The HOME and CHAMACOS cohorts reported statistically significant decreases of approximately 4 to 5 FSIQ points per tenfold increase in maternal prenatal concentrations (either Σ_4PBDEs or BDE-47) whereas we observed a corresponding decrease of only 1 to 2 points (analysis not stratified for sex). It should be noted that the children in these American studies

were aged between 5 and 8 years old, whereas the children in the present investigation were 3 years old. This is a particularly relevant difference given that adverse effects of *in utero* PBDE exposure might become more evident in older children. Indeed, it has been argued that an initial, early life insult on the brain might lead to a cascade of events, both biological and behavioral, detrimental to long-term optimal developmental trajectories. In addition, the smaller association estimates observed here may be explained by the fact that exposure levels in the HOME and CHAMACOS studies were subtantially higher than in the present study. For instance, the median concentration of the sum of four congeners (BDE-47, -99, -100, and -153) was 34.6 ng/g in the HOME cohort (Chen et al., 2014) and 24.9 ng/g in the CHAMACOS cohort (Eskenazi et al., 2013). In the present study, exposure levels were substantially lower, with a median concentration of 12.9 ng/g for the sum of these same four congeners. These findings indicating lower PBDE exposure in Canada compared with the United States are consistent with previous reports on PBDE blood concentrations from biomonitoring surveys (Gravel et al. 2018) and studies of PBDEs in dust (Harrad et al., 2008). A review investigating external sources of exposure and blood levels in different countries concluded that fire safety regulations was the most important driver of exposure differences between countries (Frederiksen et al., 2009).

Associations between prenatal exposure to PBDEs and adverse developmental outcomes have been reported in many studies, but there is still much to investigate regarding underlying mechanisms. One hypothesized mechanism that is well-supported in the literature is a disruption in the functioning of thyroid hormones (Costa & Giordano, 2007; Gibson et al., 2018). Thyroid hormones play an important role in fetal brain development, such that maternal hypothyroidism has been related to various neuroanatomical and behavioural alterations in offspring (Costa & Giordano, 2007; Schreiber et al., 2010). PBDEs have a similar chemical structure to that of

thyroxine (T_4) and have been found to bind to the thyroid hormone transport protein transthyretin and to thyroid hormone receptors. PBDEs have thus been related to a decrease in circulating T_4 levels in rodents (Costa & Giordano, 2007; Dingemans et al., 2011; Gibson et al., 2018) and a decrease in triiodothyronine (T_3) in rats (Dingemans et al., 2011). In the CHAMACOS study, it was found that PBDEs were not significantly associated with T_4 in maternal serum but rather that PBDEs were significantly inversely related to thyroid stimulating hormone (Chevrier et al., 2010). However, disruption of thyroid hormones did not fully explain the PBDE-related neurodevelopmental alterations, suggesting that other mechanisms may be involved (Eskenazi et al., 2013). For instance, animal studies suggest that PBDEs are related to neuronal oxidative stress and apoptosis in various brain regions, reduced neural cell differentiation and migration, and alteration in inter- and intracellular calcium homeostasis and signaling (Dingemans et al., 2011). Furthermore, animal studies suggest that exposure to PBDEs can alter the functioning of the central nervous system. Researchers have found adverse effects of PBDE exposure on neural circuitry of the frontal cortex and the hippocampus in rodents, which have important roles in cognition and memory (Costa et al., 2014). In addition, many neurotransmitter systems critical for behavioural and cognitive functioning, such as acetylcholine, dopamine, GABA, and glutamate, have also been found to be disrupted following PBDE exposure (Costa et al., 2014). However, these findings have not yet been confirmed in humans.

The sex differences observed in the present study and reported in the literature (Vuong et al., 2016) may be explained by a disruption in thyroid hormone function, as well as other mechanisms. Indeed, there is some evidence suggesting that alterations in thyroid hormone function following PBDE exposure may vary based on infant sex (Leonetti et al., 2016). There is also evidence that PBDEs and other brominated flame retardants may accumulate differently in

the placenta based on infant sex (Leonetti et al., 2016). Alternatively, there is evidence that estrogen, which is higher in females, may serve as a protective factor against oxidative stress (Behl et al., 1997). Further studies are necessary to fully elucidate the mechanisms underlying sex differences in PBDE-induced neurodevelopmental alterations.

The present study had a larger sample size than previous studies (Gibson et al., 2018). The sample size of the present study, approaching 600 mother-child pairs, allowed for sufficiently powered sex-stratified analyses. Two published studies based on data from the MIREC cohort have examined sex differences by using sex-stratified analyses. First, prenatal PBDE exposure was not significantly related to visual acuity in 6-month-old infants in either sex (Polevoy et al., 2020). Second, the association between prenatal PBDE exposure and physical reactivity to frustration at the age of 7 months varied based on child sex (Oulhote et al., 2018). More specifically, greater prenatal PBDE exposure was related to a greater predisposition to negative vocalizations in both boys and girls. However, when evaluating frustration using physical reactivity, greater prenatal PBDE exposure was associated with greater odds of an extreme response (either no physical reactivity or high physical reactivity) in girls, but lower odds of an extreme response in boys (Oulhote et al., 2018).

Limitations

The main limitation of this study is the relatively low detection rate for PBDEs in maternal blood. The congener with the highest concentration, BDE-47, was detected in 66% of samples. Other congeners were detected even less frequently (i.e., 19% for BDE-99, 21% for BDE-100, and 42% for BDE-153). The higher analytical limit of detection in the present study compared with previous cohort studies negatively impacted our ability to detect low blood PBDE concentrations. For example, the LOD for BDE-47, the most detected congener across studies,

was 0.3 to 2.6 ng/g lipid in the CHAMACOS study (Eskenazi et al., 2013), 0.3 to 8.2 ng/g lipid in the HOME study (Vuong et al., 2016), and 5.0 ng/g lipid in the present study. These differences are due to the use of a conventional gas chromatograph coupled with mass spectrometry in the MIREC study as opposed to gas chromatography coupled with isotope dilution high-resolution mass spectrometry in the HOME and CHAMACOS studies. This choice of method was made in the MIREC study because of its availability, its lower cost of operation, and the ability to analyse a wide variety of compounds, given that one of the original goals of the MIREC study was measure exposure to a large number of chemicals during pregnancy.

Furthermore, our study sample was primarily of high socioeconomic status and was not ethnically diverse. Mothers who participated in the MIREC study were more likely to be White, born in Canada, older, and more educated than the average of pregnant women in the same time period. As such, our results may not be generalizable to more disadvantaged or diverse populations. Research on other neurodevelopment toxicants showed that children living in higher socioeconomic environments might be less susceptible to the detrimental effects of exposure, through increased presence of mitigating factors such as cognitive stimulation or less frequent risk factors such as exposure to cigarette smoke or other environmental contaminants (Bellinger, 2008). Nonetheless, the PBDE exposure levels in the present sample were comparable to those of the full MIREC cohort (Fisher et al., 2016) and of an independent sample of Canadian women of reproductive age (20-39 years) from the Canadian Health Measures Survey (Health Canada, 2010; Oulhote et al., 2016).

Lastly, our results do not account for pre- or postnatal exposure to other neurotoxic contaminants or the potential influence of postnatal exposure to PBDEs. Notable sources of postnatal exposure to PBDEs include house dust and human milk (Frederiksen et al., 2009).

However, it is important to note that prenatal and postnatal exposure levels to these persistent contaminants are correlated (Eskenazi et al., 2013; Sagiv et al., 2015) and that it may be difficult to disentagle their specific effect on neurodevelopment.

Conclusions

Our results suggest that prenatal PBDE exposure is associated with a decrease in cognitive ability in preschool-age boys, but not girls, at the levels of exposure experienced in Canada. This provides evidence of sex differences in the potential impact of PBDEs on cognitive development. These findings are important despite the fact that regulations were implemented to ban or reduce the use of some PBDEs. Indeed, exposure is expected to continue for decades to come given that they are common contaminants found in existing consumer goods, are highly persistent in the environment, and bioaccumulate up the food chain.

Chapter 4: Brain Structure as a Potential Mechanism in the Association Between Contaminant Exposure and Cognitive Function

Brain Structure as a Potential Mechanism in the Association Between Contaminant Exposure and Cognitive Function

Throughout the thesis thus far, the focus has been on the role of environmental contaminants on symptoms of altered neurodevelopment in children. Based on the scoping review in Chapter 2 and the empirical study in Chapter 3, there is ample evidence in the literature to support the claim that environmental contaminants have a detrimental impact on neurodevelopment. What remains unknown is the specific mechanism through which these impacts come to be. Understanding mechanistic pathways can open the door to more appropriate prevention or intervention strategies.

Alterations in brain structure and function is expected to be part of the mechanistic pathway between contaminant exposure and cognition. It has been widely demonstrated that individual differences in brain structure and function are associations with individual variation in neuropsychological test scores in both typically and atypically developing children (Andre et al., 2020; Baum et al., 2017; Casey et al., 2000; Squeglia et al., 2013). However, few studies on contaminant exposure and cognition include a brain imaging component. Emerging evidence suggests that prenatal exposure to various contaminants is associated with brain structure and function (Cecil, 2022; Fowler et al., 2023), which may in turn mediate the association between contaminants and neurodevelopment in children (e.g., Grohs et al., 2019). Most studies that examine the effect of contaminants on children's brains focused on air pollution or metals while only two studies examined PBDEs (de Water et al., 2019; Fowler et al., 2023; Margolis et al., 2020; Vuong et al., 2020). These two studies used functional magnetic resonance imaging (fMRI) to examine functional network organization and connectivity (de Water et al., 2019; Margolis et al., 2020). .

The initial plan for this thesis was to include an original empirical study conducted in the MIREC cohort in which we would examine whether measures of brain structure and function mediated the association between prenatal PBDE exposure and cognition in children around the age of 10 years old. However, restrictions on in-person research in hospital settings during the COVID-19 pandemic interfered with the data collection process. Considering pandemic-related delays, we decided to postpone the MIREC imaging study and rather begin with a proof-of-concept study.

First, we wanted to investigate whether measures of cognition could be used as a marker of cortical morphology. While many studies indicate that cortical morphology predicts cognitive function (e.g., Kharitonova et al., 2013), few studies have examined the reverse association (e.g., Tamnes, Ostby, Walhovd, et al., 2010). We aimed to examine the effect of cognitive function on cortical morphology due to practical considerations for the clinical utility of these findings. When a person presents with neuropsychological symptoms and is referred to a psychologist for a cognitive assessment, the aim is to reach an accurate diagnosis in order to obtain appropriate interventions to reduce present and future functional impairment. It is unlikely that brain imaging would be conducted alongside the typical standardized testing even though there is evidence that early cortical morphology and connectivity predict future cognitive functioning (Gilmore et al., 2018; Woodburn et al., 2021). Unfortunately, given the costs and resources needed for brain imaging, it is not realistic to expect that brain scans would become routine, even if they could assist in more accurately predicting the risk of future impairment. It would therefore be helpful to establish whether psychological testing could be used to make inferences about the state of an individual's brain so that appropriate interventions can be put in place early to promote positive

long-term outcomes (Ferschmann et al., 2018; Pagliaccio et al., 2018; Sheehan et al., 2021; Sylvester et al., 2016).

Second, we wanted to identify whether cortical thickness is an optimal measure of cortical morphology in relation to executive function in youth. Cortical thickness is one possible measure of brain structure alongside surface area, cortical volume, and structural connectivity measures. While there is evidence that executive function is associated with cortical thickness (Tamnes, Ostby, Walhovd, et al., 2010), some evidence suggests that cortical volume and surface area may be more sensitive to variations in morphology in relation to various cognitive outcomes (Li et al., 2020). In the broader context of the thesis, the study in the following chapter is intended to help design future studies on the potential mediating role of brain structure in the association between contaminant exposure and cognition in children by helping to elucidate whether cortical thickness is an appropriately sensitive measure of morphology in youth.

Chapter 5: Associations Between Executive Function Components And Cortical Thickness in Youth – A Study in the NKI-RS Cohort

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Abstract

Background: Executive function (which encompasses set-shifting, inhibition, and working memory) is a set of cognitive processes that contribute to goal-directed behaviour and self-regulation. The development of executive function is believed to be supported by the development of brain regions like the prefrontal cortex, which undergoes both linear and nonlinear structural changes through the lifespan.

Objective: To characterize the association between each component of executive function and cortical thickness in a youth sample and contribute to the understanding of the role of age and sex in these associations.

Method: Participants were recruited as part of the Nathan Kline Institute Rockland Sample (NKI-RS) study. Youth aged 6 to 20 years underwent magnetic resonance imaging (MRI) scans and cognitive testing at baseline and may have participated in an additional one or two follow-up visits scheduled 15 months apart from each other. Data were analyzed using linear mixed models.

Results: While results were mostly null, there was a significant interaction between set-shifting and sex in predicting cortical thickness. However, the sex-stratified model was only marginally significant in boys. There was also a small positive association between working memory and cortical thickness in frontal brain regions, controlling for the quadratic effect of age. There was no association between inhibition and cortical thickness.

Conclusions: The results of this study highlight possible avenues for future research. Studies should consider examining developmental trajectories as a phenotype and using finer measures of morphology like white-matter connectivity.

Keywords: Cortical thickness; brain development; executive function; neuropsychology; adolescence

Introduction

Executive function is a set of domain-general cognitive processes and skills. Specifically, executive function is generally thought to encompass three distinct, yet related domains: set-shifting, inhibition, and working memory (Friedman & Miyake, 2017; McKenna et al., 2017; Miyake & Friedman, 2012; Miyake et al., 2000). These three processes contribute to self-regulation and goal-directed behaviour, thus broadly impacting a variety of spheres in everyday life (Diamond, 2013; Miyake & Friedman, 2012). Executive function begins to emerge in infancy, rapidly develops in childhood, and matures in adolescence, though the three components may develop at different rates (Anderson, 2002; Diamond, 2013; Moriguchi, 2014; Zelazo & Carlson, 2012).

The protracted development of executive function is thought to be supported by the maturation of the prefrontal cortex which continues until early adulthood (Fiske & Holmboe, 2019). The road to maturity for the prefrontal cortex (and the brain in general) includes both synaptogenesis and synaptic pruning, leading to both linear and non-linear changes in cortical morphometry (Blakemore & Choudhury, 2006; Foulkes & Blakemore, 2018). White matter volume increases throughout childhood and adolescence, reflecting increases in myelination. As for grey matter, evidence suggests that cortical volume increases in childhood, while both cortical volume and thickness then decrease in adolescence (Blakemore, 2012; Foulkes & Blakemore, 2018). This grey matter developmental pattern may be explained by greater synaptogenesis occurring up to puberty, followed by greater synaptic pruning in adolescence (Blakemore, 2012). Importantly, the frontal lobes are typically the last regions to reach maturity and the timing of cortical thinning may occur later than in other brain regions (Blakemore, 2012; Fiske & Holmboe, 2019). Overall, the finding that grey matter volume and thickness increase

through childhood, followed by steady reductions in adolescence is well documented (Blakemore, 2012; Gogtay et al., 2004; Nie et al., 2013; Tamnes et al., 2017; Tamnes, Ostby, Fjell, et al., 2010; Tamnes, Ostby, Walhovd, et al., 2010; Vijayakumar et al., 2016; Zhou et al., 2015).

Many studies in healthy and clinical adult populations have found associations between brain structure and/or function and executive function (Kim et al., 2012; Mace et al., 2019; Nowrangi et al., 2014; Pa et al., 2010). However, there are relatively fewer studies investigating the association between cortical morphology and cognitive function or behaviour in youth. Even fewer studies have specifically investigated the association between executive function (as opposed to other aspects of cognition like intelligence and language) and cortical morphology in youth. Some cross-sectional studies in healthy youth report that thinner cortex in various regions is associated with better performance on tests of cognitive function, including verbal learning, memory, and visuospatial functioning (Squeglia et al., 2013), verbal fluency (Porter et al., 2011), and executive function (Tamnes, Ostby, Walhovd, et al., 2010). Some longitudinal studies have also found that thinner cortex was associated with better performance on IQ (Burgaleta et al., 2014; Sowell et al., 2004; van der Meer & Kaufmann, 2022).

In addition, the impact of sex on cortical thickness and maturation remains poorly understood. For example, a study by Sowell and colleagues (2006) reported that women have a thicker cortex in certain regions of the brain across the lifespan, despite having smaller brains overall compared to men. As for the process of cortical maturation measured based on cortical thickness, a study by Lenroot and colleagues (2007) reported that girls reach peak cortical thickness and begin the process of cortical thinning approximately one year earlier (at age 9.5 years) than boys (at 10.5 years) while a study by Squeglia and colleagues (2013) reported that

adolescent males demonstrated more cortical thinning between ages 12 and 14 than their female counterparts. Another study by Mutlu and colleagues (2013) found that cortical maturation occurs faster in boys and in girls depending on the brain region. Meanwhile, some studies report that there is no difference in the cortical development trajectory of male and female adolescents (Raznahan et al., 2011; Wierenga et al., 2019; Zhou et al., 2015).

The aim of the present study was to determine whether individual components of executive function, namely set-shifting, inhibition, and working memory, predict cortical thickness in youth aged 6 to 20 years old. Given that our sample is within the pivotal age range for brain maturation, we hypothesized there would be non-linear effects of age on cortical thickness and that the direction of associations between executive function and cortical thickness may vary across brain regions as they mature at different rates (Blakemore, 2012; Foulkes & Blakemore, 2018). Lastly, we were interested in examining whether the association between executive function and cortical thickness is modified by sex. Examining the predictive association of executive function on cortical thickness in youth will add to the understanding of the neurological underpinnings of executive function development (Tamnes, Ostby, Walhovd, et al., 2010) as well as contributing to the development of early markers for suboptimal neurodevelopment (Ferschmann et al., 2018; Pagliaccio et al., 2018; Sheehan et al., 2021; Sylvester et al., 2016). Early brain health has important theoretical implications for healthy aging, but brain imaging is not routinely conducted for most people. Therefore, being able to make inferences about the brain's structure based on neuropsychological testing could be helpful in order to implement interventions that promote long-term cognitive function and brain health.

Method

Participants

We performed a secondary analysis of data obtained from the Nathan-Kline Institute Rockland Sample (NKI-RS) (Nooner et al., 2012; Tobe et al., 2022). Youth aged 6 to 20 years were invited to participate at baseline and may have participated in an additional one or two follow-up visits scheduled 15 months apart from each other. Therefore, participants may have provided data at one, two, or three timepoints. Participants were included in the analysis if they had complete data for age and sex, had at least one magnetic resonance imaging (MRI) scan, and at least one measure of executive functioning.

Executive Function Testing

Tasks were selected from two executive function batteries to measure each of the three components of executive function. Two tasks were selected from the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001; Delis et al., 2004). The D-KEFS is composed of nine independent subtests that assess functions believed to be mediated by the frontal lobe. The D-KEFS is normed in individuals aged 8 to 89 years (Delis et al., 2001). D-KEFS subtests were administered by trained study staff and scored by hand (NKI-RS, 2023b). Meanwhile, the Penn Computerized Neurocognitive Battery (CNB), which was administered via computer, is normed in individuals aged 6 to 85 years old (Gur et al., 2010; Moore et al., 2015; NKI-RS, 2023b).

Set-Shifting

Set-shifting was measured using the Verbal Fluency task on the D-KEFS (Delis et al., 2001; Delis et al., 2004). There are three conditions in this task. For each condition, there was four trials, each lasting 15 seconds. The three conditions are Letter Fluency (where the participant is asked to name as many words as possible that start with a given letter), Category

Fluency (where the participant is asked to name as many words as possible that belong to a given category), and Category Switching (where the participant is asked to name as many words as possible, shifting between two categories when specified). To measure set-shifting, we were particularly interested in the Category Switching condition, where the raw score represents the sum of correct responses (Delis et al., 2001).

Inhibition

Inhibition was measured using the Color-Word Interference task of the D-KEFS (Delis et al., 2001; Delis et al., 2004). In this task, participants are presented with a list of color-words printed in colored ink. There are 4 conditions on the Color-Word Interference task, specifically Color Naming (where the participant is asked to name the color of the ink), Word Reading (where the participant is asked to read the color's name), Inhibition (where the participant is looking at color names that are printed in a different color and asked to name the color of the ink without reading the word), and Inhibition/Switching (where the participant is asked to switch between reading the word and naming the ink color). To measure inhibition, we were interested in the Inhibition condition. The raw score represents the time to completion in seconds. Based on administration guidelines in the D-KEFS manual, this task is discontinued after all words are read or after 180 seconds, whichever comes first (Delis et al., 2001).

Working Memory

Working memory was assessed using the computerized Letter N-Back task on the Penn CNB (Gur et al., 2010). During this task, capital letters appear on the screen for 500ms and the participant is asked to press the spacebar based on certain criteria. There are three conditions, namely the 0-Back (press the spacebar if the letter on the screen is an X), 1-Back (press the spacebar if the letter on the screen is the same as the previous letter), and 2-Back (press the

spacebar if the letter on the screen is the same as the letter before the previous one). Following an initial practice period, the test period contains three blocks of each condition leading to a total of 135 trials (Gur et al., 2010). This task produces an accuracy score (i.e., the number of correct responses) and a reaction time score (i.e., the mean of the median reaction time on correct trials). The accuracy score for the 1- and 2-Back trials was used in analyses.

Cortical Thickness

Details of data acquisition can be found elsewhere (Nooner et al., 2012; NKI-RS, 2023a). Structural MRI data were pre-processed and cortical thickness was calculated with the CIVET pipeline (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET). Cortical thickness was measured at 81,924 vertices across the whole cortex. T1-weighed images were corrected for non-uniformity and linearly registered to a standard space (Talairach-like MNI152 template, established from the ICBM152 dataset) (Mazziotta et al., 1995; Talaraich & Tournoux, 1988). Cortical tissue was categorized as grey matter, white matter, and cerebrospinal fluid based on non-linear registration and the artificial neural network using priors defined in the MNI152 template. Inner and outer grey matter surfaces were extracted using the Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm (Kim et al., 2005). Cortical thickness was measured based on the Laplacian distance between the two surfaces at 81,924 vertices. The map of cortical thickness of each participant was blurred using a 30-millimeter full width at half maximum surface-based diffusion smoothing kernel in order to force a normal distribution on the corticometric data and to increase the signal to noise ratio.

Quality control (QC) of the pre-processed data was conducted by two experts. Scans were scored (0 = failed, 1 = questionable, 2 = passed) by both experts independently. Scans must have received the same score by both experts in order to be included in the present study. QC steps

included exclusion of data with low signal-to-noise ratio, motion artifacts, artifacts due to hyperintensities from blood vessels, surface-surface intersections, or poor placement of the GM or WM surface. Overall, 530 longitudinal MRI scans from 162 participants were downloaded from the NKI-RS website (http://fcon_1000.projects.nitrc.org/indi/enhanced/). Of these, 125 scans failed the QC process and 97 scans were questionable, resulting in 308 scans from 144 participants. Filtering for the relevant scores for Verbal Fluency, Color-Word Interference, and the Letter N-Back task, the final study sample included N=284 scans from 140 participants (Table 1).

Table 1

Participant Characteristics

Characteristics	Mean (SD) or *N* (%)
Sex (boys/girls)	82/58 (58.6%/41.4%)
Mean age at first scan (years)	12.29 (3.00), range 6.73 – 17.94
Mean age across all included scans	13.03 (3.07), range 6.73 – 20.37
Executive function scores	
Verbal Fluency (n=265)	11.75 (3.01), range 5 – 22
Color-Word Interference (n=263)	61.76 (23.52), range 25 – 143
Letter N-Back (n=275)	17.57 (3.16), range 0 – 20
MRI scans	
Number of individuals with one scan	34
Number of individuals with two scans	68
Number of individuals with three scans	38

Statistical Analyses

Mixed effect generalized linear models (GLM) were conducted at vertex-level (81,924 vertices covering the entire cortex without ventricle region). All models included the intercept, age, sex, and a random subject effect and tested for the effect of the executive function scores and any interactions. Results were quantified using t-statistics. We corrected p-values for multiple comparisons across the number of vertices using the false discovery rate (FDR), resulting in q-values. Statistical analyses were conducted in MATLAB (R2023a) using SurfStat (https://www.math.mcgill.ca/keith/surfstat/).

We first examined the association between executive function and cortical thickness. Separate models were conducted for each of the three executive function scores (i.e., Verbal Fluency, Color-Word Interference, and Letter N-back task accuracy). In each model, the outcome was cortical thickness. Test score, age, and sex were included as predictors while participant was added as a random factor in the model to account for the fact that participants provided data at one, two, or three timepoints. While SurfStat uses one-tailed tests as a default we chose to conduct more conservative two-tailed tests as we were interested in both positive and negative associations. Results for the two-tailed t-tests are therefore reported as t_{df} = minimum value of *t*, maximum value of *t*; *p*-value; *q*-value; and number of vertices (*nvert*) passing the $q < .05$ threshold for statistical significance.

Second, to investigate sex-specific patterns in the association between executive function and cortical thickness, we examined the interaction of executive function and sex. When the interaction was statistically significant, we re-estimated separately for boys and girls.

Third, to clarify the role of age in the association between executive function and cortical thickness, we examined the interaction between executive function and age. We also ran models with a quadratic term for age given our hypothesis that the direction of association would change based on age, therefore reflecting the notion that the association between age and cortical thickness may be non-linear.

Results

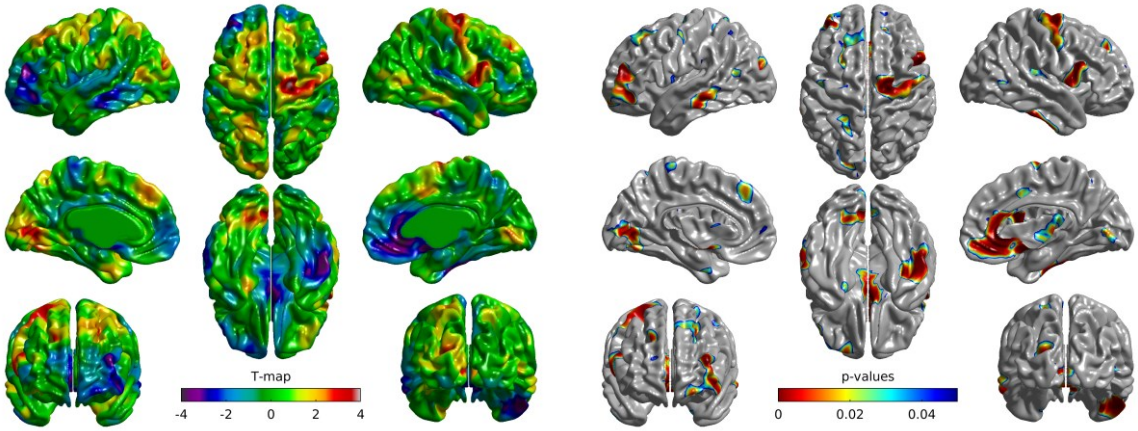
Main Effects of Sex and Age

There was no main effect of sex on cortical thickness, suggesting that cortical thickness did not vary significantly between boys and girls. We also examined the quadratic effect of age on cortical thickness. While the model testing for the quadratic effect of age did not reach

statistical significance, the q-value was 0.16, indicating that including the quadratic effect of age as a covariate remains relevant. Based on the p-map of the quadratic effect, there are large areas of positive and negative curvilinear associations (see Figure 1). As such, in combination with our a priori rationale, we decided to include age as a quadratic covariate in all subsequent models.

Figure 1

Quadratic Association Between Age and Cortical Thickness



Note. The q-value map is not included as it was above the significance threshold and therefore does not display any areas of interest.

Association between Set-Shifting and Cortical Thickness

There were no significant associations between set-shifting and cortical thickness, controlling for the quadratic effect of age. In addition, the interaction between set-shifting and age was not significant either. Interestingly, there was a significant interaction between set-shifting and sex (see Figure 2; t_{260} = -4.87, 3.40; $p < .01$; $q = .03$; *nvert* = 43). Given the small number of vertices, the areas of significance are likely too small to be visible on the q-map. In sex-stratified models, the association between set-shifting and cortical thickness was null in girls and marginally significant in boys (see Figure 3; t_{157} = -3.94, 4.34; $p < .01$; $q = .09$; *nvert* = 0).

Figure 2

Interaction of Set-Shifting and Sex on Cortical Thickness

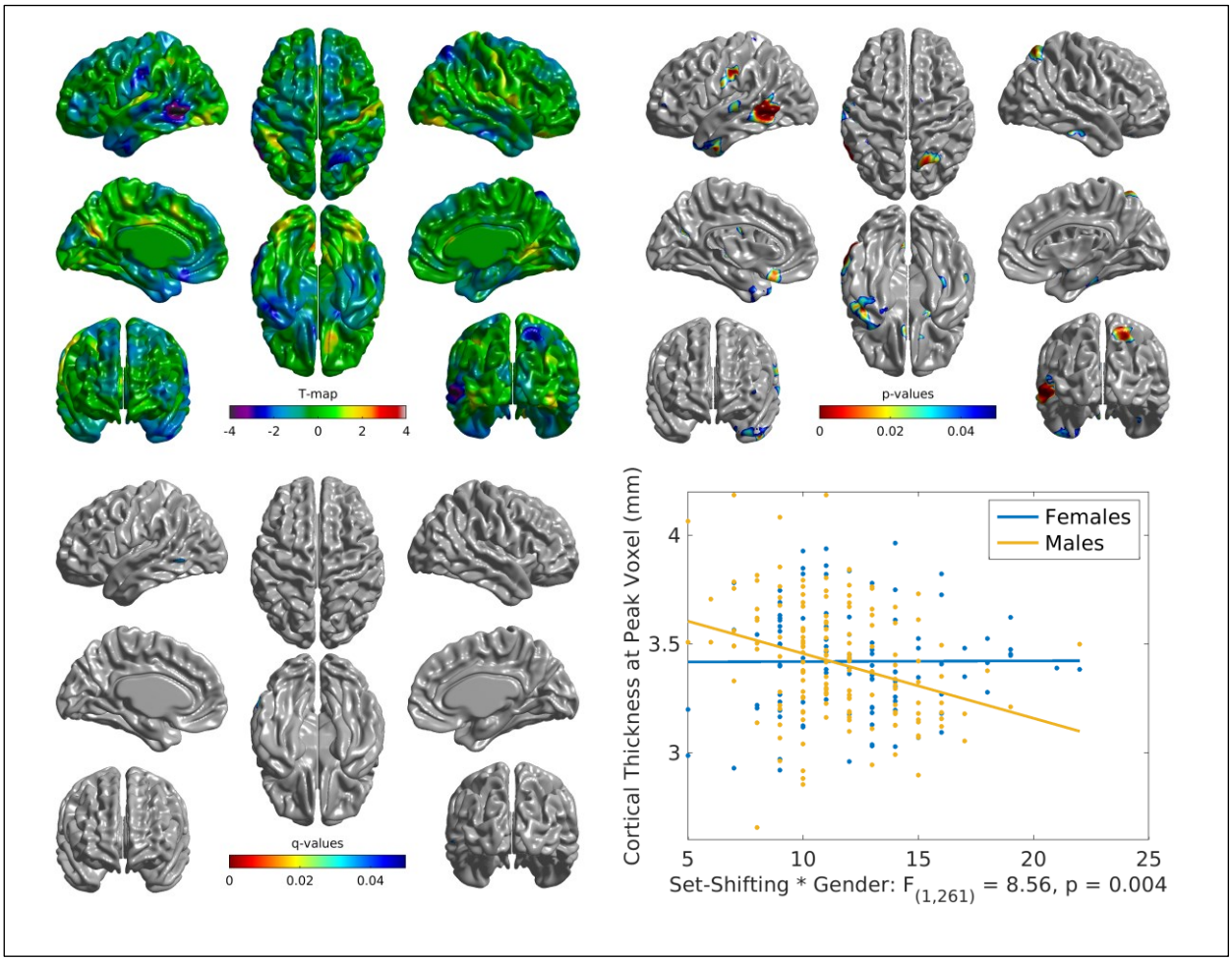
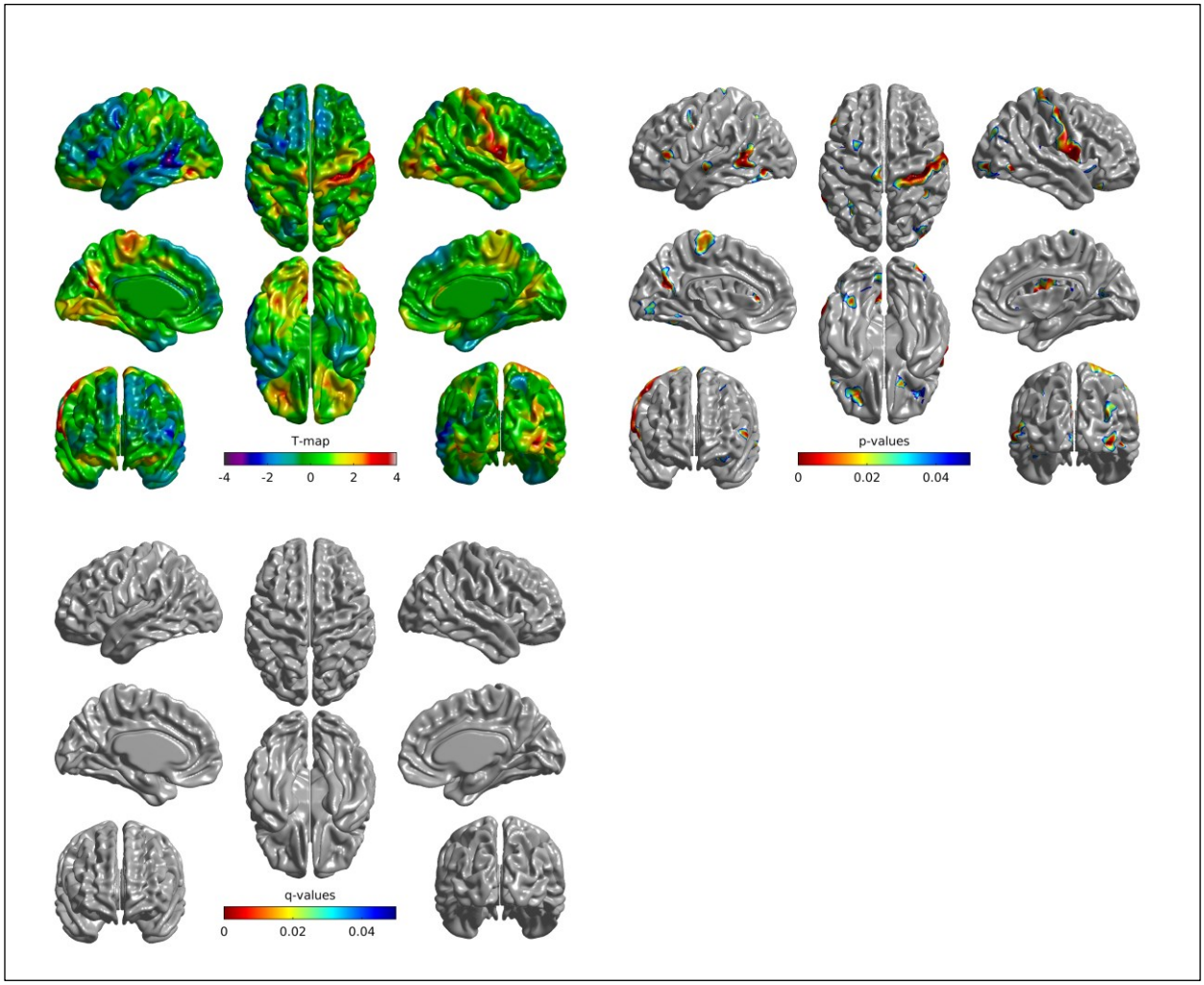


Figure 3

Association Between Set-Shifting and Cortical Thickness in Males



Association between Inhibition and Cortical Thickness

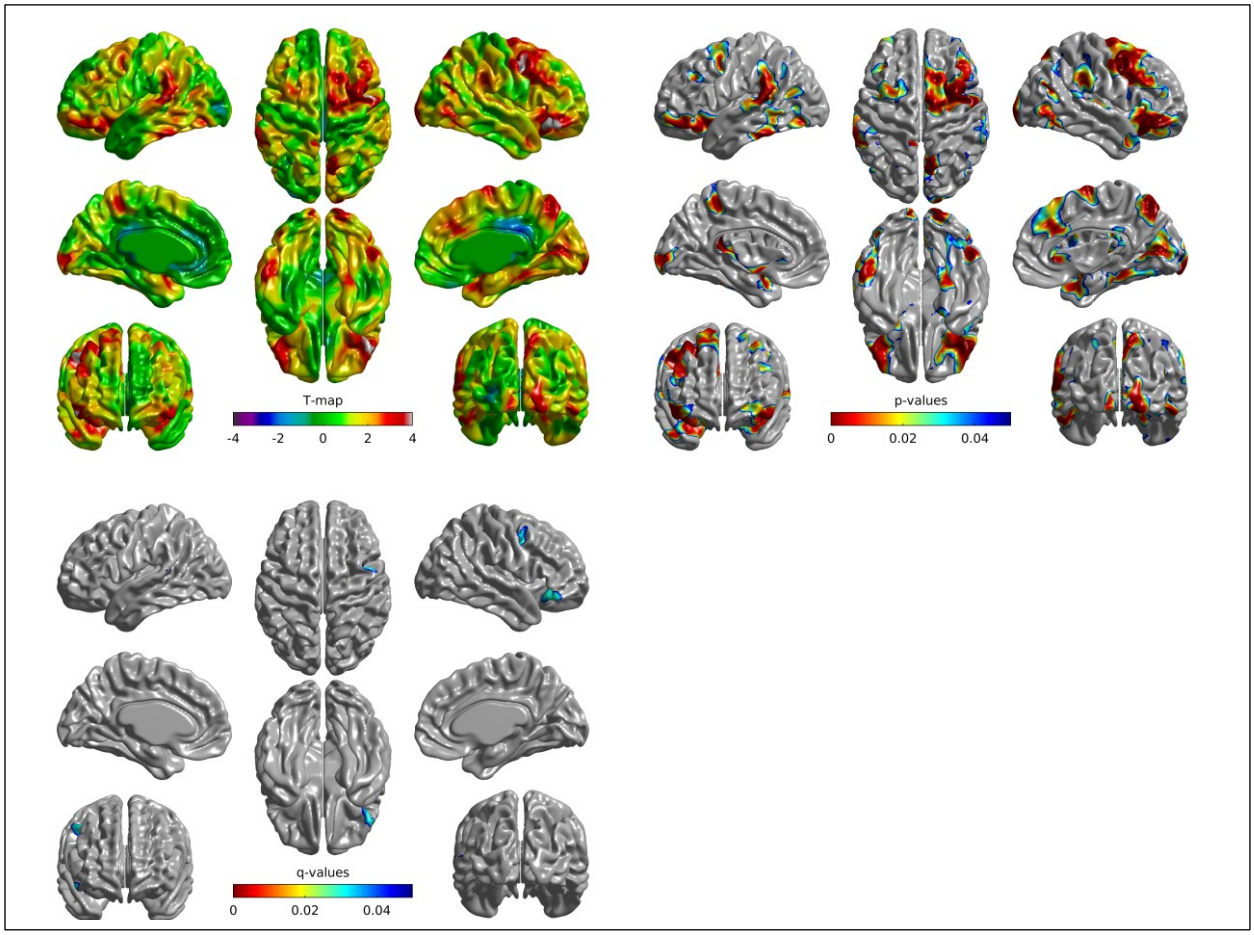
There were no significant associations between inhibition and cortical thickness controlling for the quadratic effect of age. The models with interaction terms for age and sex were not significant.

Association between Working Memory and Cortical Thickness

While the models with interactions terms for sex and age were not significant, the model with a quadratic age covariate was statistically significant (see Figure 4; t_{253} = -2.42, 4.60; p < .01; q = .03; *nvert* = 414). Visual inspection suggested a positive association between working memory and cortical thickness in the right inferior orbitofrontal gyrus and the right middle frontal gyrus.

Figure 4

Association Between Working Memory and Cortical Thickness



Discussion

The present study aimed to examine the associations between components of executive function and cortical thickness in children and adolescents as well as the role of age and sex in the associations. Our findings are mostly null, suggesting that cortical thickness may be less sensitive than other metrics of cortical morphology (i.e., surface area, cortical volume, white matter connectivity) in capturing subtle associations between brain structure and cognitive function (Goddings et al., 2021; Li et al., 2020). There are nonetheless a few interesting conclusions. Our results suggest that the association between components of executive function and cortical thickness may be domain-specific and differentially impacted by age and sex. Specifically, there was an interaction between set-shifting and sex on cortical thickness, suggesting there may be a negative association between set-shifting and cortical thickness in boys only. However, in a sex-stratified model with male participants, the association did not pass the threshold for statistical significance. It is possible that our analysis was underpowered to detect such a small effect. Alternatively, this interaction result may be due to chance. As for inhibition, there was no association with cortical thickness and the results did not vary with age or sex. Lastly, working memory was positively associated with cortical thickness when controlling for the curvilinear effect of age.

While we did not explicitly test the difference between the three components of executive function, the apparent difference in the pattern of results may reflect the diversity component of the unity-and-diversity model of executive function whereby set-shifting, inhibition, and working memory are distinct abilities (Friedman & Miyake, 2017; McKenna et al., 2017; Miyake & Friedman, 2012; Miyake et al., 2000). In that sense, our results are consistent with a study of adults in the NKI-RS cohort whereby different tasks from the D-KEFS were associated with

cortical volume in different brain regions (Mace et al., 2019). While the three components of executive function are understood to be separate, they also have a shared basis (i.e., unity) (Friedman & Miyake, 2017; McKenna et al., 2017; Miyake & Friedman, 2012; Miyake et al., 2000). However, we did not include a broad composite measure of executive function in this study. As such, we cannot make any inferences on the unity of set-shifting, inhibition, and working memory or any shared neurobiological underpinnings.

Our results for the set-shifting task indicated an interaction with sex in the association with cortical thickness, suggesting that a thinner cortex may be associated with better performance in boys while the association was null in girls. The interaction may have been due to differences in performance on the set-shifting task between male and female participants, though there is generally little support for sex differences in executive function (Grissom & Reyes, 2019). This result should be interpreted cautiously and conservatively, especially as the sex-stratified models were not statistically significant. Additional studies in larger samples are needed to further confirm or reject the present findings.

As for working memory, it was positively associated with cortical thickness when controlling for the curvilinear effect of age. Specifically, greater accuracy on the working memory task was associated with thicker cortex in the right inferior orbitofrontal gyrus and the right middle frontal gyrus. This result is contrary to much of the literature, which reports that cortical thinning in adolescence is associated with better executive function and working memory performance (Kharitonova et al., 2013; Krogsrud et al., 2021; Squeglia et al., 2013; Tamnes, Ostby, Walhovd, et al., 2010). As the brain is known to mature gradually and regionally (Gogtay et al., 2004), it is possible that regions maturing later such as the frontal lobe would still be undergoing thickening while other regions have started thinning. Since the regions identified

to be associated with working memory in our study are in the frontal lobe, it is possible that these regions had not yet reached maturity in our sample. In addition, a study by Li and colleagues (2020) found that cortical thickness was less sensitive than cortical volume or surface area to identify associations between morphology and cognitive function. As such, perhaps our choice to use cortical thickness as a measure of cortical morphology inhibited our ability to detect small effect sizes. The identified regions nonetheless make theoretical sense. The right inferior orbitofrontal gyrus is recognized to be associated with executive function and inhibitory control in particular (Hampshire et al., 2010). The middle frontal gyrus has also been associated with cognitive control and attention orienting (Friedman & Robbins, 2022; Japee et al., 2015). While n-back tasks are typically used to measure working memory, there is also recognition that they perhaps measure other aspects of cognitive function such as inhibitory control and processing speed (Jaeggi et al., 2010; Kane et al., 2007; Miller et al., 2009). In addition, the finding that the model was significant when controlling for the curvilinear effect of age is consistent with several studies that identified that changes in cortical thickness over time are nonlinear (Mutlu et al., 2013; Raznahan et al., 2011; Tamnes, Ostby, Fjell, et al., 2010; Zhou et al., 2015).

Limitations

This study had certain limitations. For example, we had a relatively small sample, which limited the complexity and number of statistical models we could conduct while maintaining statistical power and limiting the risk of type I error. Another potential limitation is the choice of cortical thickness as a measure of morphology as it may be less sensitive to capture normal variation or subtle differences in the general population. In addition, the structure of our sample limited our ability to look at developmental trends over time. There were few participants at each age and the number of brain scans was not the same at each age or for each participant either. As

such, we used linear mixed models with participants as a random factor to maximize the sample size in analyses. The structure and size of our sample limited our ability to take advantage of longitudinal data to examine developmental trajectories, which may be stronger predictors of cognitive function than cross-sectional morphological measures (Burgaleta et al., 2014; Khundrakpam et al., 2022; Ramsden et al., 2011).

Strengths

Despite the preceding limitations, this study nonetheless has strengths and contributes to our understanding of the neurobiological underpinnings of executive function in youth. The NKI-RS cohort is representative of the population of the Rockland County in New York State, which is also representative of the larger United States population in terms of socioeconomic characteristics and ethnicity as per the 2010 census (Nooner et al., 2012). The NKI-RS cohort also makes use of a standardized imaging protocol which facilitates data sharing and replication. Extensive behavioural data were also collected in the sample, allowing a broad range of research questions to be addressed. In this particular study, we were able to access data from a wide age range within childhood and adolescence, allowing us to examine the effect of age in the association between executive function and cortical thickness Lastly, the mixed models approach allowed us to maximize the sample size available for analyses.

Conclusions

Overall, our results find little support for an association between executive function and cortical thickness. It would therefore be premature to claim that executive functioning could be used as an early marker of suboptimal cortical development. Our results nonetheless indicate that the associations between components of executive function and cortical thickness may be domain-specific and differentially impacted by age and sex. This study, therefore, contributes to

our understanding of sex differences in the neural underpinnings of executive function development. It also adds to a body of literature suggesting that the effect of age on cortical thickness may be nonlinear. Further research is needed to better characterize sex- and age-related processes in the development of executive function and its correlates at the level of cortical morphology. Future studies should also consider examining developmental trajectories over several years as they may be more helpful than examining cortical morphology a one or two points in time (Giedd et al., 2008). Data sharing and data repositories may be helpful in overcoming the practical barriers to conducting this kind of large-scale study over an extended follow-up period. Other helpful paths include the examination of finer-grained measures of cortical morphology such as white matter connectivity as grosser measures like cortical thickness, volume, or surface area may be insufficiently sensitive to detect small developmental changes (Goddings et al., 2021).

Chapter 6: General Discussion

General Discussion

The primary objective of this doctoral thesis was to study the association between prenatal contaminant exposure and neurodevelopment in children as well as potential underlying associations between cognitive function and cortical morphology. In doing so, a related aim is to improve dissemination of toxicology research findings to healthcare professionals and advocate for a larger role of psychologists in prevention, intervention, and policy.

In this concluding chapter, I will begin by reviewing the main findings from each of the three manuscripts composing the thesis. I will then integrate the overall conclusions of these three manuscripts and discuss some key issues to frame the relevance of the results of the thesis. I will review the difference between clinical significance and epidemiological significance, the societal burden and cost of contaminant exposures, the concern due to simultaneous exposure to multiple contaminants and the concept of the exposome, the ways in which contaminants may interact with other neurodevelopmental risk factors, and the potential long-term impacts of exposures in early life. From the issue of significance, I will then discuss the regulatory framework relevant to contaminant exposures and its limitations in promoting environmental health. The benefits of improving policy are discussed along with the importance of considering the principles of social and environmental justice. Next, I will advocate for an increased involvement of psychologists in toxicology policy and research as well as outline the ways in which greater awareness of neurotoxicology research can improve clinical practice. The thesis will conclude with a final review of the significance of these findings as well as some remarks on future research directions.

Conclusions and Key Issues of Each Thesis Manuscript

Scoping Review on Environmental Contaminants and Childhood Neurodevelopment

The first manuscript in this thesis was a scoping review examining the relation between prenatal exposure to various environmental contaminants and neurocognitive development from birth to adolescence.

The focus of the review was on the neurodevelopmental outcomes of contaminant exposures at the community-based level rather than describing the neurodevelopmental toxicity of high levels of specific chemicals and metabolites. This approach was favored because humans are constantly exposed to co-occurring chemicals. Disentangling and quantifying the impact of each contaminant separately is impossible (Dorea, 2019; Mitro et al., 2015; Padula et al., 2020). In addition, the aim was to promote the dissemination of toxicological research to academic and professional audiences in mental health and child development-related fields. As such, we chose to center the (sub)clinical outcomes and focus on the practical implications in research and clinical practice.

Another significant contribution of the review is its broad developmental range. Several different neurodevelopmental domains were considered, spanning from birth to the end of adolescence. This broad range allowed us to examine how associations might differ over time. Research has suggested that a deficit appearing early in life may resolve over time with factors like environmental stimulation, parental nurturance, and education (Bellinger, Matthews-Bellinger, et al., 2016; Horton et al., 2012). Alternatively, an early adverse outcome may worsen in the absence of these protective environmental factors. In other cases, early development may appear typical, with neurodevelopmental deficits only appearing later, long after the initial exposure, either because measures used in early life are not sensitive enough, the affected ability

is one that only emerges later, or the deficit is the result of a cascade of events over time (Bellinger, Matthews-Bellinger, et al., 2016; Rice & Barone, 2000).

Our review suggested that up to a quarter of studies identified adverse effects of prenatal contaminant exposure on neurodevelopment in childhood. The proportion of adverse outcomes was largest in infancy studies, then waned somewhat in preschool- and school-age, and was smallest in adolescence. While many factors may explain this pattern, early adverse outcomes may improve over time, either through normal developmental progression or protective factors that mitigated the adverse outcome over the span of development (Bellinger, Matthews-Bellinger, et al., 2016; Horton et al., 2012). It is nonetheless important to specify that there were fewer studies in adolescence than in younger children, which may contribute to the different proportions of adverse results.

Importantly, the review targeted studies conducted in community cohorts as opposed to clinical or high-risk cohorts. The literature in the field generally suggests that populations in industrialized countries have fairly low exposure levels (Lanphear, 2017). Rather than acute poisoning, the primary concern is low-dose, widespread, chronic exposure over time. As a result, it is generally recognized that the neurodevelopmental impact is more likely to be an increase in subclinical presentations across the population (Lanphear, 2015). Nonetheless, an increase in subclinical presentations across the population still presents great real-world significance and dramatically increase the proportion of the population that now meets criteria for the full-blown clinical presentation (Lanphear, 2015). This issue is discussed in greater detail later in this chapter (please refer to the “Significance: Beyond $p < .05$” heading).

Prenatal PBDE Exposure and IQ in the MIREC Cohort

The second manuscript included in this thesis was an empirical study in a pan-Canadian birth cohort examining the association between prenatal exposure to a specific contaminant (PBDEs) and IQ in 3-year-old children. This study provided a specific example of empirical research in the field of developmental neurotoxicology. The results indicated that PBDEs were associated with a decrease of 3 to 4 IQ points per tenfold increase in PBDE concentration in maternal blood. The association varied by sex, whereby it was only significant in boys. The effect size in the unstratified sample was a decrease of approximately 1 to 2 IQ points.

These findings fit nicely in the context of the broader human epidemiological literature on PBDEs and cognitive ability in children. A meta-analysis by Lam and colleagues (2017) indicated that prenatal PBDE exposure was associated with a decrease of 3.7 IQ points. While the results in our overall sample are below this estimate, the 95% confidence intervals overlap. In addition, the effect size we found in boys fits perfectly with the conclusions of the meta-analysis.

Overall, this study is a helpful example of the research methodology of community-based neurotoxicology studies. For example, it demonstrates some of the inclusion criteria for pregnant persons to participate in this kind of epidemiological cohort study. It also gives an example of exposure assessment through maternal biological samples (in this case maternal blood in the first trimester of pregnancy).

Some limitations of this study are that the sample was fairly homogenous (e.g., primarily White, high family income) and is not representative of the general Canadian population, which limits the generalizability of findings. In addition, it does not account for postnatal exposure or exposure to other contaminants, though some studies report that pre- and postnatal exposures are correlated and that prenatal exposure has a stronger effect on neurodevelopment than postnatal

exposure (e.g., Forns et al., 2018; Grandjean & Landrigan, 2014; Grohs et al., 2019; Harris et al., 2021; Harris et al., 2018; Sagiv et al., 2015; Simeone et al., 2022). That being said, the exposure levels in the study are comparable to those of the broader Canadian population. The study also had a larger sample size than many other comparable studies, which allowed us to investigate sex differences with stronger statistical power and make an important contribution to the developmental neurotoxicology literature.

Executive Function and Cortical Thickness in the NKI-RS Cohort

The third manuscript in this thesis was an empirical study in an American community cohort examining the association between executive function and cortical thickness across childhood and adolescence. Our models placed executive function as the independent variable as we were interested in determining whether psychological tests could be used as markers of brain morphology. In addition, the study was meant as a basis for future research on the association between cognitive domains shown to be sensitive for prenatal environmental exposures and brain development. More specifically, the study investigated the association between three components of executive function (i.e., set-shifting, inhibition, and working memory) and cortical thickness in youth. After controlling for the curvilinear effect of age in our linear mixed models, there was a positive association between working memory and cortical thickness in the right frontal lobe. While the regions make theoretical sense considering that executive function is believed to be supported by the prefrontal cortex (Fiske & Holmboe, 2019; Friedman & Robbins, 2022; Hampshire et al., 2010; Japee et al., 2015), the direction of the association was contrary to our hypothesis. There was also an interaction between set-shifting and sex in the association with cortical thickness, and subsequent testing using a sex-stratified model suggested a tendency (statistical trend) towards greater set-shifting and lower cortical thickness in males but not in

females. Overall, our results are not sufficient evidence to support the use of executive function testing as a marker of cortical thickness. Results should be interpreted with caution, and future studies with a larger sample are needed to further confirm the findings.

While results warrant future replication in a larger sample, a possible explanation for the limited findings of the study is that cortical thickness measures might not be sensitive enough to reflect variations in brain morphology or cognitive development in typically developing youth (Goddings et al., 2021; Li et al., 2020).

It could also be suggested that rather that developmental changes in cortical thickness, rather than measures of cortical thickness at a single point in time might be more predictive of cognitive development (Khundrakpam et al., 2022). Indeed, in a sample of typically developing adolescents, Khundrakpam and colleagues (2022) showed that executive function at timepoint 3 was better predicted using baseline executive function combined with the change in cortical thickness between timepoints 1 and 2 rather than cross-sectional cortical thickness at timepoints 1 and 2 (Khundrakpam et al., 2022). Other studies have also shown that change in cortical morphology in adolescents is associated with cognitive performance (Burgaleta et al., 2014; Ramsden et al., 2011). The structure of the sample of the present study was such that there were few participants at each age and the number of scans per participants was not the same. We therefore used linear mixed models to maximize the sample size for analytical purposes, but could not take advantage of longitudinal data. Longitudinal analyses with a large sample having multiple brain measures during development are thus needed to further test related hypotheses.

Integration and Important Issues

Overall, there is mounting evidence indicating that environmental contaminants are associated with various neurodevelopmental alterations in children. As discussed in the scoping

review presented in Chapter 2, these associations may vary over the course of development and may be domain-specific. The study presented in Chapter 3 is a clear example of the type of study commonly conducted in developmental neurotoxicology and their effect sizes. Based on these two chapters, there is ample support for an association between environmental contaminants and neurodevelopment in children. However, little is known about the mechanistic pathways of these associations. Emerging evidence suggests that environmental contaminants may alter brain structure and function, which in turn impact neuropsychological functioning (Cecil, 2022; Fowler et al., 2023). The study presented in Chapter 5 on the association between cognitive function and cortical thickness was meant as a basis for the design of a future study on the impact of prenatal environmental contaminants and brain development. We were interested in identifying whether cortical thickness might be an appropriately sensitive measure of developmental changes in brain structure. Surprisingly, we did not find convincing support for an association between executive function and a gross measure of cortical morphology, namely cortical thickness. In light of these findings, future studies examining brain structure as a mediator in the association between contaminant exposure and cognition should consider using more refined measures of cortical morphology. For example, measures of structural connectivity between brain regions may be more sensitive to small effect sizes than gross anatomical measurements. Further, recent studies also highlight the relevance of studying changes in cortical development as predictor of cognition rather than using measures of cortical morphology at a single point in time. The use of more refined or longitudinal measures to study the association between cognitive function and brain development might be even more important when studying the moderating role of environmental exposures, considering that impacts of environmental

contaminants on cognition or the brain might be subtle, albeit meaningful. The issue of significance in the context of cognitive effects are discussed in the next section.

Significance: Beyond $p < .05$

Anecdotally, discussing results of studies on environmental contaminants with audiences outside epidemiology often results in tremendous concern. Many media articles appear to generate the same outcome with titles designed to elicit fear. PFAS have been branded as "forever chemicals" in the media (e.g., Thurnton, 2023, May 20). While this is a helpful way to address the fact that many chemicals have long half-lives and can bioaccumulate, it lacks important nuance. The discussion that follows applies specifically to associations between prenatal exposure to environmental contaminants and neurodevelopment and may not generalize to other health outcomes affected by contaminant exposure.

Significance at the Level of the Individual VS at a Population Scale

Most of the detrimental neurodevelopmental outcomes reported in population studies have quite small effect sizes and some studies may have been underpowered to find significant associations due to sample size. The MIREC study in Chapter 3 is a prime example of such small effect sizes. Our results suggested that prenatal PBDE exposure was associated with a decrease of 1 to 2 IQ points in the overall sample (not statistically significant) and a decrease of 3 to 4 IQ points in boys. There were no significant associations in girls (Azar et al., 2021). Several studies examining prenatal PBDE exposure and IQ in children report a similar decrease of 2 to 5 points in FSIQ (Chen et al., 2014; Eskenazi et al., 2013; Lam et al., 2017; Zhang et al., 2017b). While these results may be statistically significant, they are not clinically significant. Indeed, given that the standard deviation of most IQ scores is 15 points, an IQ decrease of 2-5 points is not

clinically significant for a given individual. One would not be able to tell the difference between a child who was exposed to PBDEs and one who was not based on their cognitive ability.

While the impact of PBDEs on IQ is not clinically relevant, it remains highly concerning at a population scale. Professionals in mental health and child development related fields are trained to work with individuals and often think in terms of individual clinical significance. A shift to a population lens may therefore feel somewhat counter-intuitive. However, it is a critical lens to take in order appreciate the scale of the issue. A variable such as IQ is considered to be normally distributed across the population with a mean of 100 and a standard deviation of 15. There should be an equivalent proportion of the population at both the lower and upper end of the distribution. In this case, the lower end is comprised of individuals with an IQ below 70 (two standard deviations below the mean), who are likely to meet criteria for an intellectual disability. The upper end represents people with an IQ of 130 or more (two standard deviations above the mean) and who would be characterized as being "gifted". If a contaminant resulted in a 5-point decrease in the population mean IQ, resulting in a mean IQ of 95, this small shift would have dramatic consequences at the tails of the normal curve. Specifically, this hypothetical drop in the mean IQ would result in a 60% decrease of the proportion of the population with an IQ over 130 and a 57% increase in the proportion of the population with an IQ below 70 (Gilbert & Weiss, 2006; Lanphear, 2015). This large increase at the lower tail of the normal curve would in turn translate to a greater need for resources, such as healthcare, social services, and remedial education (Gilbert & Weiss, 2006; Lanphear, 2015). While the IQ cut-off of 70 is used here to illustrate the argument that small population shifts are meaningful, additional resources are needed to support individuals above that threshold as well. In addition, the increase at the lower tail and decrease at the upper tail of the distribution may represent a loss of productivity at the

scale of the population. Overall, these impacts go far beyond the individual and have large financial and macroeconomic implications for societies.

Societal Burden and Cost

As discussed in the previous section, a hypothetical 5-point decrease in the population mean IQ could substantially increase the proportion of children who have an IQ below 70 (Lanphear, 2015). The societal impact of small decrements is so large in part because of how ubiquitous chemical exposures are. The overall societal impact of widespread small decrements may ultimately be more problematic than large decrements impacting a small number of individuals (Bellinger, 2012a, 2012b; Bellinger et al., 2019; Bellinger, O'Leary, et al., 2016). It is important to specify that the concern with a decrease in the average IQ is not only due to the increase in individuals in the lower tail of the distribution. The concern is also due to the small losses in the middle of the IQ distribution which are more widespread and therefore add even greater burden than the extreme losses in the tails (Bellinger, 2012a).

There are many different strategies for calculating the societal cost of contaminant-related neurotoxicity. One approach begins by estimating disease burden, which involves calculating the product of the disease rate (i.e., either prevalence or incidence rates), the proportion of disease that would be eliminated if environmental risk factors were reduced to their lowest possible level, and the population size. The cost of that burden is then obtained by multiplying the previously calculated value with the cost per case. The cost per case encompasses all costs related to the disease, from the direct healthcare costs to the associated reduction in work productivity and everything in between (Grandjean & Bellanger, 2017; Trasande et al., 2015; Trasande et al., 2016). This approach, which considers both the direct and indirect costs of disease, is referred to as the “human capital approach” (Grandjean & Bellanger,

2017; Trasande et al., 2015; Trasande et al., 2016). Another approach is to determine the sum of lost ability across a population. Using the example of IQ, researchers have calculated the sum of IQ points lost based on the dose-response curve of a given environmental factor. The calculation might end there (e.g., Bellinger, 2012b) or might be extended to determine societal cost. There are established estimates of the lifetime financial value of an IQ point. Multiplying this estimate by the number of IQ points lost results in the overall societal cost (e.g., Bellanger et al., 2015; Bellanger et al., 2013; Pichery et al., 2012). Overall, while specific estimates vary across studies, most are aligned in reporting that the cost of contaminant-related cognitive losses is on the order of hundreds of billions to trillions of dollars (Grandjean & Bellanger, 2017; Trasande et al., 2015; Trasande et al., 2016)

Importantly, even though the effect sizes in the associations between contaminants and adverse neurodevelopmental outcomes appear small in clinical terms, they may be similar to those of other known perinatal risk factors for neurodevelopment, such as low birth weight, prematurity, low maternal thyroid hormones, and maternal tobacco, alcohol, or opioid consumption (Corrêa et al., 2021; Gu et al., 2017; Jacobson et al., 2021; Lee et al., 2020; Levie et al., 2018; Twilhaar et al., 2018). For instance, an analysis by Bellinger (2012b) suggested that contaminants like lead and organophosphate pesticides were responsible for more IQ points lost across society than most other medical, socioeconomic, and psychosocial factors, including traumatic brain injuries. Preterm birth was the only condition that resulted in greater IQ decreases than lead exposure (Bellinger, 2012b). Over a population of 25.5 million children, the researchers estimate that preterm birth is associated with 34.0 million IQ points lost. Meanwhile, lead and organophosphate pesticides were associated with 22.9 million and 16.9 million IQ

points lost respectively. Comparatively, iron deficiency is associated with 9.4 million IQ points lost while postnatal brain injury is associated with 5.8 million IQ points lost (Bellinger, 2012b).

Interaction of Contaminant Exposures with Other Neurodevelopmental Risk Factors

In addition, prenatal contaminant exposure is not the only potential risk factor for adverse child development. As is the case with many other perinatal risk factors for behavioural and cognitive problems, perinatal contaminant exposure could interact with other variables known to be associated with child development, such as genetic susceptibility and other environmental adversities/stressors (e.g., Engel et al., 2011; Julvez et al., 2019; Snoj Tratnik et al., 2017; Stein et al., 2016; Yu et al., 2022).

Several studies have considered the role of genetics in the susceptibility for contaminant-related adverse neurodevelopment. For example, studies have investigated the APOE gene, which codes for the apolipoprotein E (*Apoe*) and plays a role in myelination and synaptogenesis. The epsilon 4 (ε4) polymorphism is thought to be a risk factor in the development of Alzheimer's disease (Buttini et al., 1999; Liu et al., 2013). In a study by Snoj Tratnik and colleagues (2017), APOE genotype modified the association between prenatal mercury exposure and cognitive functioning at 18 months, whereby there was a negative association only in carriers of the ε4 polymorphism. Other genes under study include the peroxisome proliferator-activated receptor alpha (PPARα) gene in relation to phthalates, (Yu et al., 2022) or the paraoxonase 1 (PON1) gene in relation to organophosphate pesticides (Engel et al., 2011).

Early life adversity may also modify or interact with contaminant exposure. For example, Stein and colleagues (2016) found that the association between prenatal exposure to organophosphate pesticides and childhood IQ was modified by psychosocial stressors defined according to the adverse childhood experiences (ACEs) model. This moderation also varied

based on sex. In boys, the association between pesticide exposure and IQ was most strongly moderated by adversities related to the learning environment (e.g., low parental education). In girls, the strongest moderators were maternal adversities (e.g., maternal depression) and economic adversities (e.g., family income below the poverty line, food insecurity) (Stein et al., 2016).

The study by Stein and colleagues (2016) also highlights that sex is an important covariate to consider in characterizing the impact of contaminant exposures. As discussed in Chapter 2, many studies in developmental neurotoxicology identify that the association between contaminant exposure and neurodevelopment varies based on sex. The manuscript in Chapter 3 is an example of a study reporting sex differences in the association between PBDE exposure and IQ. However, there is no established consensus about the presence of sex differences for any given contaminant and the underpinnings of such differences remain poorly understood.

Overall, future studies are needed to better understand the variables and risk factors that may modify the association between contaminants and neurodevelopment.

Single Chemical Exposure, Cumulative Exposure, and the Exposome

Contaminant exposures are now so ubiquitous that we are all exposed to a multitude of contaminants from a multitude of sources all the time. For largely practical reasons, studies have historically focused on one contaminant or a small handful of them at a time. This kind of approach unfortunately does not account for the combination of all the contaminants humans are now exposed to. In addition, contaminant exposure is chronic across the lifespan, with certain contaminants accumulating in the body. It is therefore important to consider the cumulative impact of multiple exposures across the lifespan. All these contaminants may have an interactive or synergistic effect on human health and wellbeing, which may differ from the effect of the

individual contaminants (Carpenter et al., 2002; Coker et al., 2017; Kalloo et al., 2021; Yonkman et al., 2023). More research is needed to characterize such interactions between contaminants and quantify their impact.

Research and statistical methodologies are evolving to allow more comprehensive exposure assessments. One emerging design is the examination of the exposome. The exposome considers the sum of internal and external environmental exposures starting at the time of conception (Wild, 2005). The exposome can be considered alongside the genome to understand health and disease. The exposome has three components: internal, specific internal, and general external (Wild, 2005, 2012). The internal component refers to processes inside the body, such as metabolism, hormones, inflammation, epigenetic regulation, and many more. The specific external component is the one that encompasses chemical exposures along with other proximal environmental factors such as diet and lifestyle. The general external component of the exposome includes broader environmental influences such as socioeconomic status, urban/rural environments, and climate (Wild, 2012). The three components of the exposome overlap and interact, so it can be difficult to pinpoint in which component a given variable best fits (Wild, 2012). To further complicate matters, the exposome is dynamic over the course of the lifespan (Krausová et al., 2023). Overall, the aim of the exposome is to create a more holistic picture of non-genetic influences in the development and maintenance of health and disease (Wild, 2005, 2012). In practical terms, studying the exposome is incredibly complex and challenging. It requires large samples and extensive, repeated measurement of a nearly infinite number of variables. These studies are therefore costly, resource intensive, difficult to fund (Potera, 2014). While the term ‘exposome’ was coined by Wild in 2005, comprehensive exposome studies including environmental contaminants remain scarce (Krausová et al., 2023).

A great example of an exposome study on early life contaminant exposure is the Human Early Life Exposome (HELIX) study (Maitre et al., 2018; Vrijheid et al., 2014). This project pools data from six existing European birth cohorts, creating an overall cohort of 32,000 mother-child pairs (Maitre et al., 2018; Vrijheid et al., 2014). Existing data from these six cohorts is being harmonized. In addition, the research team can obtain estimates of exposure from existing databases on environmental factors like air pollution and drinking water. Full biomarker data were collected from a subset of 1200 mother child-pairs for practical and financial reasons (e.g., Jedynak et al., 2021; Julvez et al., 2021; Maitre et al., 2021). From this subcohort, 150 children were selected to conduct repeat measurements to better characterize temporal variability of exposome factors. One hundred and fifty pregnant individuals were also recruited to obtain similar temporal variability data during pregnancy (Donaire-Gonzalez et al., 2019; Maitre et al., 2018; Vrijheid et al., 2014). The eventual goal is to be able to make inferences on the impact of environmental exposures on the broader European population (Vrijheid et al., 2014). Statistical analyses must be chosen carefully to account for a large number of comparisons in a relatively small sample (Agier et al., 2016; Barrera-Gómez et al., 2017; Jedynak et al., 2021; Julvez et al., 2021; Maitre et al., 2021). Despite challenges and limitations, the kind of multilevel study design and nested samples in the HELIX study is a creative solution to address critical research questions while also adapting to the practical restrictions faced by large-scale epidemiological studies.

Impacts of Early Life Contaminant Exposures Across the Lifespan

While the present manuscripts focus solely on childhood impacts of contaminant exposure, it is important to consider that the impacts may be lifelong. Neurotoxicity might look different across the lifespan, which is reflected in the discussion of developmental progressions

and cascades in the scoping review included in Chapter 2. In some cases, neurotoxicity might be delayed until the individual is faced with greater challenges or triggers. In other cases, an outcome of neurotoxicity in adulthood might look very different than the outcome observed in childhood through a series of interconnected events (Bellinger, Matthews-Bellinger, et al., 2016).

For example, there is evidence that prenatal and early childhood lead exposure is associated with later criminal and delinquent behaviour (Dietrich et al., 2001; Wright et al., 2008; Wright et al., 2021). There is limited evidence for other chemicals (e.g., Vernet et al., 2021), though they have also been less scrutinized than lead and there are few studies to date that extend beyond early adolescence. Authors in these studies suggest that the underlying mechanism of these findings is likely an alteration in neurotransmitter function, which in turn may decrease behavioural inhibition and increase the probability of risky behaviour (Dickerson, 2023; Wright et al., 2008; Wright et al., 2021). Bellinger and colleagues (2016) suggest an alternative explanation through developmental cascades. They argue that prenatal lead exposure is associated with lower cognitive ability and higher risk for symptoms of ADHD. Such factors may then contribute to lower educational attainment and hamper future occupational opportunities. Individuals with lower cognitive ability and higher impulsivity are also more likely to engage in more risky and impulsive behaviour. Taken together, it is plausible that prenatal lead exposure activates a cascade of events that eventually culminates in delinquent or criminal behaviour (Bellinger, Matthews-Bellinger, et al., 2016).

Importantly, prenatal contaminant exposure can alter functioning throughout the lifespan in a multitude of ways. The risk of delinquent behaviour represents one extreme end of the externalizing behaviour spectrum. Beyond such behavioural concerns, alterations in cognitive functioning can result in an obstacle to attaining one's full social, educational, or occupational

potential (Bellinger, 2018). If prenatal contaminant exposures result in lower cognitive ability and executive functioning skills, academic achievement will likely be reduced as well (Best et al., 2011; Cortés Pascual et al., 2019; Samuels et al., 2016; Zelazo & Carlson, 2020). In turn, this lower academic achievement might result in overall lower educational attainment, which may then be associated with lower socioeconomic advancement and/or upward social mobility.

There may also be an intergenerational impact worth noting (Bellinger, Matthews-Bellinger, et al., 2016). Research indicates that parental ADHD is associated with less effective parenting (e.g., poorer parental emotion regulation, more permissiveness, more harshness, less positive parenting) and an overestimation of positive parenting (Lui et al., 2013; Mazursky-Horowitz et al., 2015; Park et al., 2017; Woods et al., 2021). Intellectual disability also impacts parenting, with research suggesting it is associated with greater parenting stress, lower financial resources, greater risk for social isolation, and lower offspring educational attainment (Collings et al., 2017; Meppelder et al., 2015; Taylor et al., 2010). It is well documented that parenting plays a key role in children's development (e.g., Kong & Yasmin, 2022; Lanjekar et al., 2022; Neel et al., 2018; Wang et al., 2022). Overall, the children whose neurodevelopment is adversely affected by prenatal contaminant exposure will one day become adults. Their parenting style and abilities may be impacted by their own neurodevelopment, which in turn can shape the neurodevelopment of their children. As such, a future generation of children could indirectly be adversely affected by early life contaminant exposure (Bellinger, Matthews-Bellinger, et al., 2016).

Bellinger and colleagues (2016) also posited that the subclinical alterations in child neurodevelopment due to early life contaminant exposure may in turn have an adverse impact on aging. Research documents that neurodegeneration takes place in the brain far before cognitive

decline can be observed behaviourally (e.g., Beason-Held et al., 2013). The time between the emergence of neurodegeneration and the beginning of clinical symptoms of cognitive decline depends at least partially on cognitive reserve. Cognitive reserve can be defined as one's cognitive resources at a given point in time, which can help buffer against the functional impairments in cognition due to brain pathology or neurological decline (Barulli & Stern, 2013; Kremen et al., 2022; Stern, 2012; Stern et al., 1995). Lifestyle factors such as educational and occupational attainment, social functioning, bilingualism, and physical activity are documented to increase cognitive reserve and therefore help provide more buffer against both normal and pathological brain aging (Alvares Pereira et al., 2022; Bialystok, 2021; Oosterhuis et al., 2022). While education has historically been used as a proxy for cognitive reserve, some argue that IQ may be a better measure as it better reflects the fact that reserve can change throughout the lifespan (Kremen et al., 2022). If IQ is an indicator of cognitive reserve and if early-life contaminant exposure reduces cognitive ability, we can hypothesize that early-life contaminant exposure translates into a reduction of cognitive reserve. Research showed that adult exposure to airborne pollutants, pesticides, heavy metals and other contaminants is associated with greater cognitive decline in later adulthood (Clouston et al., 2022; Keating et al., 2023). If early-life contaminant exposure reduces cognitive ability, we can hypothesize that it translates into a reduction of cognitive reserve (Bellinger, Matthews-Bellinger, et al., 2016; de Rooij, 2022). Research already demonstrates that adult exposure to airborne pollutants, pesticides, heavy metals and other contaminants is associated with greater cognitive decline in later adulthood (Clouston et al., 2022; Keating et al., 2023). Beyond directly reducing cognitive reserve, contaminant exposure might inhibit the ability to engage in the lifestyle factors that promote greater reserve. As discussed previously, prenatal contaminant exposure may interfere with an

individual's ability to fulfill their full social, educational, and occupational potential (Bellinger, Matthews-Bellinger, et al., 2016). As these lifestyle factors are known to promote greater cognitive reserve (Alvares Pereira et al., 2022; Oosterhuis et al., 2022), we can hypothesize that prenatal contaminant exposure penalizes individuals in both directions.

Another factor to bear in mind is the concept of brain reserve. Similar to cognitive reserve, brain reserve refers to the structural integrity of the brain and its ability to withstand risk and degeneration (de Rooij, 2022). There is emerging evidence to suggest that early-life contaminant exposure may adversely alter structural brain development and that these alterations may mediate the association between contaminant exposure and cognition/behaviour (e.g., Grohs et al., 2019). These findings highlight a related risk, namely that contaminant exposure might reduce brain reserve in addition to cognitive reserve. The combination of these two factors suggests that early life contaminant exposure may increase the risk for steeper or earlier neurological and/or cognitive decline in later adulthood.

Significance: The Take-Home Message

Overall, it's important to note that the results of most neurotoxicology studies do not reach clinical significance for any given individual. However, contaminant exposures can be seen as reflecting greater risk for adverse neurodevelopmental outcomes across the lifespan. In addition, the results do reflect great real-world significance when examined at the scale of a whole population. In addition, the current picture may be incomplete as there is little research examining the impact of cumulative exposures to multiple contaminants across the lifespan and the progression of neurotoxicity over time. In light of the breadth of potential impacts of contaminant exposures, individuals can certainly take steps to limit their own exposure.

However, individual action can only go so far, and policy changes are necessary to promote the long-term health and wellbeing of the general population.

Policy Implications of Toxicology Studies

It is important to note that while better regulations and bans of harmful environmental contaminants are key long-term strategies, their short-term effectiveness is limited. Given that some chemicals can linger in the environment for many years, exposure will persist for some time after the contaminant is banned (Grandjean & Landrigan, 2014). In addition, exposure is widespread and originates from so many sources that individual behaviour changes to reduce exposure would likely be ineffective (Azar, 2022, May; Dorea, 2019; Mitro et al., 2015; Sears & Braun, 2020). Nonetheless, changes in environmental health policy are needed for long-term improvements in health and safety.

Regulatory Process in Environmental Health

Historically, environmental contaminants have been introduced on the market quite liberally. They could be marketed and utilized widely before they were stringently tested for toxicity risks (Bennett et al., 2016; Lanphear, 2015). These concerns existed across the world, including in Western countries that had extensive laws and regulations meant to frame how these chemicals were approached. Beyond rigorous safety testing not being consistently upheld, there are two major concerns about current environmental health policy. First, the regulatory framework treats individual chemicals as distinct entities, even within a given chemical class such as PBDEs or PFAS. Second, once a given chemical is banned, it tends to be replaced by another with as much ease as the original one was introduced. Some concrete recent examples of both these concerns are presented next.

Concern #1: Contaminants As Distinct Entities, Even Within Chemical Classes

Canada began restricting the use of BPA in 2008. While BPA had many uses, some of the most well-known sources were plastic products (including baby bottles) and food packaging (e.g., lining of cans) (Buka et al., 2009; Health Canada, 2018). Concerns were emerging as BPA was found to be an endocrine-disrupting chemical which had wide-ranging adverse impacts on human health (Buka et al., 2009). BPA was listed as a toxic substance under the Canadian Environmental Protection Act and measures were taken to remove BPA from baby bottles and other products destined for infants under the Canada Consumer Product Safety Act (Health Canada, 2021a). However, these measures do not indicate an outright ban of BPA.

Once the use of BPA was more restricted, replacements were introduced. Among those replacements are bisphenol F (BPF) and bisphenol S (BPS). Accumulating evidence is now suggesting that BPF and BPS have similar endocrine-disrupting effects as BPA (Rochester & Bolden, 2015). To date, BPF and BPS are not regulated or restricted in Canada.

Concern #2: Banned Contaminants Are Replaced by Alternatives of Unknown Safety

PBDEs were designated as persistent organic pollutants in the Stockholm Convention in 2004. That year marks the beginning of restrictions on the use and production of PBDEs in several countries across the world (Sharkey et al., 2020). While evidence was accumulating regarding the health hazards of PBDEs, the need for flame retardant chemicals remained and their utility was deemed to outweigh possible risks. PBDEs were eventually replaced by organophosphate esters. Emerging research now suggests that organophosphate esters may pose similar concerns for neurodevelopment (Doherty, Hammel, et al., 2019; Doherty, Hoffman, et al., 2019a, 2019b; Liu et al., 2021; Percy et al., 2021). As evidence of toxicity accumulates,

organophosphate esters may become restricted as well, only to be replaced by another contaminant, which in turn will be suspected of toxicity a few years later (Bennett et al., 2016).

Broader Regulatory Context and Amendments

The way environmental contaminants are regulated is dependent on the specific jurisdiction. While Western countries generally have similar environmental policy, it is important to keep in mind that laws and regulations will vary. In Canada, the Canadian Environmental Protection Act (or CEPA) was adopted in 1999 (Government of Canada, 1999). The aim of this legislation was to protect the health of the Canadian population as well as the environment. However, it is now clear the regulations were insufficient, with investigations into toxicity claims being insufficiently thorough and the legislative system itself being too slow to react (Singh, 2023, June 1). While it was amended several times since then, the CEPA underwent its first major revisions in June 2023 with the adoption of Bill S-5 titled "Strengthening Environmental Protection for a Healthier Canada Act" (Gordner et al., 2023, June 28; Parliament of Canada, 2023). One of the key changes brought by this amendment is the recognition of the right to a healthy environment (Gordner et al., 2023, June 28).

In addition, there is increasing recognition that chemical classes should be legislated as a whole rather than regulating one individual congener at a time. Along this vein, Canada has made great progress in modernizing the legislation of PFAS. The PFAS chemical class has been under increased scrutiny in recent years and has been labelled as 'forever chemicals' in the media (e.g., Khandaker, 2023, July 19; Singh, 2023, June 1; Thurnton, 2023, May 20). In the spring of 2023, the government released a draft of the report titled "State of Per- and Polyfluoroalkyl Substances (PFAS)", which aims to review legislation of PFAS. Part of the goal of this report is to advocate for the importance of considering PFAS as a chemical class rather

than legislating on individual PFAS variants (e.g., PFOS, PFOA, PFHxS) (Aker et al., 2023, June 29; Government of Canada, 2023).

Given how recent these changes are, it is unclear yet whether they will be effective at improving the regulatory landscape (Aker et al., 2023, June 29).

Societal, Economic, and Ethical Benefits of Improving Regulations

As discussed previously in this chapter, contaminant exposure comes at great economic cost to societies across the world. There is also evidence that stricter regulations and more stringent neurotoxicity assessments is highly cost-effective (Gaylord et al., 2020). For example, great efforts were made in the last few decades to reduce lead exposure by removing it from paint and gasoline. Research now suggests that every dollar invested in reducing lead exposure through paint in the United States produced a return between 17 and 221 dollars (Gould, 2009). Similarly, efforts to reduce methylmercury exposure in Europe are associated with a return of over nine billion euros (Bellanger et al., 2013).

In both these studies, the return-on-investment calculation was based on a single chemical. As there are few studies that account for multiple cumulative exposures over time, it is hard to evaluate the cost and benefits of changing environmental health policy across the board. However, as detailed earlier in this discussion, it is well recognized that contaminant-related neurotoxicity costs billions to trillions of dollars worldwide in terms of lost productivity, increased healthcare costs, and so on. We can therefore hypothesize that a similar return-on-investment calculation accounting for cumulative exposure would result in even greater economic benefits.

Beyond any economic or financial arguments for safer regulations, it is a government's responsibility to ensure the wellbeing of its population. We cannot expect industry players to

have population wellbeing at heart when their model is predicated in generating profits. In fact, journalistic investigations into PFAS toxicity revealed that industry players were aware of the health risks brought on by this chemical class, decades before their regulation became a hot-button issue (Singh, 2023, June 1). Industry members are in a clear conflict of interest and cannot be expected to put the protection of the public as their first and foremost goal. Meanwhile, governments have an ethical responsibility to do so and follow scientific guidance (Bennett et al., 2016).

Social and Environmental Justice

Environmental health policy should also be guided by principles of social and environmental justice. Evidence suggests that socioeconomic status (SES) is associated with contaminant exposure. For example, individuals in high SES groups may have greater exposure to contaminants like mercury, arsenic, and PFAS (Montazeri et al., 2019; Nelson et al., 2012; Tyrrell et al., 2013; Vrijheid et al., 2012) while individuals in low SES groups have greater exposure to contaminants like lead and BPA (Nelson et al., 2012; Tyrrell et al., 2013). In Western countries, contaminant exposure also varies based on race and/or ethnicity, with BIPOC communities facing greater contaminant exposure than White communities (Attina et al., 2019). Overall, environmental health policies need to shift to dismantle structural racism and systems of oppression to reduce the disproportional burden of contaminant exposure on marginalized groups (Dean & Thorpe, 2022; Payne-Sturges et al., 2021).

Marginalized communities have greater risk and vulnerability to the potential adverse neurodevelopmental effects of contaminant exposure. Low SES and greater socioeconomic adversity are associated with poorer neurodevelopment in children (Gonzalez et al., 2020; Stein et al., 2016). Socioeconomically vulnerable groups also have higher exposures to certain

contaminants, thus further increasing their risk for contaminant-related adverse neurodevelopmental outcomes (Engel et al., 2021; Zota & Shamasunder, 2017). Some researchers hypothesize that poorer neurodevelopment in marginalized groups may be due to greater exposure to contaminants like lead (Lupone et al., 2020; Payne-Sturges et al., 2021). There are many ways in which marginalized groups have greater contaminant exposure, including occupation (e.g., agricultural workers and pesticides, factory workers and toxic fumes) (Evans & Kantrowitz, 2002; Pampel et al., 2010) and housing (e.g., older, lower quality housing, which may contain more hazardous chemicals like lead-based paint) (Bellinger, 2008; Dunn, 2020; Evans & Kantrowitz, 2002; Moody et al., 2016; Pampel et al., 2010). Marginalized groups also have lower access to healthy foods, which may protect against the adverse effects of contaminants (Choi et al., 2014; Evans & Kantrowitz, 2002; Kordas et al., 2007; Kupsco et al., 2020; Lanphear et al., 2002; Liu et al., 2014; McCullough et al., 2022; Shah-Kulkarni et al., 2016; van Wijngaarden et al., 2017). Meanwhile, fast-food and processed food may be easier to access (Baraldi et al., 2018; French et al., 2019), but they often have greater concentrations of contaminants like BPA or PFAS due to their packaging or the manufacturing process (Nelson et al., 2012; Susmann et al., 2019).

Beyond having greater actual exposure, individuals in lower SES neighbourhoods, racial or ethnic minorities, or otherwise marginalized communities are more vulnerable to the adverse health effects of environmental contaminants (Morello-Frosch et al., 2011). For instance, marginalized communities are less likely to have access to care for neurodevelopmental concerns (Bax et al., 2019; Bishop-Fitzpatrick & Kind, 2017; Shi et al., 2021). Families with lower also have less access to educational resources, which could have helped mitigate the negative impact of other risk factors (Evans & Kantrowitz, 2002; Rosen et al., 2020; Sanrey et al., 2021). Their

vulnerability is therefore greater as they have access to fewer resources or services to promote healthy adjustment in the context of neurodevelopmental symptoms (DeFur et al., 2007; Dickerson & Dickerson, 2023). In addition, socioeconomic adversity may potentiate the association between contaminants and neurodevelopment (Elliott et al., 2004; Fernandez-Bou et al., 2021; Payne-Sturges et al., 2021; Weiss & Bellinger, 2006). The synergistic effect of exposure to contaminants and socioeconomic adversity may be understood through the construct of increased allostatic load, whereby health is negatively affected by the cumulative burden of various stressors over the lifespan (McEwen, 1998; Morello-Frosch & Shenassa, 2006).

Overall, marginalized communities not only face greater risk due to greater exposure but also have greater vulnerability due to greater cumulative stressors and less access to resources. When thinking about environmental health policy, decision-makers should therefore take greater care in conducting cumulative risk assessments and further protecting these disadvantaged communities (DeFur et al., 2007; Dickerson et al., 2023; Koehler et al., 2018; Morello-Frosch et al., 2011; Payne-Sturges et al., 2021; Payne-Sturges et al., 2018; Payne-Sturges et al., 2023).

Psychology, Child Development, and Neurotoxicology

It may seem that psychologists' training is not directly relevant for epidemiology or toxicology research. After all, psychologists are most often concerned about the individual and small groups like families or work teams. They sometimes focus on how an individual or small group fit within a population. Meanwhile, epidemiologists are focused on entire populations. The scale of the work of these two professions have been considered entirely different in the past (Miller & Swartz, 1992). Yet, both have much to gain from collaborating. I would argue that psychologists are ideally positioned to contribute to epidemiology research, policy, and intervention planning. In addition, psychologists would benefit from including the conclusions of

neurotoxicology studies in their clinical practice. The idea of bridging the gap between toxicology and psychology is far from new (e.g., Matthews & Avis, 1982; Miller & Swartz, 1992; Weiss, 1983), though there remains significant distance between the professions.

Role for Psychologists in Toxicology Beyond the Clinic

Clinical psychologists most often have Ph.D. degrees and are typically well-trained in research. In the context of concerns for neurodevelopment, it is only natural that psychologists would be a part of neurotoxicology research teams. They possess expertise in psychometrics as well as brain development, cognitive development, and child development more broadly. They are ideally trained to collaborate with epidemiologists and public health experts so that neuropsychological measures are used and interpreted appropriately in population studies. Psychologists are also in a unique position to disseminate neurotoxicology research findings. They are often skilled communicators and routinely need to vulgarize complex concepts in their clinical work. They can also draw on knowledge from social psychology about effective means of communicating complex and important health information (Clayton et al., 2016). Beyond the skills learned through their training, psychologists are somewhat on the outside of epidemiology and neurotoxicology, which means they are likely to have a keen sense of the foundational knowledge the public needs to understand the research findings because they had to build that foundation for themselves as well. Psychologists may therefore be a great asset in disseminating knowledge on exposure reduction and health promotion behaviours.

Psychologists also have relevant expertise in program development. As discussed previously, environmental health policy changes are necessary for long-term improvements in population health. However, given the ubiquitous presence and persistent nature of many contaminants, these policy changes would be ineffective in the short-term. Rather, harm

reduction plans should target the adverse health outcomes directly through prevention, intervention, and disability-reduction strategies (Atli & Baran, 2022; Bann et al., 2016; Bigorra et al., 2016; Blauw-Hospers et al., 2007; Burger, 2010; Chen et al., 2021; Kitzman et al., 2010; Obradović et al., 2016; Ramey & Ramey, 1998; Reyno & McGrath, 2006; Rosen et al., 2020; Watanabe et al., 2005). To that end, psychologists can be assets in developing intervention programs that target neurodevelopmental symptoms and disorders directly. When children are strongly suspected of having notable contaminant exposure, the same interventions can be seen as secondary or tertiary prevention in the sense that they may mitigate a negative progression of symptoms through a developmental cascade. Such suspicion of exposure can be based on known correlates of contaminant exposure, such as housing and socioeconomic indicators. In addition, psychologists could be leaders in developing primary intervention programs aimed at promoting healthy neurodevelopment in children regardless of exposure status, particularly in under-resourced and marginalized communities. As experts in behaviour change, psychologists can also contribute to developing interventions that promote exposure reduction for individuals and families.

Lastly, while doctoral psychology programs rarely include formal training on advocacy, psychologists are uniquely positioned to advocate for the communities they serve (Carr et al., 2023; Parris et al., 2020). Pairing an increased awareness of neurotoxicology research with their expertise in neuropsychological function, they can advocate for neurodevelopmental health promotion at many levels. Advocating to improve accessibility to screenings for contaminant exposure could be one possible avenue. Prenatal screenings may be a useful and cost-effective strategy to assist pregnant persons in limiting their exposure, in turn reducing prenatal exposure for the fetus and future developmental consequences (Gaskin et al., 2015). Whether at a

community, institutional, or political level, psychology as a profession could make an impactful contribution in advocating for healthier environments (Carr et al., 2023; Parris et al., 2020).

Implications for Clinical Practice

Greater awareness of the impact of contaminant exposures also has implications for clinical practice, even if the effect sizes reported in studies are typically not clinically significant. For example, understanding the role of contaminant exposures in neurodevelopment can contribute to biopsychosocial conceptualizations of neuropsychological conditions in children. While contaminant exposure as a sole risk factor may not result in clinically significant cognitive impairment and is unlikely to be evaluated for individual children in the context of a neuropsychological assessment, it remains an additional risk factor for poor neurodevelopmental outcomes. Just as clinicians routinely assess lifestyle factors and pregnancy/birth complications during the intake process, it would be important to consider potential pre- and postnatal contaminant exposures, especially as certain groups are disproportionately affected. In the event that specific significant exposures are strongly suspected (e.g., parental occupational exposure during pregnancy resulting in prenatal exposure for the child, living in housing with confirmed lead-soldered pipes), recommendations can be made to mitigate individual risk and decrease exposure accordingly.

Conclusion

Prenatal exposure to environmental contaminants is associated with small adverse alterations in cognitive function for individuals and significant implications at a societal level in terms of environmental health, cognitive development and aging, societal burden, public finances, policy/legislation, and social justice. While we did not find convincing evidence that set-shifting, inhibition, and working memory were associated with cortical thickness in youth,

future studies should aim to better characterize the associations between cognitive abilities and cortical morphology. Based on our findings, future studies should consider focusing on more refined measures of brain structure, including measures of white matter microstructure and connectivity that are sufficiently sensitive to detect subtle shifts. The ability to detect small changes in cortical morphology is especially important in the context of prenatal contaminant exposure, where it is widely recognized that exposure is associated with subtle decrements in cognitive functioning. Any potential underlying changes in cortical morphology would therefore also be relatively subtle. Even in studies of prenatal maternal smoking, which is known to negatively alter offspring brain development, statistically significant changes in gross cortical morphology remain quite small (El Marroun et al., 2014; Zou et al., 2022). In addition, studying morphological trajectories rather than measures of brain structure at one or two timepoints may be highly informative (Burgaleta et al., 2014; Giedd et al., 2008; Khundrakpam et al., 2022; Ramsden et al., 2011), especially considering concerns about the long-term impact of contaminant exposure on aging and cognitive/brain reserve.

An increasing number of recent studies have examined the association between contaminant exposure and brain structure or function (Binter et al., 2020; Binter et al., 2019; Binter et al., 2022; England-Mason et al., 2020; Grohs et al., 2019; Rauh et al., 2012; Sagiv et al., 2019; Stewart et al., 2003; Sussman et al., 2022; van den Dries et al., 2020; Weng et al., 2020; White et al., 2011). Some studies focused on the direct association between prenatal contaminant exposure and neurological outcomes (e.g., van den Dries et al., 2020) while others treated brain structure/function as a mechanism in the association between exposure and cognition (e.g., England-Mason et al., 2020; Grohs et al., 2019). While there is an increasing number of studies on this topic, it is still relatively little compared to the broad body of research

on neurotoxicology and there is little replication between studies. Interestingly, the study by van den Dries and colleagues (2020) investigated the association between prenatal organophosphate pesticide exposure and various measures of cortical morphology. The study concluded that there was an association between pesticide exposure and white matter microstructure in children, but there were no associations with grosser morphological measures like cortical thickness, volume, or surface area (van den Dries et al., 2020). This finding echoes the hypothesis presented previously that cortical thickness may not be sufficiently sensitive to detect subtle shifts in morphology.

There may also be other mechanisms involved depending on the specific contaminant. For example, several studies have considered the hypothesis that certain contaminants might interfere with maternal thyroid hormones or sex hormones, which are known to play a key role in prenatal brain development (Demeneix, 2019; Ghassabian & Trasande, 2018; Özel & Rüegg, 2023). Such an endocrine mechanism through thyroid hormones may be involved in the decrements in cognitive functioning observed for contaminants like PBDEs or phthalates (Chevrier et al., 2010; Itoh et al., 2022), though there is some conflicting evidence (Eskenazi et al., 2013; Ghassabian & Trasande, 2018; Gibson et al., 2018). Androgens and estrogens are also important for fetal neurodevelopment and certain contaminants (e.g., BPA, phthalates) are suspected to disrupt their functioning (Özel & Rüegg, 2023). It is important to note these findings with the caveat that very few studies have tested mediation effects and it is therefore difficult to determine with confidence whether these putative endocrine mechanisms underlie the associations between exposure and cognition.

Our understanding of endocrine mechanisms may in turn inform our understanding of sex differences in developmental neurotoxicology. There is evidence that hormones like estradiol

and progesterone, which females have more receptors for in their central nervous system than males, have a protective effect for neurodevelopment (Azcoitia et al., 2019; Schumacher et al., 2020; Torres-Rojas & Jones, 2018; Vahter et al., 2007). Some therefore hypothesize that males may be more vulnerable to the negative effects of prenatal contaminant exposure (Goodman, Green, et al., 2023). Depending on the contaminant and its impact on hormonal pathways, an endocrine mechanism affecting sex hormones may contribute to sex differences in neurodevelopmental outcomes following exposure.

Another interesting avenue for future study involves investigating epigenetic mechanisms. The term "epigenetic" refers to a change in gene expression that leaves the gene itself unchanged (Szyf & Bick, 2013). DNA methylation is the most commonly studied epigenetic process. It involves the addition of a methyl group to a cytosine-phosphate-guanine dinucleotide sequence (CpGs) of DNA and typically silences the associated gene. Epigenetic changes may occur as a result of experience and other environmental exposures (Szyf & Bick, 2013). Some studies suggest that prenatal contaminant exposure is associated with DNA methylation in genes relevant for neurobehavioural development, suggesting it may be a potential mechanism (Appleton et al., 2017; Bozack et al., 2021; Mattonet et al., 2022). More research is needed to characterize the role of epigenetic processes in the association between contaminant exposure and cognition. Research on prenatal maternal stress and its impact on offspring mental health suggests epigenetic processes likely underlie this association (Azar & Booij, 2022). Conceptually, it would make sense to consider prenatal chemical exposure as a form of prenatal stress, especially in the context of known correlations between contaminant exposure and socioeconomic factors which are themselves associated with more psychosocial stress/adversity (please refer to the subsection titled "Social and Environmental Justice").

Epigenetic modifications of germ cells (i.e., sperm and egg) can be transmitted to the next generation in a process called epigenetic inheritance (Nilsson et al., 2022). If contaminant exposure modified gene expression in germ cells and if such epigenetic processes underlie the adverse neurodevelopmental effects of exposure, then the offspring of an exposed person may experience similar detrimental outcomes without ever being exposed themselves. Epigenetic inheritance of potential risk factors adds to the concerns of intergenerational transmission through parenting described in the subsection titled "Impacts of Early Life Contaminant Exposures Across the Lifespan". This potential epigenetic inheritance could also add further concern for marginalized groups who are already disproportionately affected by greater exposure and more adverse neurodevelopmental outcomes by resulting in an epigenetic intergenerational transmission of risk for poor neurodevelopment.

In conclusion, the aim of this thesis was to describe the state of affairs about the impact of prenatal contaminant exposure on cognition in children as well as explore avenues for future research on underlying mechanisms. While many questions remain unanswered, there is growing evidence that environmental contaminants are associated with poor neurodevelopmental outcomes across childhood, which poses significant problems at the scale of the population. Future research should endeavor to better characterize the underlying mechanisms by ensuring that the selected measures are sufficiently sensitive to detect subtle changes. The field of neurotoxicology would benefit from greater involvement from psychologists, who can play important roles in toxicology research, policy, advocacy, and program development. Improving the dissemination of neurotoxicology research to professional audiences in health and allied health fields can also contribute to biopsychosocial conceptualizations of neuropsychological

profiles and a more complete consideration of risk factors for poor neurodevelopmental outcomes.

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Appendices

Appendix A: Chapter 2 Supplementary Tables

List of abbreviations

Abbreviation	Full name
ALSPAC	Avon Longitudinal Study of Parents and Children
ADHD	Attention-Deficit/Hyperactivity Disorder
APrON	Alberta Pregnancy Outcomes and Nutrition
As	Arsenic
ASD	Autism Spectrum Disorder
BASC	Behavior Assessment System for Children
Beery VMI	Beery-Buktenica Developmental Test of Visual Motor Integration
BNT	Boston Naming Test
Brazelton NBAS	Brazelton Newborn Behavioral Assessment Scale
BRIEF	Behavior Rating Inventory of Executive Function
BRIEF-P	Behavior Rating Inventory of Executive Function, Preschool Version
BSID-II	Bayley Scales of Infant Development, 2nd Edition
CADS	Conners ADHD/DSM-IV [Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition] Scales
CANTAB	Cambridge Neuropsychological Test Automated Battery
CCCEH	Columbia Center for Children's Environmental Health
CDIIT	Comprehensive Developmental Inventory for Infants and Toddlers
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas
CPT	Continuous Performance Test
CVLT	California Verbal Learning Test
DDE	Dichlorodiphenyldichloroethylene
DDST-II	Denver Developmental Screening Test II
D-KEFS	Delis-Kaplan Executive Function System
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELEMENT	Early Life Exposure in Mexico to ENvironmental Toxicants
FSIQ	Full Scale IQ
FTII	Fagan Test of Infant Intelligence
GCI	General Cognitive Index
GDS	Gesell Developmental Schedules

GW	Gestational week
HEALS	Health and Environment-wide Associations based on Large population Surveys
HELIX	Human Early-Life Exposome Project
Hokkaido Study	Hokkaido Study on Environment and Children's Health
HOME	Health Outcomes and Measures of the Environment
IKIDS	Illinois Kids Development Study
INMA	INfancia y Medio Ambiente
K-ABC	Kaufman Assessment Battery for Children
KBIT	Kaufman Brief Intelligence Test
MDI	Mental Development Index
MIREC	Maternal-Infant Research on Environmental Chemicals
Mn	Manganese
MOCEH	Mothers and Children's Environmental Health Study
Movement ABC	Movement Assessment Battery for Children
MSCA	McCarthy Scales of Children's Abilities
NBNA	Neonatal Behavioral Neurological Assessment
NEPSY	A Developmental Neuropsychological Assessment
NES2	Neuropsychological Examination System
NNNS	NICU Network Neurobehavioral Scale
OC pesticide	Organochlorine pesticide
ODD	Oppositional defiant disorder
OP pesticide	Organophosphate pesticide
PBDEs	Polybrominated diphenyl ethers
PCBs	Polychlorinated biphenyls
PDI	Psychomotor Development Index
PELAGIE	Perturbateurs Endocriniens : Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance
PFAS	Per- and polyfluoroalkyl substances
PHIME	Public Health Impact of Metals Exposure
PIPA Project	The Rio Birth Cohort Study on Environmental Exposure and Child Development
PROGRESS	Programming Research in Obesity, Growth, Environment and Social Stressors
REPRO_PL	Polish Mother and Child Cohort
SB	Stanford-Binet
SDQ	Strengths and Difficulties Questionnaire
SRS	Social Responsiveness Scale
TEA-Ch	Test of Everyday Attention for Children

TIDES	The Infant Development and Environment Study
WCST	Wisconsin Card Sorting Test
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WRAML	Wide Range Assessment of Memory and Learning
WRAVMA	Wide Range Assessment of Visual Motor Abilities

Table A1

Result Summary for Studies in Infancy (Birth to 11 Months)

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Bahena-Medina et al. (2011)	Four municipalities in Morelos, Mexico N=265 (43.4% female)	DDE in maternal blood in each trimester	1 month - Graham–Rosenblith Scale (Neurological Soft Signs only) - BSID-II - Brazelton NBAS (Reflex Scale only)	No significant results.	No significant interactions with sex.
Berghuis et al. (2014)	Northern Netherlands N=98 (46.9% female)	PCBs in maternal blood in the second or third trimester	3 months - Touwen Infant Neurological Examination	One PCB congener was associated with lower odds of non-optimal development.	Significantly lower odds of non-optimal development in boys only.
Boucher et al. (2014)	Nunavik Environmental Contaminants and Child Development Study N=94 (36.2% female)	Hg and Pb in cord blood. PCBs in cord plasma	**6.5 months** - FTII **11 months** - FTII - A-not-B task - BSID-II	**Repeated measures.** PCBs were associated with lower FTII scores (impaired visual recognition memory). Pb was associated with longer fixation duration (slower information processing). **At 11 months,** Hg and PCBs were associated with poorer performance on the A-not-B task (weaker working memory).	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
H. K. Chen et al. (2023)	Taiwan Mother Infant Cohort Study N=283 (47.7% female)	Phthalates in maternal urine in the third trimester	0-5 days - Neonatal Neurobehavioral Examination-Chinese version (NNE-C)	Maternal phthalate metabolites were associated with improvements in neurobehavioral reflexes.	Phthalates were associated with better neurobehavior in boys and worse neurobehavior in girls.
Chung et al. (2015)	MOCEH N=232 (53.4% female)	Mn in maternal blood at delivery	6 months - BSID-II	Inverted U-shaped associations between Mn and MDI and PDI scores, where lower MDI and PDI scores were associated with both low and high blood Mn concentrations.	N/A
Daniels et al. (2003)	Collaborative Perinatal Project N=1207 (% female not specified)	PCBs in maternal serum in the third trimester	8 months - BSID	PCBs were associated with marginally better PDI scores as they increased slightly across five levels of PCB exposure.	N/A
Darvill et al. (2000)	Oswego Study N=202-230 (% female not specified)	PCBs, DDE, and Pb in cord blood. Hg measured in maternal hair	6 and 12 months - FTII	PCBs were associated with lower FTII scores at **6** and **12 months** (suggesting lower working memory)	N/A
Davidson, Strain, et al. (2008)	Seychelles Child Development Study, N=229-265 (50.7% female)	Hg in maternal hair for	**5 months** - FTII (Novelty preference and Fixation duration)	No significant associations at either 5 or 9 months of age.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- Visual Expectation Paradigm (VEXP) **9 months** - BSID-II - VEXP		
de Assis Araujo et al. (2022)	PIPA Project N=48 (38% female)	Pb, Hg, and Arsenic in maternal blood in the third trimester and in cord blood	6 months - DDST-II (fail or no fail)	Significantly higher maternal blood Arsenic in the "fail" group compared to the "no fail" group for the overall score. Marginally higher Arsenic in maternal and cord blood in the “fail” group compared to the “non fail” group for the Gross Motor domain.	N/A
Donauer et al. (2015)	HOME N=349 (53% female)	PBDEs and PFAS in maternal serum around GW 16	5 weeks - NNNS	No significant associations.	N/A
Dzwilewski et al. (2021)	IKIDS N=244 (49.6% female)	Phthalates in maternal urine in GW 10-14, 16-18, 22-24, 28-30, and 34-36 (pooled)	7-8 months - Paired comparison visual recognition memory (VRM) paradigm	Phthalates were negatively associated with time to familiarization (suggesting better visual attention) and novelty preference (suggesting poorer recognition memory).	In boys, positive association between phthalates and run duration (suggesting slower information processing).

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Engel et al. (2007)	Mount Sinai Children's Environmental Health Cohort N=144-253 (% female not specified)	DDE and PCBs in maternal blood and OP pesticides in maternal urine around GW 31	Newborn (before hospital discharge) - Brazelton NBAS	OP pesticides were associated with a higher risk of abnormal reflexes.	N/A
Engel et al. (2009)	Mount Sinai Children's Environmental Health Cohort N=295 (41.4% female)	Phthalates in maternal urine between GW 25 and 40	Newborn (before hospital discharge) - Brazelton NBAS	Marginally significant positive association between phthalates and Motor Performance and marginally significant negative association with Orientation.	In girls, negative association on the Orientation and Quality of Alertness scales. In boys, positive association on the Motor scale.
Enright et al. (2023)	ECHO.CA.IL cohort (composed of subsets of the IKIDS cohort and the Chemicals in Our Bodies cohort) N=163 (54.6% female)	PFAS in maternal serum in the second trimester	7-8 months - Visual Recognition Memory task	PFAS were associated with better attention on the VRM task.	In girls, PFAS were associated with better attention.
Eskenazi et al. (2006)	CHAMACOS N=360 (51.4% female)	DDT and DDE in maternal serum around GW 26 or at delivery	6 months - BSID	DDT and DDE were associated with lower PDI scores.	No significant sex differences.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Eskenazi et al. (2007)	CHAMACOS N=372-447 (50.6% female)	OP pesticides in maternal urine between GW 14 and 27	6 months - BSID	No significant associations.	No significant sex differences.
Farías et al. (2022)	Mexico's National Institute of Public Health cohort N=253 (47.9% female)	Hg, Mn, and Pb in maternal blood in the third trimester	1, 3, 6, & 12 months - Bailey-III	Pb was associated with lower Language Development scores.	N/A
Gao et al. (2007)	Zhoushan City, China N=384 (50.2% female)	Hg measured in maternal hair 1-3 days postpartum and in cord blood	3 days - NBNA	N/A (sex-stratified analyses only)	Cord blood and maternal hair Hg were negatively associated with scores on the Behavior scale in boys.
Golding, Gregory, Iles-Caven, et al. (2016)	ALSPAC N=2875–3264 (% female not specified)	Hg in maternal blood early in pregnancy	6 months - DDST	Hg was associated with better Total DDST and Social Skills subscale scores.	N/A
Goudarzi et al. (2016)	Hokkaido Study N=173-183 (50.4-52.0% female)	PFAS (PFOA and PFOS) in maternal blood after the second trimester	6 months - BSID-II	No significant associations.	PFOA was associated with lower MDI scores in girls.
Gunier et al. (2015)	CHAMACOS N=197 (57.4% female)	Mn in dentine from children's shed teeth	6 months - BSID-II	No significant associations.	No significant interactions with sex.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Ipapo et al. (2017)	CCCEH N=168 (54.2% female)	Phthalates in maternal urine in the third trimester	27 weeks - FTII	No significant associations.	Negative association with novelty preference (suggesting poorer visual recognition memory) in girls.
Jedrychowski et al. (2008)	Krakow Inner City Study N=452 (% female not specified)	Pb measured in cord blood	6 months - FTII	Significant negative association between Pb and FTII (suggesting poorer visual recognition memory).	N/A
Jusko et al. (2012)	Collaborative Perinatal Project N=1042-1142 (49-51% female)	DDT and DDE in maternal serum in the third trimester	8 months - BSID	No significant associations.	N/A
Kim et al. (2011)	MOCEH N=460 (48.9% female)	Phthalates in maternal urine in the third trimester	6 months - BSID-II	Phthalates were negatively associated with both MDI and PDI scores.	Phthalates were negatively associated with MDI and PDI scores in boys.
Kim et al. (2013)	MOCEH N=884 (47.5% female)	Pb in maternal blood in early and late pregnancy	6 months - BSID-II	Late pregnancy Pb was negatively associated with MDI scores.	N/A
Kongtip et al. (2017)	Hospitals in Northeastern, lower North, and West Thailand N=50 (40% female)	OP pesticides in maternal urine at GW 28	5 months - Bayley-III (Cognitive and Motor scales only)	OP pesticide metabolites were negatively associated with Cognitive and Motor scores.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Liang et al. (2020)	Ma'anshan Birth Cohort N=2315 (49.2% female)	Arsenic in cord blood	6 months - ASQ of China (ASQ-C)	Arsenic was associated with significantly greater odds of scoring in the "suspected developmental delay" (SDD) range in the Personal-Social domain and marginally greater odds in the Problem Solving domain.	In girls, significantly greater odds of scoring in the SSD range in the Personal-Social domain.
Liu, Chen, et al. (2014)	Guangdong, China N=243 (46.9% female)	Pb in cord blood	6 months - BSID-II	Pb was associated with lower MDI scores.	N/A
Liu, Gao, et al. (2014)	BaoAn District Maternal and Child Health Center N=332 (52.5% - 36.8% female)	Pb measured in maternal blood once in each trimester and in cord blood at delivery	3 days - NBNA	Significant negative association between first trimester Pb and NBNA total score.	N/A
Minatoya et al. (2016)	Hokkaido Study N=328 (51.8% female)	Phthalates in maternal blood samples between GW 23 and 41	6 months - BSID-II	No significant associations.	No significant sex differences.
Minatoya et al. (2017)	Hokkaido Study N=285 (55.4% female)	BPA in cord blood	6 months - BSID-II	No significant associations	No significant sex differences.
Nakajima et al. (2006)	Hokkaido Study N=134 (49.3% female)	PCBs in maternal blood in the second trimester	6 months	No significant associations.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
			- BSID-II (Japanese adaptation)		
Nakajima et al. (2017)	Hokkaido Study N=121-190 (25.6-47.9% female)	PCBs in maternal blood in the second trimester	**6 months** - BSID-II	N/A	In boys, several PCBs were associated with lower PDI scores. In girls, one PCB congener was associated with lower PDI scores.
Nyanza et al. (2021)	Mining and Health Study in Northern Tanzania N=439 (51.4% female)	Pb and Hg in maternal blood and Arsenic in maternal urine in the second trimester	6-12 months - Malawi Developmental Assessment Tool (MDAT)	Hg was associated with a significantly higher prevalence ratio of impaired Global Neurodevelopment and Language Development.	Arsenic was associated with a significantly higher prevalence ratio of impaired Social Development in girls.
Oh et al. (2022)	Hamamatsu Birth Cohort (HBC) Study N=598 (48.2% female)	PFAS in cord blood	4, 6, and 10 months - Mullen Scales of Early Learning (MSEL)	PFAS were positively associated with the Fine Motor subscale at **4 months** and negatively associated with the Visual Reception and Receptive Language subscales at **10 months**.	In boys, PFAS were positively associated with the Fine Motor subscale at **4 months.** In girls, PFAS were negatively associated with the Receptive Language subscale at **10 months**.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Parajuli et al. (2013)	Chitwan Valley, Nepal N=100 (% female not specified)	Pb and Arsenic in cord blood	Newborn (day after birth) - Brazelton NBAS 3rd edition (NBAS-III)	Significant negative associations between Pb and the Motor cluster score and between Arsenic and the State Regulation cluster score.	N/A
Parajuli et al. (2014)	Chitwan Valley, Nepal N=79-100 (53% female)	Pb and Arsenic in cord blood	6 months - BSID-II	No significant associations.	N/A
Ruiz-Castell et al. (2012)	Toxicity in Bolivia (ToxBol) N=246 (47.56% female)	Pb in maternal blood between the second and third trimesters	10.5-11.5 and 11.5-12.5 months - BSID Spanish version	**Longitudinal analysis only.** Pb was positively associated with MDI and PDI scores (when outliers were excluded).	N/A
Sagiv et al. (2008)	New Bedford Cohort N=542 (49.5% female)	PCBs and DDE in cord serum	2 weeks - NBAS	PCBs and DDE were each negatively associated with NBAS item scores reflecting attentional skills (i.e., Alertness, Quality of Alert Responsiveness, Cost of Attention, Self-Quieting, and Motor Maturity).	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Shah-Kulkarni et al. (2016)	MOCEH N=965 (48% female) at 6 months	Pb in maternal blood in early pregnancy (before GW 20) and at delivery (representing late pregnancy) and in cord blood	6 months - Korean version of the Bayley-II (K-BSID-II)	Marginally significant negative association between late-pregnancy Pb and MDI score.	N/A
Shy et al. (2011)	Four hospitals in southern Taiwan N=36 (% female not specified)	PBDEs in cord blood (divided by median split into high and low exposure)	8-12 months - Bayley-III	Those in the high PBDE exposure group had greater odds of obtaining a low cognitive score and lower odds of a low adaptive score.	N/A
Silver et al. (2017)	Fuyang Maternal and Children's Hospital N=233 (48.1% female)	OP pesticides (chlorpyrifos) in cord blood	6 weeks and 9 months - Peabody Developmental Motor Scales 2nd edition (PDMS-2)	At **9 months**, chlorpyrifos was associated with reduced Gross Motor, Fine Motor, and Total Motor skills.	In 9-months-old girls, chlorpyrifos was associated with lower Gross Motor and Total Motor quotients as well as a marginally lower Fine Motor quotient.
Sittiwang et al. (2022)	SAWASDEE (cohort in Chiang Mai province, Thailand) N=320 (51% female)	OP pesticides in maternal urine (up to 6 samples, averaged) in early, mid, and late gestation	5 weeks - NNNS	OP pesticides were negatively associated with the arousal and excitability scales of the NNNS.	No significant sex differences.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Sprowles et al. (2022)	IKIDS (Illinois) N=123 (38.2% female)	Phthalates in maternal urine samples collected across pregnancy and pooled	4.5 and 7.5 months - ASQ-3	In the **longitudinal analyses**, certain phthalates were associated with better Problem Solving and Fine Motor Skills, and marginally better Gross Motor Skills. At **4.5 months**, certain phthalates were associated with better Communication.	In the **longitudinal analysis**, phthalates were associated with marginally better Personal-Social and Fine Motor skills in boys. At **4.5 months**, phthalates were associated with better Communication and Fine Motor scores in girls. At **7.5 months**, phthalates were associated with worse Personal-Social and Fine Motor skills, but better Gross Motor skills in boys. Phthalates were associated with worse Gross Motor and Problem Solving in girls.
Stewart et al. (2000)	Oswego Study, N=292 (50.3% female)	PCBs and DDE in cord blood	12-24 hours and 25-48 hours after birth - NBAS	PCBs were negatively associated with Habituation and Autonomic scores at 25-48 hours.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Suzuki et al. (2010)	Tohoku Study of Child Development N=498 (48.4% female)	Hg in maternal hair and PCBs in cord blood	3 days - NBAS	Maternal hair Hg was negatively associated with the Motor cluster on the NBAS.	N/A
Takser et al. (2003)	Robert Debré Maternity (Paris, France) N=247 (45% female)	Mn in maternal blood, cord blood, maternal hair, newborn hair, and placental tissue (all collected at delivery/birth)	9 months - Brunet-Lézine scales	No significant associations.	No significant sex differences.
Torres-Sanchez et al. (2007)	Four municipalities in Morelos, Mexico N=244 (43.3% female)	DDE in maternal serum at the baseline interview and/or at each trimester visit	1, 3, 6, and 12 months - BSID-II	**Longitudinal analysis only.** First-trimester DDE was associated with lower PDI scores.	N/A
Tung et al. (2022)	Rhode Island Child Health Study (RICHS) N=192 (47.4% female)	Mn from placental tissue	Newborn (24-72 hours after delivery) - NNNS	No significant associations.	N/A
Valdez Jimenez et al. (2017)	Jalisco, Mexico N=65 (69.2% female)	Fluoride in maternal urine in the first and second trimesters	3-15 months - BSID-II (MDI only)	Fluoride in each trimester was negatively associated with MDI scores.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Wang et al. (2018)	Shanghai, China N=892 (53.5% female)	Arsenic in cord blood	3 days - NBNA	Arsenic was associated with significantly greater odds of having a low score on the NBNA for the total score, the Behaviour scale, and the Passive Muscle Tone scale.	No significant sex differences.
Xu et al. (2016)	HOME N=344 (53% female)	Hg in cord blood at delivery and in maternal whole blood (averaged based on samples collected at GW 16, GW 26, and at delivery)	5 weeks - NNNS	Comparable results with cord blood and maternal blood. Hg was associated with better outcomes on the Attention and Special handling (i.e., requiring less special handling) scales.	Marginally significant interaction with sex for Asymmetry, such that there was a significant positive association (worse outcome) in girls.
Yamamoto et al. (2022)	Japan Environment and Children's Study (JECS) N=3,787 (49.5% female)	Mn in maternal blood in the second and third trimesters and in cord blood	6 months - ASQ, 3rd edition, Japanese version (J-ASQ-3)	Maternal blood Mn was associated with lower scores for Gross Motor, Problem Solving, and Personal-social.	No significant sex differences.
Yamazaki et al. (2018)	Hokkaido Study N=115-164 (51.8-55.7% female)	DDE in maternal blood after the second trimester	6 months - BSID-II	No significant associations.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Yim et al. (2022)	Hokkaido Study N=259 (51.7% female)	PCBs in maternal blood after the second trimester	6 months - BSID-II	Several PCB congeners were related to lower MDI and PDI scores in single-congener multiple regression models, but no significant associations in multi-congener models.	N/A
Yolton et al. (2011)	HOME N=350 (53% female)	Phthalates and BPA in maternal urine measured at GW 16 and GW 26	5 weeks - NNNS	Marginally significant positive association between GW 16 BPA and Hypotonia (worse outcome). Phthalates at GW 26 were negatively associated with Arousal and Handling, and positively associated with Self-Regulation and Movement Quality (all better outcomes).	Significant positive association between phthalates at GW 26 and Nonoptimal Reflexes in boys.
Yolton et al. (2013)	HOME N=350 (53% female)	OP pesticides in maternal urine at GW 16 and GW 26	5 weeks - NNNS	Significant positive association between OP pesticides and attention (better outcome).	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
				Significant negative association between OP pesticide metabolites at GW 16 and both Lethargy and Hypotonia (better outcomes), and between OP pesticide metabolites at GW 26 and Autonomic Stress (better outcome).	
Young et al. (2005)	CHAMACOS N=381 (47.5% female)	OP pesticides in maternal urine GW 14 and 26 (averaged)	7 days - Brazelton NBAS	Significant negative association between OP pesticides and the Reflex cluster.	N/A
Yu et al. (2011)	Shanghai, China N=1652 (45.8% female)	Pb, Hg, and Arsenic in cord blood	3 days - NBNA	Significant negative association between Arsenic and NBNA scores.	N/A
Yu et al. (2014)	Shanghai, China N=933 (47.0% female)	Mn in cord serum	3 days - NBNA	Significant negative association between the highest quartile of Mn and NBNA total score. Mn was also associated with significantly greater odds of having a “low” NBNA score. Exposure levels above a set threshold were associated with lower scores in the Behavior, Active tone and General reactions clusters.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Zhang et al. (2014)	Shenyang, China N=249 (44.6% female)	OP pesticides in maternal urine samples prior to delivery	3 days - NBNA	Significant negative associations between OP pesticides and each NBNA cluster (Behavior, Passive tone, Active tone, Primary reflexes, Summary score).	No significant sex differences (interaction and sex-stratified analyses).
Zhou et al. (2023)	Shanghai Maternal-Child Pairs Study N =1285 (47.2% female)	PFAS in cord serum	**2 and 6 months** - ASQ-3	At **6 months**, PFAS were associated with lower gross motor, communication, and total scores.	At **2 months**, PFAS were associated with marginally lower communication scores and marginally higher total score in girls. At **6 months**, PFAS were associated with lower gross motor, fine motor, communication, and total scores in boys.

Table A2

Result Summary for Studies in Toddlerhood and Preschool-Age (12 Months to 5 Years)

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Alampi et al. (2021)	MIREC N=478 (50.8% female)	All maternal biological samples were collected in early pregnancy - Metals: Pb, Hg, Mn, and Arsenic in maternal whole blood - PCBs and DDE in maternal plasma - OP pesticides, BPA, and phthalates in maternal urine	3-4 years - SRS-2	Pb and several phthalate metabolites were associated with higher SRS scores (more symptoms) at the 90th percentile of the SRS distribution (compared to the mean). Mn, several OP pesticide metabolites, and one phthalate metabolite were associated with lower SRS scores (fewer behaviours) at the 90th percentile of the SRS distribution.	For some phthalate metabolites, the association (either positive or negative) was stronger in boys than in girls.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
An et al. (2022)	Venda Health Examination of Mothers, Babies and the Environment (VHEMBE) N=683 (48.0% female)	DDE and DDT in maternal blood and pyrethroids in maternal urine at delivery	2 years - CBCL 1.5-5 (ADHD, Aggressive behavior, Attention problems, Externalizing, and ODD subscales)	DDE/DDT were associated with significantly higher risk of scoring in the borderline/clinical range on the ODD scale. Pyrethroids were associated with significantly higher risk of scoring in the borderline/clinical range on the Externalizing scale.	No significant sex differences (interactions or sex-stratified analyses).
Andiarena et al. (2020)	INMA N=304 (49.7% female)	Mn in newborn hair	4 years - MSCA Basque version	No significant associations.	No significant sex differences (interactions or sex-stratified analyses).
Azar et al. (2021)	MIREC N=592 (50.8% female)	PBDEs in maternal blood in the first trimester	3-4 years - WPPSI-III	Significant negative association between PBDEs and Performance IQ (PIQ).	Significant negative associations between PBDEs and Verbal, Performance, and Full-Scale IQ in boys only.
Barbone et al. (2019)	PHIME N=1308 (51.4% female)	Hg in maternal blood (timing of collection during pregnancy varied by study site), maternal hair, and cord blood	18 months - Bayley-III	Significant positive associations between maternal hair Hg and scores on the Language composite and the Receptive Communication subscale.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Barbone et al. (2020)	Friuli-Venezia Giulia region N=53 (47.2% female)	Hg in maternal hair	2 years - DDST-II	In the Fine Motor-Adaptive performance domain, Hg was significantly lower in children who scored better-than-normal compared to those with normal or reduced scores.	N/A
Bashash et al. (2017)	ELEMENT N=211-287 (55.0-55.7% female)	Fluoride in maternal urine in each trimester	4 years - MSCA (GCI only)	Fluoride was associated with lower GCI scores.	N/A
Bernardo et al. (2019)	MIREC N=546 (52.2% female)	PCBs in maternal plasma around GW 12	3-4 years - SRS-2	No significant associations.	No significant sex differences.
Braun et al. (2009)	HOME N=218-389 (51.4-53.5% female)	BPA in maternal urine at GW 16, GW 26, and delivery	2 years - BASC-2	Significant positive association between GW 16 BPA and Externalizing scores.	Mean and GW 16 BPA concentrations were associated with Externalizing scores in girls only.
Braun et al. (2011)	HOME N=237-239 (approx. 53.3% female)	BPA in maternal urine at GW 16, GW 26, and delivery	3 years - BASC-2 (Aggression, Attention, Hyperactivity) - BRIEF-P	Significant positive association between mean prenatal BPA and BRIEF Emotional Control scores.	In girls, mean prenatal BPA was positively associated with BASC-2 Hyperactivity and BRIEF Emotional Control and Inhibition scores.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Braun et al. (2014)	HOME N=175 (54.3% female)	All samples collected at GW 16. BPA and phthalates in maternal urine. PCBs, PBDEs, DDE, and PFAS in maternal serum.	4-5 years - SRS	Results varied based on specific congeners and were mostly null. One significant positive association (one PBDE congener) and three significant negative associations (one PBDE, one PFAS, and one PCB).	N/A
Braun, Muckle, et al. (2017)	MIREC N=497-812 (approx. 50.9% female)	BPA in maternal urine around GW 12	3-4 years - BASC-2 - BRIEF-P - SRS-2 - WPPSI-III - NEPSY Affect Recognition	Significant positive associations between prenatal BPA and several SRS scores (Total, Cognition, Communication, Restricted, DSM Social, and DSM Restricted), suggesting poorer outcomes.	Significant positive association between BPA and BRIEF Working Memory in boys only.
Calamandrei et al. (2020)	HEALS N=527 (46.9-52.7% female)	Pb in cord blood and Hg in maternal hair	12-24 months - Bayley-III	Significant positive association between Hg and Motor scores.	N/A
Carrizosa et al. (2021)	INMA N=1240 (48.5% female)	PFAS in maternal plasma in the first trimester (around GW 13)	**14 months** - BSID-II **4-5 years** - MSCA - Conners' Kiddie CPT (K-CPT)	PFAS was associated with lower Motor scores on the BSID-II at **14 months,** and better Verbal Reasoning and marginally better GCI scores on the MSCA at age **4-5 years**.	At **age 4-5 years**, PFAS was associated with better scores in girls and worse scores in boys on the MSCA Quantitative subscale.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Casas et al. (2015)	INMA N=438 (47% female)	BPA in maternal urine in the first and third trimesters (averaged)	**1 year** - BSID **4 years** - MSCA - Teacher-reported ADHD-DSM-IV behaviours	At **age 1**, infants in the highest BPA tertile showed significantly lower PDI scores. At **age 4**, BPA was associated with more teacher-reported hyperactivity.	At **age 4**, BPA was associated with more teacher-reported Hyperactivity in boys and less Attention Problems in girls.
Chen et al. (2014)	HOME N=165-309 (54-56% female)	PBDEs in maternal serum at GW 16	**1, 2, and 3 years** - BSID-II **2, 3, 4, and 5 years** - BASC-2 (Externalizing Problems and Hyperactivity scales only) **5 years** - WPSSI-III	PBDEs were associated with more Externalizing Problems at **ages 2, 3, and 5,** and with more Hyperactivity at **age 3**. PBDEs were associated with decreased FSIQ on the WPPSI-III at **age 5**.	No significant interactions.
Chen et al. (2013)	Taiwan Birth Panel Study N=239 (45% female)	PFAS in cord plasma	2 years - CDIIT	PFAS was negatively associated with CDIIT Total and Gross Motor scores.	N/A
H. Chen et al. (2023)	Wuhan Medical and Healthcare Center for Women and Children N=1006 (47.8% female)	Arsenic in maternal urine in early (GW 12), middle (GW 23, and late (GW 34) pregnancy	24 months - BSID	Maternal arsenic was associated with significantly lower MDI scores.	No significant sex differences (data not shown in paper or supplement).

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Chiu et al. (2021)	Taiwan Birth Panel Study N= 425 (49.9% female)	OP pesticides (chlorpyrifos) in placental and cord blood	2 years - CDIIT	No significant associations.	Significant negative association with Cognitive and Language scores in boys only.
Claus Henn et al. (2017)	Tar Creek Superfund Site N=224 (40.6% female)	Mn in maternal blood at delivery and cord blood	2 years - BSID-II	Maternal blood Mn was negatively associated with MDI and PDI scores.	No significant sex differences.
Cohen-Eliraz et al. (2023)	Mother, Child, and Environment Longitudinal Study, Jerusalem N=158 (46% female)	Phthalates in maternal urine at GW 11-18	2 years - ASQ-3 - CBCL	Phthalates were associated with more Externalizing problems, Attention problems, and Aggressive behavior on the CBCL.	In boys, phthalates were associated with worse personal-social scores on the ASQ and more Externalizing problems on the CBCL.
Colicino et al. (2021)	PROGRESS N=514 (50.4% female)	Phthalates in maternal urine in the second and third trimesters (averaged)	4-6 years - BASC-2 (Externalizing composite and Attention and Hyperactivity subscales only)	One phthalate metabolite positively associated with Hyperactivity scores.	Significant positive and negative associations between different phthalate metabolites and Hyperactivity scores in girls only.
Cowell et al. (2015)	WTC N=107-109 (47-48% female)	PBDEs in cord plasma	4 years - CBCL (Attention subscale only)	PBDEs were marginally associated with more Attention Problems at age 4.	No significant sex differences.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Dalsager et al. (2019)	Odense Child Cohort N=948 (55% female)	Pyrethroids and OP pesticides (chlorpyrifos) in maternal urine in GW 28	27 months - CBCL 1.5-5 ADHD scale	Pyrethroids and the combination of pyrethroids and OP pesticides were each associated with significantly greater odds of scoring above the 90th percentile.	Combined pyrethroids and OP pesticides were associated with significantly greater odds of scoring above the 90th percentile in boys only.
Dalsager et al. (2021)	Odense Child Cohort N=1138 (% female not specified)	PFAS in maternal serum in the second trimester	2 and 5 years - CBCL 1.5-5 (ADHD scale only)	No significant associations.	No significant interactions.
Daniels et al. (2004)	ALSPAC N=1054 (% female not specified)	Hg in cord blood	18 months - DDST	No significant associations.	N/A
Davidson, Strain, et al. (2008)	Seychelles Child Development Study, N=229-265 (50.7 % females)	Hg in maternal hair for	**25 months** - A-not-B test - Delayed Spatial Alternation (DSA) **30 months** - BSID-II	Hg was marginally associated with lower PDI scores on the BSID-II at **30 months**.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Day et al. (2021)	TIDES N=501 (51.5% female)	Phthalates in maternal urine in early (GW 11) and late (GW 33) pregnancy	4- 6 years - BASC-2 - SRS-2	Phthalates at GW 11 were positively associated with the SRS-2 Total score and negatively associated with the BASC-2 Adaptive Skills scale.	GW 11 phthalates were positively associated with SRS-2 (significantly in boys, marginally in girls) and negatively associated with BASC-2 Adaptive Skills in girls only. GW 33 phthalates were positively associated with Externalizing Problems in boys only.
de Water et al. (2019)	Endocrine Disruption in Pregnant Women: Thyroid Disruption and Infant Development Study N=106 (43% female)	PBDEs in maternal blood in first half of pregnancy (around GW 12)	5 years - BRIEF-P	Significant positive associations of PBDEs with the Global Executive Composite (GEC), the Flexibility Index (FI), and the Inhibitory Self-Control Index (ISCI). Marginal positive association with the Emergent Metacognition Index (EMI).	N/A
Desrochers-Couture et al. (2018)	MIREC N=609 (51.2% female)	Pb in maternal blood in first and third trimester and cord blood	3-4 years - WPSSI-III	No significant associations.	Significant negative association between cord blood Pb and PIQ in boys only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Dewey et al. (2023)	APrON N=448 (49.6% female)	Phthalates in maternal urine around GW 17	2 years - Bailey-III - BRIEF-P - CBCL 1.5-5	N/A	In boys, phthalates were associated with lower cognitive, language, and motor scores on the Bailey-III. In girls, phthalates were associated with worse inhibitory control, flexibility, and metacognition on the BRIEF-P, and more Externalizing problems on the CBCL.
Ding et al. (2015)	Laizhou Wan Bay Cohort N=149-192 (47-49% female)	PBDEs in cord blood	12 and 24 months - GDS	At **24 months**, PBDEs were associated with lower Language and Social Development scores.	No significant associations in sex-stratified analyses (data not shown in paper).
Doherty et al. (2017)	Mount Sinai Children's Environmental Health Center N=258 (45.7% female)	Phthalates in maternal urine between GW 25 and 40	2 years - BSID-II	No significant associations.	Significant associations between phthalates and both MDI and PDI scores, where these associations were negative in girls and positive in boys.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Doherty et al. (2020)	New Hampshire Birth Cohort N=318-371 (50.9-51.3% female)	Arsenic, Mn, and Pb in maternal toenails (2-8 weeks post-partum as markers of middle pregnancy) and in infant toenails (at 6 weeks of life as markers of late pregnancy)	3 years - SRS-2 - BASC-2	Negative association between infant toenail Mn and Adaptive Skills on the BASC-2. Negative association between infant toenail Pb and BASC-2 Externalizing Problems.	In boys, negative association between maternal and infant toenail Mn and BASC-2 Adaptive Skills, and positive association between maternal toenail Pb and Externalizing Problems. In girls, toenail Pb was positively associated with BASC-2 Adaptive Skills and negatively associated with Externalizing Problems.
Donauer et al. (2016)	HOME N=327 (55% female)	OP pesticides in maternal urine at GW 16 and 26	**1, 2, and 3 years** - BSID-II **5 years** - WPPSI-III	No significant associations.	N/A
Engel et al. (2011)	Mount Sinai Children's Environmental Health Study N=169-276 (%female not specified)	OP pesticides in maternal urine and PCBs in maternal blood in the third trimester	1 and 2 years - BSID-II	PCBs were associated with lower MDI scores on the BSID-II at **age 1**. OP pesticide metabolites were associated with lower BSID-II MDI scores at **age 2**.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Engel et al. (2016)	4 cohorts: Mount Sinai, CCCEH, HOME, and CHAMACOS N=936 (51.8% female)	OP pesticides in maternal urine between GW 16 and 32	2 years - BSID-II	Marginally significant negative association between OP pesticides and MDI in the analysis pooling the four cohorts together.	N/A
England-Mason et al. (2021)	APrON N=312 (49.2% female)	BPA in maternal urine in the second trimester	**2 and 4 years** - BRIEF-P	No significant associations.	No significant sex differences.
England-Mason et al. (2020)	APrON N=313 (50.1% female)	Phthalates in maternal urine in the second trimester (around GW 17)	3-4 years - BASC-2 - CBCL 1.5-5	Phthalates were associated with significantly greater odds of scoring in the Borderline or Clinical ranges on the BASC-2 Hyperactivity, Aggression, and Externalizing Problems scales as well as the CBCL Externalizing Problems scale.	No significant interactions with sex. In sex-stratified linear regression, significant positive association between one phthalate metabolite and BASC-2 Externalizing Problems in boys only.
Eskenazi et al. (2006)	CHAMACOS N=360 (51.4% female)	DDT and DDE in maternal serum around GW 26 or at delivery	**12 and 24 months** - BSID	At **age 12 months**, DDT was associated with lower MDI and PDI scores. At **age 24 months**, DDT was associated with lower MDI scores.	At age **12 months**, DDT was associated with lower PDI scores in boys only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Eskenazi et al. (2007)	CHAMACOS N=372-447 (50.6% female)	OP pesticides in maternal urine between GW 14 and 27	**12 and 24 months** - BSID **24 months** - CBCL (Attention Problems, ADHD, and PDD scales only)	At **age 24 months**, OP pesticides were associated with lower MDI scores and greater odds of scoring in the Clinical or Borderline range on the Pervasive Developmental Disorder syndrome scale.	No sex differences.
Eskenazi et al. (2013)	CHAMACOS N=212-266 (% female not specified)	PBDEs in maternal serum around GW 26	**5 years** - CBCL 1.5-5 (Attention Problems and ADHD Problems subscales only) - Conners' Kiddie CPT (K-CPT) - MSCA Gross Motor skills - WRAVMA Pegboard Test - Behavioral Assessment and Research System (BARS) Finger-Tapping task - WPPSI-III (Performance IQ)	**At age 5**, PBDEs were associated with more errors of omission and a greater ADHD Confidence Index on the K-CPT. PBDEs were also associated with worse nondominant hand fine motor skills on the WRAVMA Pegboard.	At **age 5**, the negative association between PBDEs and nondominant hand WRAVMA Pegboard scores was significant in boys only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Eskenazi et al. (2018)	Venda Health Examination of Mothers, Babies and the Environment (VHEMBE) N=681-705 (48.2% female)	DDT and DDE in maternal blood and pyrethroids in maternal urine at delivery	**1 and 2 years** - Bayley-III	**At age 1**, DDE was associated with higher Cognitive scores while pyrethroid metabolites were associated with lower Social-Emotional scores. **At age 2**, one pyrethroid metabolite was associated with lower scores for Expressive Communication and the Language Composite.	In **1-year-old boys**, DDE and DDT were associated with higher Cognitive scores while pyrethroid metabolites were associated with lower Social-Emotional scores. In **1-year-old girls**, one pyrethroid metabolite was associated with a lower Language Composite score. In **2-year-old girls**, DDT was associated with lower Fine Motor scores while pyrethroid metabolites were associated with lower scores for the Receptive Communication, Expressive Communication, and Gross Motor Skills subscales, and the Language and Motor Composites.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
					In **2-year-old boys**, pyrethroid metabolites were associated with higher Gross Motor skills and Motor Composite scores.
Fage-Larsen et al. (2023)	Odense Child Cohort N=614 (46.3% female)	Chlorpyrifos and pyrethroids in maternal urine around GW 28	5 years - CBCL 1.5-5 (ADHD scale only)	No significant associations.	No significant sex differences in sex-stratified models.
Farmus et al. (2021)	MIREC N=596 (51.2% female)	Fluoride in maternal urine in each trimester	3-4 years - WPPSI-III	Significant negative associations between prenatal fluoride and FSIQ and PIQ.	Significant negative associations between prenatal fluoride and FSIQ and PIQ in boys.
Forns et al. (2014)	INMA, N=385 (48.31% female)	Pb and Arsenic in maternal urine in the first and third trimester	4 years - MSCA - Teacher-report ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (ADHD-DSM-IV)	No significant associations.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Forns, Lertxundi, et al. (2012)	INMA N=1391 (50.9% female)	DDE and PCBs in maternal blood between GW 7 and 26	14 months - BSID	Significant negative association between PCBs and PDI scores.	N/A
Forns, Torrent, Garcia-Esteban, Grellier, et al. (2012)	INMA N=355 (50.1% female)	PCBs in cord blood	4 years - MSCA	Significant negative associations between PCBs and the GCI, Verbal, Perceptual-Performance, Quantitative, and Memory scores.	N/A
Freire et al. (2018)	INMA N=302 (28.5% female)	Pb, Hg, Mn and Arsenic in placental tissue	4-5 years - MSCA	Arsenic was associated with lower Executive Function and Verbal Executive Function scores and greater odds of low Quantitative scores. Mn was associated with a better Memory Span, greater odds of low scores in the Perceptual-Performance domain and lower odds of low scores in the Quantitative domains. Hg was associated with greater odds of low scores in the Verbal domain.	Significant interaction with sex in the association between Hg and the GCI, but the association was not significant in either boys or girls individually.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Freire et al. (2020)	INMA N=191 (% female not specified)	BPA in placental tissue	4-5 years - MSCA	BPA was associated with greater odds of scoring below the 20th percentile on the MSCA Verbal and Gross Motor subscales.	BPA was associated with greater odds of scoring below the 20th percentile on the MSCA Verbal and Gross Motor subscales in boys only.
Gao et al. (2022)	Ma'anshan Birth Cohort study, N=1660 (48.4% female)	Phthalates in maternal urine in each trimester	2.5-6 years - WPPSI-IV (Chinese version)	First trimester phthalates were negatively associated with FSIQ, Verbal Comprehension, and Processing Speed. Second trimester phthalates were positively associated with Processing Speed.	N/A
Gascon et al. (2011)	INMA N=88 (51.1% female)	PBDEs measured in cord blood	4 years - MSCA	No significant associations.	N/A
Gascon et al. (2012)	INMA N=290 (51.6% female)	PBDEs in colostrum 48-96 hours after delivery	14 months - BSID	Marginal negative association between PBDE exposure and MDI scores.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Gascon et al. (2015)	INMA N=336-367 (49% female)	Phthalates in maternal urine at GW 12 and 32	**1 year** - BSID **4 years** - MSCA - California Preschool Social Competence Scale (CP-SCS) (teacher report) - ADHD Criteria of the ADHD-DSM-IV (teacher report)	At **age 4**, phthalates were associated with lower PDI scores, better teacher-reported Social Competence on the CP-SCS, and fewer teacher-reported Inattention symptoms on the ADHD-DSM-IV scale.	No significant sex differences.
Geiger et al. (2023)	IKIDS N=68 (48.5% female)	BPA in maternal urine, pooled across 5 timepoints in early, mid, and late pregnancy	26-28 months - CBCL 1.5-5	BPA was associated with more aggressive behavior.	No sex differences.
Golding, Gregory, Iles-Caven, et al. (2016)	ALSPAC N=2875-3264 (% female not specified)	Hg in maternal blood early in pregnancy	**18, 30, and 42 months** - DDST	At **18 and 42 months**, Hg was associated with better Total DDST scores. Hg was also associated with a better Fine Motor subscale score at **18 months** and better Social Skills subscale score at **42 months**.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Golding, Gregory, Emond, et al. (2016)	ALSPAC N=1599-2776 (% female not specified)	Hg in maternal blood in early pregnancy	**4 years** - SDQ	**At age 4**, Hg was associated with fewer parent-reported Conduct problems and Peer problems. Hg was also associated with marginally less Hyperactivity.	N/A
Goodman, Bashash, et al. (2022)	ELEMENT N=348 (52% female)	Fluoride in maternal urine in one or more trimesters	**4 and 5 years** - MSCA (Spanish version; VIQ, PIQ, and FSIQ only)	At **ages 4 and 5**, fluoride was associated with lower FSIQ and PIQ on the MSCA.	No significant interactions with sex.
Goodman, Hall, et al. (2022)	MIREC N=366 (49.2% female)	Fluoride in maternal urine, averaged across 3 trimesters	3-4 years - WPPSI-III (FSIQ only)	Fluoride was associated with lower FSIQ.	Fluoride was associated with lower FSIQ in boys.
Goodman et al. (2023)	MIREC N=522 (51.3% female)	PFAS in maternal urine in the first trimester (around GW 11)	3-4 years - WPPSI-III (FSIQ, VIQ, & PIQ) - BRIEF-P (Working Memory & Plan/Organize subscales only)	No significant associations.	PFAS were associated with lower FSIQ and PIQ in boys.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Goudarzi et al. (2016)	Hokkaido Study N=173-183 (50.4-52.0% female)	PFAS (PFOA and PFOS) in maternal blood after the second trimester	**18 months** - BSID-II	No significant associations.	No significant sex differences.
Gunier et al. (2015)	CHAMACOS N=197 (57.4% female)	Mn in dentine from children's shed teeth	**12 and 24 months** - BSID-II	No significant associations at either age.	No significant interactions with sex.
Guo et al. (2019)	Sheyang Mini Birth Cohort Study N=377 (48.8% female)	OP pesticide (chlorpyrifos) in maternal urine at delivery	3 years - GDS	No significant associations.	N/A
Haggerty et al. (2021)	Archives for Research on Child Health N=77 (% female not specified)	Phthalates in maternal urine in the first trimester	3-6 years - SRS-2 - CBCL	No significant associations.	In boys, phthalates were positively associated with SRS-2 scores when controlling for CBCL Internalizing and Externalizing scores.
Hamadani et al. (2010)	Matlab, Bangladesh, N=2112 (47% female)	Arsenic in maternal urine in GW 8 and 30	18 months - BSID-II	No significant associations.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Hamadani et al. (2011)	Matlab, Bangladesh, N=1700 (48% female)	Arsenic in maternal urine in GW 8 and 30	5 years - WPPSI	GW 8 Arsenic was negatively associated with VIQ. GW 30 Arsenic was negatively associated with PIQ.	In girls, arsenic at GW 8 and GW 30 was associated with lower VIQ, while only GW 30 arsenic was associated with lower FSIQ.
Hansen et al. (2021)	Odense Child Cohort N=427-658 (46.9-47.3% female)	BPA measured in maternal urine in GW 28	**2 and 5 years** - CBCL 1.5-5 (ADHD and Pervasive Developmental Disorder scales only)	BPA was associated with higher odds of scoring over the 75th percentile on the Pervasive Developmental Disorder (PDD) subscale at **age 5**.	BPA was associated with higher odds of scoring over the 75th percentile on the Pervasive Developmental Disorder (PDD) subscale at **age 5** in girls.
Harris et al. (2018)	Project VIVA N=875-986 (48% female)	PFAS in maternal plasma between GW 4 and 21	**3 years** - WRAVMA	At **age 3**, PFAS was associated with better Total, Visual-Motor, and Visual-spatial scores on the WRAVMA.	No sex differences (data not shown in paper).
Herbstman et al. (2010)	CCCEH N=96-152 (49.3% female)	PBDEs in cord blood	**12, 24, and 36 months** - BSID-II **48 months** - WPPSI-R	PBDEs were associated with marginally lower PDI scores at **12 months** and significantly lower MDI scores at **24 months**. PBDEs were also associated with lower VIQ, PIQ, and FSIQ at **48 months**.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Horton et al. (2011)	CCCEH N=348 (53.2% female)	Pyrethroids in maternal plasma within 48h of delivery and cord plasma	3 years - BSID-II	No significant associations.	N/A
Hsi et al. (2014)	Taipei Mackay Memorial Hospital N=83 (56.6% female)	Hg in meconium at birth	3 years - Bayley-III	No significant associations.	N/A
Hu et al. (2006)	Mexican Institute of Social Security (IMSS) N=146 (47.9% female)	Pb in maternal blood in each trimester (approx. GW 12, 24, and 36)	2 years - BSID-II (MDI only)	First trimester Pb was negatively associated with MDI scores.	N/A
Hu et al. (2016)	Laizhou Wan Birth Cohort N=410 (47.8%)	Hg in maternal blood at delivery and cord blood	1 year - GDS	No significant associations between maternal blood Hg and GDS scores. Cord blood Hg was positively associated with scores in the Adaptive domain and the Social domain.	N/A
Huang et al. (2022)	China-Anhui Birth Cohort Study (C-ABCS) N=1782	BPA in maternal blood in the first trimester	3-4 years - BRIEF-P - SDQ	BPA was associated with a significantly higher relative risk for Conduct Problems and Prosocial Behavior Problems on the SDQ.	In boys, BPA was associated with a significantly higher relative risk for Conduct Problems on the SDQ.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- Conners' Abbreviated Symptom Questionnaire (C-ASQ) Chinese version - Clancy Autism Behavior Scale	BPA above the 25th percentile was associated with increased relative risk of ADHD on the C-ASQ in children aged 3 years, but not in children aged 4 years.	In girls, BPA was associated with a significantly higher relative risk for Inhibitory Self-Control Impairment and Emergent Metacognition Impairment on the BRIEF-P and Peer Relationship Problems, and Prosocial Behavior Problems on the SDQ.
Ibarluzea et al. (2022)	INMA N=316 (49.6-53.9% female)	Fluoride in maternal urine in the first and third trimesters	**1 year** - BSID (MDI only) **4 years** - MSCA (Verbal, Performance, Quantitative, Memory and GCI)	At **age 4**, average prenatal fluoride was associated with better MSCA scores for Performance, Quantitative, Verbal, Memory, and General Cognitive.	At **age 4**, fluoride was associated with better Verbal, Memory, and General Cognitive scores on the MSCA in boys only.
Ibroci et al. (2022)	TIDES N=244 (100% female)	BPA in maternal urine at GW 11	4-5 years - BASC-2 - SRS-2	No significant associations.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Ikeno et al. (2018)	Hokkaido Study N=141 (53.2% female)	PCBs in maternal blood after the second trimester	3.5 years - K-ABC Japanese version	No significant associations with the Mental Processing Composite Score (MPCS).	Negative associations between some PCBs and the MPCS in boys only.
Irizar et al. (2021)	INMA N=839 (49% female)	Mn in maternal serum in the first trimester	4 years - MSCA	No significant associations.	Significant positive associations with the GCI, Verbal, and Quantitative scores in girls only.
Jedrychowski et al. (2007)	Krakow Epidemiologic Study N=270-374 (48.9% female)	Hg in cord blood	**12, 24, and 36 months** - BSID-II	In **longitudinal** analyses, Hg was associated with marginally lower PDI scores. At **12 months**, Hg was associated with lower MDI and PDI scores.	N/A
Jedynak et al. (2021)	HELIX N=708 (44.2% female)	Exposome study with 47 markers of exposure. Of relevance for this review:	3-7 years - SDQ (Externalizing scale only)	BPA and one phthalate were negatively associated with the Externalizing Problems scale. However, the association was no longer significant after correcting for multiple comparisons.	No significant interactions with child sex.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
		DDT, DDE, PCBs, PBDEs, PFAS, Arsenic, Pb, Mn, and Hg in maternal blood. Phthalates, BPA, and OP pesticides in maternal urine.			
Jensen et al. (2019)	Odense Child Cohort N=658 (47.1% female)	BPA in maternal urine in the third trimester	18-36 months - CBCL (ADHD subscale only)	No significant associations.	No significant sex differences in stratified analyses.
Ji et al. (2019)	Shanghai-Minhang Birth Cohort Study N=192-307 (42.0-44.8% female)	PBDEs in cord blood	**2 and 4 years** - CBCL	N/A	In **longitudinal analyses**, PBDEs were associated with more attention problems in boys only. At **age 2 years**, the middle tertile of PBDEs was associated with more Aggressive Problems in girls only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Jia et al. (2023)	Wuhan Medical and Healthcare Center for Women and Children N=2361 (47.5% female)	Pb in maternal blood in the first trimester	24 months - BSID	Pb was associated with greater odds of having an MDI below the cut-off for cognitive developmental delays (score of 79 or below).	Pb was associated with greater odds of having an MDI below the cut-off for cognitive developmental delays in girls only.
Jiang et al. (2022)	Taiwan Longitudinal Birth Cohort Study N=53 (58.5% female)	Pb and Arsenic in meconium at birth	3 years - Bayley-III	No significant associations.	N/A
Jiang et al. (2020)	Wuhan Medical and Healthcare Center for Women and Children N=456 (% female not specified)	BPA in maternal urine in each trimester	24 months - BSID	Exposure to BPA in the second trimester was negatively associated with the MDI score.	N/A
Jones et al. (2018)	Growing Up in Singapore Toward Healthy Outcomes (GUSTO) N=373 (42% female)	Phthalates in maternal hair between weeks 26 and 28	2 years - Bayley-III	No significant associations.	N/A
Kim et al. (2021)	Environment and Development of Children (Korea) N=344-477 (46.4-46.8% female)	Phthalates in maternal urine in the second trimester	**4 years** - SCQ	Phthalates were associated with worse outcomes on the SCQ.	Phthalates were associated with worse SCQ scores in boys.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Kim et al. (2018)	Children's Health and Environmental Chemicals in Korea (CHECK) N=140 (51% female)	BPA and phthalates in maternal urine; Pb, Hg, and Mn in maternal blood and cord blood; PCBs, PBDEs, and DDT in maternal blood. All samples were collected at the time of delivery	13-24 months - BSID-II - Social Maturity Scale (SMS) - CBCL	Significant negative association between phthalates and the BSID-II MDI and PDI scores, and the SMS Social Quotient (SQ). Significant negative association between Pb and the PDI. Compared to children scoring in the Normal range, children scoring in the “Clinical range” on the CBCL Externalizing Problems scale had significantly higher exposure to maternal and cord blood Hg, and maternal blood PCBs and PBDEs.	In boys, cord blood Hg was negatively associated with the MDI. In girls, BPA was negatively associated with the MDI while phthalates were negatively associated with the MDI, PDI, and SQ scores.
Kornvig et al. (2021)	Adapting to Climate Change, Environmental Pollution and Dietary Transition (ACCEPT)	DDE, PCBs, PBDEs, PFAS, Pb, and Hg in maternal blood in the first trimester	3-5 years - SDQ (Hyperactivity score)	PCBs were associated with higher odds of an abnormal Hyperactivity score while PFAS was associated with lower odds of an abnormal Hyperactivity score.	No significant sex differences in stratified analyses.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
	N=102 (46.1% female)				
Kupsco et al. (2020)	PROGRESS N=571 (49.9% female)	Mn in maternal blood in the second trimester (GW 12-34), third trimester (GW 26-38), and at delivery	4-6 years - MSCA	No main effect of Mn on MSCA scores.	No significant sex differences (interactions or sex-stratified analyses).
Kyriklaki et al. (2016)	Rhea Study N=695 (48.4% female)	PCBs and DDE in maternal blood around the 3rd and 4th month of pregnancy	4 years - MSCA - SDQ	PCBs were negatively associated with Working Memory on the MSCA.	No significant interactions with sex.
Lee et al. (2018)	Dhaka Community Hospital, Bangladesh N=764 (49.5% female)	Mn in cord blood	20-40 months - Bayley-III (cognitive score only)	Significant negative association between Mn and cognitive scores.	N/A
C. Li et al. (2020)	Wuhan Women and Children Medical Care Center N=544 (44.1% female)	Mn in maternal urine prior to delivery	2 years - BSID	Significant negative association between Mn and PDI scores.	No significant sex differences in stratified analyses.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
F. Li et al. (2020)	Shanghai-Minhang Birth Cohort Study N=745 (44.0% female)	BPA in maternal urine in GW 12-16)	**2 and 4 years** - CBCL 1.5-5	**Longitudinal analysis only.** BPA was associated with greater risk of scoring above the 75th percentile on the CBCL Externalizing Problems scale.	BPA was associated with a greater risk of scoring above the 75th percentile on the CBCL Aggressive Behavior and Externalizing Problems scales in boys.
Liew et al. (2018)	Danish National Birth Cohort (DNBC) N=1592 (47.8% female)	PFASs in maternal plasma in early pregnancy (approx. GW 8-9)	5 years - WPPSI-R	Significant positive association between one PFAS and Verbal IQ.	No significant sex differences (interactions or sex-stratified analyses).
Lim et al. (2017)	Environment and Development of Children N=304 (47.4% female)	BPA in maternal urine between GW 14 and 27	4 years - Korean Social Communication Questionnaire (K-SCQ)	Non-linear association where BPA at or above a threshold was associated with a higher SCQ Total score.	Significantly higher SCQ Social Communication score with BPA at or above the threshold in girls only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Lin et al. (2013)	Taiwan Birth Panel Study N=230 (44.3% female)	Pb, Hg, Mn, and Arsenic in cord blood. Each exposure was categorized as low (below the 75th percentile) or high (at or above the 75th percentile)	2 years - CDIIT	Children in the high Mn group had significantly lower scores in the Cognitive and Language domains. Children in the high Pb group had significantly lower scores in the Global, Cognitive, and Social domains.	N/A
Lin et al. (2017)	Taiwan Birth Panel Study (TPBS) N=148-208 (43.8-47.3% female)	BPA in cord plasma	**2 years** - CDIIT	No significant associations.	No significant sex differences.
Liu et al. (2022)	Guangxi Birth Cohort Study N=703 (35% female)	Pb, Mn and Arsenic in maternal serum between first and third trimester	2-3 years - GDS Chinese version	Pb exposure was negatively associated with Gross Motor scores in single and multiple metal models.	Significant negative association between Pb and Gross Motor scores in boys only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Liu et al. (2021)	APrON N=394 (50.8% female)	BPA in maternal urine in the second trimester	2 years - Bayley-III	No significant associations.	Significant interaction with sex for the Social Emotional score whereby the association was significant and positive in girls, but marginally significant and negative in boys.
Liu, Chen, et al. (2014)	Guangdong, China N=243 (46.9% female)	Pb in cord blood	**12, 24, and 36 months** - BSID-II	Pb was associated with lower MDI scores at **each age** and with lower PDI scores at **36 months** only.	N/A
Liu et al. (2016)	Sheyang County, China N=310 (42.6% female)	OP pesticides in maternal urine prior to delivery	2 years - GDS	OP pesticide metabolites were associated with significantly higher odds of scoring in the "developmental delay" range in the Adaptive domain.	In boys, significantly higher odds of "developmental delay" in the Adaptive domain.
Llop et al. (2017)	INMA N=1362 (47.7% female)	Hg in cord blood	4-5 years - MSCA	Significant positive associations between Hg and MSCA Numeric, Memory, and GCI scores.	N/A
Loftus et al. (2021)	Conditions Affecting Neurocognitive Development and Learning in Early	Phthalates in maternal urine in the third trimester	4-6 years - Bayley-III (language score) - SB-5 (FSIQ)	No significant associations.	No significant sex differences.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
	Childhood (CANDLE) Study N=1015 (50.6% female)				
Lynch et al. (2012)	New York State Angler Cohort Study (NYSACS) N=44 (52.3% female)	PCBs in maternal serum around GW 8	24 months - BSID-II	No significant associations.	N/A
Marks et al. (2010)	CHAMACOS N=348 (53.2% female)	OP pesticides in maternal urine between GW 14 and 26	**3.5 and 5 years** - CBCL 1.5-5 (Attention Problems and ADHD subscales) **3.5 years** - NEPSY-II Visual Attention subtests **5 years** - Conners Kiddie (K-CPT)	At **3.5 years**, OP pesticide metabolites were marginally associated with more CBCL Attention problems and ADHD symptoms. At **5 years**, OP pesticide metabolites were associated with greater odds of having an ADHD Confidence Index over the 70th percentile on the K-CPT, more Attention problems and ADHD symptoms on the CBCL.	At **3.5 and 5 years**, OP pesticide metabolites were associated with more CBCL Attention Problems and ADHD symptoms in boys. At **5 years**, OP pesticide metabolites were also associated with a greater ADHD Confidence Index on the K-CPT in boys.
Minatoya et al. (2016)	Hokkaido Study N=328 (51.8% female)	Phthalates in maternal blood samples between GW 23 and 41	**18 months** - BSID-II	No significant associations.	No significant associations in sex-stratified analyses.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Minatoya et al. (2017)	Hokkaido Study N=285 (55.4% female)	BPA in cord blood	**18 months** - BSID-II **42 months** - K-ABC Japanese version - CBCL/2-3 Japanese version	At **42 months**, BPA was associated with marginally more Externalizing Problems and marginally higher Attention syndrome scores on the CBCL.	At **42 months**, BPA was associated with marginally more Externalizing problems in girls only.
Minatoya et al. (2018)	Hokkaido Study N=458 (45.4% female)	BPA and phthalates, maternal serum in the first trimester	5 years - SDQ	One phthalate metabolite was associated with significantly higher odds of Conduct Problems. BPA was associated with significantly higher odds of poor Prosocial Behavior.	In girls, one phthalate metabolite was associated with higher odds of Hyperactivity-Inattention problems. The association between BPA and Prosocial Behavior was significant in boys only.
Mora et al. (2018)	ISA study (Costa Rica), N=355 (49.9% female)	Mn in maternal hair and maternal blood at 1-2 prenatal visits	1 year - Bayley-III	Hair Mn was negatively associated with the Social-Emotional composite score.	In boys, significant negative association between Mn and the Social-Emotional score. In girls, significant negative association between Mn and the Cognitive score.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Munk Andreasen et al. (2023)	Odense Child Cohort N=658 (47.1% female)	Phthalates in maternal urine around GW 28	2-4 years - CBCL 1.5-5 (ADHD scale only)	One phthalate was associated with fewer symptoms of ADHD.	One phthalate was associated with fewer symptoms of ADHD in girls only.
Munoz-Rocha et al. (2018)	PROGRESS N=473 (48.3% female)	Mn in maternal blood in the third trimester and in cord blood	2 years - Bayley-III	Maternal blood and cord blood Mn were each negatively associated with the Cognitive, Motor, and Language scores.	N/A
Mustieles et al. (2023)	SEPAGES N=406 (46.3% female)	BPA in maternal urine in the second (GW 17) and third (GW 33) trimesters	3 years - SRS-2	Phthalates were associated with marginally better social development scores. BPA was associated with marginally worse social development.	Phthalates were associated with worse scores in boys and better scores in girls. BPA was associated to marginally higher scores in girls.
Myers et al. (2000)	Seychelles Child Development Study N=711	Hg in maternal hair	66 months - CBCL	No significant associations.	No significant interactions with sex.
Nakajima et al. (2017)	Hokkaido Study N=121-190 (25.6-47.9% female)	PCBs in maternal blood in the second trimester	**18 months** - BSID-II	N/A	In girls, PCBs were positively associated with the MDI scores.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Nakiwala et al. (2018)	Étude des Déterminants pré et post natals du développement et de la santé de l'Enfant (EDEN) N=452 (0% female)	BPA and phthalates in maternal urine between GW 22 and 29	5-6 years - WPPSI-III	No significant associations.	N/A
Nisevic et al. (2019)	PHIME N=257 (48.2% female)	Hg in cord blood	18 months - Bayley-III	No significant associations.	N/A
Niu et al. (2019)	Shanghai-Minhang Birth Cohort Study N=533 (44.3% female)	PFAS in maternal plasma in GW 12-16	4 years - ASQ-3, Simplified Chinese version	PFAS were associated with significantly greater risk ratios in the Personal-Social domain.	PFAS were associated with greater risk ratios in the Personal-Social domain in girls only. In boys, PFOA was associated with a significantly lower risk ratio in the Gross Motor domain.
Nozadi et al. (2021)	Navajo Birth Cohort Study (NBCS) N=327 (50.2% female)	Arsenic in maternal urine. Pb and Mn in maternal blood. Samples collected at GW 36 or delivery.	10-13 months - Ages and Stages Questionnaire Inventory (ASQ:I)	Significant negative associations between Pb and Fine Motor skills and between As and Problem Solving skills.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Ntantu Nkinsa et al. (2020)	MIREC N=607 (51.2% female)	OP pesticides in maternal urine in the first trimester	3-4 years - WPPSI-III	No significant associations.	Significant negative association between OP pesticides and Verbal IQ in boys only.
Oh et al. (2022)	Hamamatsu Birth Cohort (HBC) Study N=598 (48.2% female)	PFAS (PFOA and PFOS only) in cord blood	**14, 18, 24, 32, and 40 months** - Mullen Scales of Early Learning (MSEL)	PFOA was negatively associated with the Early Learning Composite at **18 month**s. PFOA was positively associated with the Fine Motor subscale at **24 months**. PFOS was positively associated with the Expressive Language subscale at **24 and 32 months**.	In girls, PFOA was negatively associated with the Composite score at **18 months**, the Visual Reception subscale at **18 and 40 month**s, and the Receptive Language subscale at **18 months**. In boys, PFOA was positively associated with the Visual Reception subscale at **14 months** while PFOS was positively associated with Expressive Language at **24 months.**
Osorio-Valencia et al. (2015)	Four municipalities in Morelos, Mexico	DDE in maternal serum in each trimester	60 months - MSCA	No significant associations.	No significant interactions with sex.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
	N=167 (41.3% female)				
Ostrea et al. (2012)	Bucalan Provincial Hospital, Philippines N=696 (45.6% female)	Carbamates and pyrethroids in meconium	24 months - Griffiths Mental Development Scales	Carbamate pesticide was negatively associated with the Griffiths Motor score.	N/A
Oulhote et al. (2020)	MIREC N=556 (52.8% female)	Phthalates in maternal urine in the first trimester	3-4 years - SRS-2	Phthalates were positively associated with Total, Social Cognition, Social Communication, Social Motivation, and Restricted Interests/Repetitive Behaviors scores.	All positive associations (see previous column) were significant in boys only. One phthalate metabolite (MEP) was negatively associated with Social Motivation in girls.
Palumbo et al. (2000)	Seychelles Main Cohort Study N=711 (% female not specified)	Hg in maternal hair	66 months - MSCA	No significant associations.	N/A
Pan et al. (2019)	Laizhou Wan Birth Cohort N=188-368 (48.6-48.9% female)	BPA in maternal urine at delivery	**12 and 24 months** - GDS	At **12 months**, BPA was associated with lower Adaptive Development.	At **12 months**, BPA was associated with lower Social Development in girls. At **24 months**, BPA was associated with lower Language Development in girls.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Parajuli et al. (2015)	Chitwan Valley, Nepal N=100 (53% female)	Pb and Arsenic in cord blood	36 months - BSID-II	No significant associations.	N/A
Park et al. (2010)	Two districts in Slovakia-Michalovce N=258-760 (48.7-52.7% female)	PCBs in maternal (N=760) and cord serum (N=258) at delivery	16 months - BSID-II	Cord and maternal blood PCBs were negatively associated with MDI and PDI scores.	N/A
Perera et al. (2012)	CCCEH N=198 (56.1% female)	BPA in maternal urine between GW 24 and 40	3-5 years - CBCL	N/A	Significant association between BPA and Aggressive Behavior was positive in boys and negative in girls.
Philippat et al. (2017)	Étude des déterminants pré et post natals du développement et de la santé de l'enfant (EDEN) N=464-529 (0% female)	Phthalates and BPA in maternal urine between GW 22 and 29	**3 and 5 years** - SDQ	No significant associations at either age after correcting for multiple comparisons.	N/A (sample was boys only)
Polanska et al. (2014)	REPRO_PL N=165 (56.4% female)	Phthalates in maternal urine in the third trimester (GW 30 to 34)	24 months - Bayley-III	Phthalate metabolites were negatively associated with Motor Development.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Prpic et al. (2017)	Rijeka, Croatia (part of the PHIME study) N=205 (50.3% female)	Hg in cord blood	18 months - Bayley-III	No significant associations.	N/A
Qi et al. (2022)	Xuan Wei County, China N=419 (53.2% female)	Pyrethroids in maternal urine in each trimester (GW 8-12, 20-23, and 32-35)	1 year - Bayley-III	Pyrethroids in the second trimester were negatively associated with Cognition, Language, and Adaptive Behavior. Pyrethroids in the third trimester were positively associated with Language and Adaptive Behavior.	N/A
Qian et al. (2019)	Wuhan Women and Children Medical Care Center N=476 (46.6% female)	Phthalates in maternal urine in each trimester (averaged)	2 years - BSID-China Revision	PDI scores were negatively associated with certain phthalate metabolites and positively associated with others. In trimester-specific analyses, first trimester phthalates were negatively associated with PDI scores and third trimester phthalates were negatively associated with MDI scores.	Phthalates in the third trimester were negatively associated with MDI and positively associated with PDI in boys only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Quaak et al. (2016)	Linking Maternal Nutrition to Child Health (LINC) N=59 (35.6% female)	PFAS in cord blood	18 months - CBCL (Externalizing and ADHD scales)	No significant associations.	PFOA was negatively associated with Externalizing Problems in boys. Overall PFAS were negatively associated with Externalizing Problems in girls.
Rauh et al. (2006)	New York Presbyterian Medical Center and Harlem Hospital, New York City N=254 (53.5% female)	OP pesticide (Chlorpyrifos) in cord plasma Exposure was dichotomized as high (highest tertile) or low (undetectable, and first and second tertiles)	**12 months** - BSID-II **24 months** - BSID-II **36 months** - BSID-II - CBCL 1.5-5 (Externalizing, Attention Problems, ADHD, and PDD scales)	At **36 months**, children in the High Exposure group had marginally lower MDI scores and significantly lower PDI scores on the BSID-II. Children in the High Exposure group also had significantly greater odds of having Attention Problems, ADHD Problems, or PDD Problems on the CBCL.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Reardon et al. (2023)	APrON N=489 (48.5% female)	PFAS and Hg in maternal blood in the second trimester	2 years - Bailey-III	PFAS were negatively associated with Cognitive and Language scores, but positively associated with Adaptive scores. There was a non-linear positive association where Hg above a given threshold was associated with higher Language scores.	There were significant interactions between PFAS and sex for adaptive behaviour, whereby associations were positive in girls and null in boys.
Ribas-Fito et al. (2003)	Flix, a village in Catalonia, Spain N=102 (41.7% female)	PCBs and DDE in cord serum	13 months - BSID - Griffiths Mental Development Scales	DDE was negatively associated with MDI and PDI scores of the BSID, as well as scores on the Locomotor, Social, Eye-Hand Coordination, and Performance scales of the Griffiths Scales.	N/A
Ribas-Fito et al. (2006)	Ribera d'Ebre cohort and Menorca cohort N=475 (49.4% female)	DDT and its metabolite DDE in cord serum	4 years - MSCA	DDT was negatively associated with all MSCA scores (GCI, Memory, Verbal, Executive Function, Memory Span, and Verbal Memory). DDE was negatively associated with Memory.	Sex-stratified analyses were only conducted between DDT and GCI, Verbal, and Memory scores. DDT was negatively associated with all 3 scores in girls.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Rolland et al. (2023)	SEPAGES N=151 (44% female)	Phthalates in maternal urine (averaged from 3 samples per day for 7 consecutive days) in each of the second (GW 18) and third (GW 34) trimesters	24 months - Eye-tracking tasks (used to derive mean fixation duration, novelty preference, percent time looking at eyes, and reaction time)	Phthalates were associated with reduced fixation duration, more time looking at eyes, and greater novelty preference.	In girls, phthalates were associated with reduced fixation duration. In boys, phthalates were associated with longer reaction times.
Rothenberg et al. (2016)	Maternal and Child Health Hospital, Daxin County, China N=270 (53% female)	Hg in maternal hair	12 months - BSID-II	Significant negative association between Hg and MDI scores.	N/A
Rothenberg et al. (2021)	Daxin County, China N=190-264 (45.2-53.0% female)	Hg in maternal hair	**1 and 3 years** - BSID-II	In **longitudinal analyses** and at **age 1**, Hg was associated with lower MDI scores.	At **age 1**, Hg was associated with lower MDI scores in boys.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Roze et al. (2009)	GIC: Groningen Infant COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens) N=62 (38.7% female)	PCBs, DDE, and PBDEs in maternal blood at GW 35	5-6 years - Movement ABC - Developmental Coordination Disorder Questionnaire (DCD-Q) - WPPSI-R - NEPSY-II - Rey's Auditory Verbal Learning Test (AVLT) - TEA-Ch - CBCL parent - CBCL teacher - ADHD questionnaire (ADHD-vragenlijst [AV])	PBDEs were associated with poorer verbal memory on the AVLT and sustained attention on the TEA-Ch. PCBs were marginally related to more Externalizing problems on the CBCL teacher form and better coordination on the Movement ABC. DDE was marginally related to better coordination on the Movement ABC and PIQ on the WPPSI-R.	N/A
Ruel et al. (2019)	RENCO: Risk of Endocrine Contaminants on Human Health GIC: Groningen Infant COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of	PCBs in maternal blood around GW 35	**18 months** (both cohorts) - BSID-II-NL (Dutch version) **30 months** (RENCO cohort only) - BSID-II-NL	At **18 months**, PCBs were associated with greater odds of having a delayed MDI in the GIC cohort, but not the combined GIC-RENCO cohort.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
	Human Health Risks of Complex Environmental Mixtures of Organohalogens) **18 months**: N=181 (42% female) **30 months**: N=63 (43% female)				
Shah-Kulkarni et al. (2016)	MOCEH N=965 (48% female) at 6 months	Pb in maternal blood in early pregnancy (before GW 20) and at delivery (representing late pregnancy) and in cord blood	**12, 24, and 36 months** - Korean version of the Bayley-II (K-BSID-II)	No significant associations.	N/A
Signes-Pastor et al. (2022)	HOME N=260 (54% female)	Arsenic in maternal urine at GW 16 and 26	**1, 2, and 3 years** - BSID-II (MDI only) **5 years** - WPPSI-III (FSIQ only)	No significant associations at any age.	N/A
Simeone et al. (2022)	Michalovce and Svidnik districts, Slovakia	PCBs in maternal blood at delivery	4 years - CBCL - WPPSI-III	No significant associations.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
	N=472 (50.9% female)				
Skogheim et al. (2020)	Norwegian Mother, Father and Child Cohort Study (MoBA) N=944 (48.6% female)	PFAS in maternal plasma from GW 17	36 months - Preschool Age Psychiatric Assessment (PAPA) Interview - SB-5 (VIQ, PIQ, and memory)	Some PFAS were negatively associated with nonverbal working memory while others were positively associated with verbal working memory on the SB-5.	The positive association between PFAS and verbal working memory was significant in boys only.
Snoj Tratnik et al. (2017)	PHIME (Ljubljana, Slovenia and Rijeka, Croatia) N=361 (48.5% female)	Hg in cord blood and maternal hair	18 months - Bayley-III	Hg in cord blood was negatively associated with Motor and Fine Motor scores. Hg in maternal hair was negatively associated with Fine Motor scores.	N/A
Soler-Blasco et al. (2020)	INMA N=1179 (% female not specified)	Mn in maternal blood in the first trimester	1 year - BSID	No significant associations.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Soler-Blasco et al. (2022)	INMA N=807 (% female not specified)	Arsenic in maternal urine in the first trimester	4 years - MSCA	Some arsenic metabolites were inversely associated with GCI, Verbal, Quantitative, Memory, Executive Function and Working Memory scores, while others were positively associated with Verbal scores.	Marginally significant interactions with sex, where there were significant negative associations of arsenic metabolites with Executive Function and Fine Motor skills in boys.
Soler-Blasco et al. (2023)	INMA N=549 (49% female)	Arsenic in maternal urine in the first trimester	4 years - MSCA	Significant negative association between arsenic and the Quantitative scale. Arsenic was marginally associated with lower scores on the GCI, Memory, Working Memory, and Gross Motor scales.	N/A
Spratlen et al. (2020)	WTC N=302 (49.7% female)	PFAS in maternal blood at delivery and cord blood	**1, 2, and 3 years** - BSID-II **4 years** - WPPSI-R	At **age 3**, certain PFAS were associated with higher MDI scores, while others were associated with lower PDI scores. At **age 4**, certain PFAS were associated with worse Verbal IQ.	At **age 2**, one PFAS was associated with higher MDI scores in girls only. At **age 3**, the positive association with MDI scores and the negative association with PDI scores were significant in girls only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
					At **age 4**, one PFAS was associated with higher Verbal IQ in girls only.
P. W. Stewart et al. (2003)	Oswego Study N=194-197 (% female not specified)	PCBs in cord blood (classified into 4 groups: Nondetectable, Low, Medium, High)	**38 and 54 months** - MSCA	At **38 months**, PCBs were associated with lower GCI, Perceptual, and Quantitative scores.	N/A
P. Stewart et al. (2003)	Oswego Newborn and Infant Development Project N=197 (55% female)	PCBs in cord blood	4.5 years - Michigan Catch-the-Cat Test (computerized CPT)	PCBs were associated with more commission errors.	N/A
Strain et al. (2015)	Seychelles Nutrition Cohort 2 (NC2) N=1265 (% female not specified)	Hg in maternal hair	20 months - BSID-II - Infant Behavior Record-Revised (IBQ-R)	No significant associations.	N/A
Takser et al. (2003)	Robert Debré Maternity (Paris, France) N=247 (45% female)	Mn in maternal blood, cord blood, maternal hair, newborn hair, and placental tissue (all collected at delivery/birth)	**3 years** - MSCA (GCI, nonverbal memory, attention, and hand skills composites)	At **age 3**, cord blood Mn was associated with lower MSCA scores, specifically Attention, Non-verbal memory, and Hand skills.	At **age 3 years**, cord blood Mn was associated with lower scores for the Hand Skill composite boys.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Tatsuta et al. (2012)	Tohoku Study of Child Development (TSCD) N=306 (48.7% female)	PCBs, Hg, and Pb in cord blood	30 months - CBCL/2-3 Japanese version (Externalizing composite)	No significant associations.	N/A
Tatsuta et al. (2014)	Tohoku Study of Child Development (TSCD) N=387 (47.8% female)	PCBs, Hg, and Pb in cord blood	42 months - K-ABC	PCBs were negatively associated with the Sequential and Mental Processing scores.	Negative association between PCBs and Sequential and Mental Processing was significant in boys only.
Tatsuta et al. (2017)	Tohoku Study of Child Development (TSCD) N=566 (49.6% female)	Hg in cord blood	18 months - BSID-II - Kyoto Scale of Psychological Development (KSPD)	Negative association between Hg and BSID-II PDI scores.	Negative association between Hg and PDI scores was significant in boys only.
Taylor et al. (2017)	ALSPAC N=404–2217 (43.3–49.3% female)	Pb in maternal blood in early pregnancy (approx. GW 9-13)	**4 years** - WPPSI-R UK	No significant associations.	No sex differences.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Tellez-Rojo et al. (2013)	ELEMENT N=135 (52.6% female)	Phthalates in maternal urine in the third trimester	**24, 30, and 36 months** - BSID-II	**Longitudinal analyses**. No significant associations.	Significant negative association between phthalates and MDI scores in girls. Significant positive association between phthalates and PDI in boys.
Thilakaratne et al. (2023)	Project VIVA N=900 (48.4% female)	Arsenic, Hg, Pb, and Mn in maternal blood in early pregnancy	**3 years** - WRAVMA (overall, visual-motor, fine-motor, & visual-spatial) - PPVT-III	Arsenic was associated with higher visual-motor scores on the WRAVMA at age 3.	N/A
Thistle et al. (2022)	Norwegian Mother, Father and Child Cohort Study (MoBA) N=340 (54% female)	OP pesticides in maternal urine around GW 17	3-4 years - BRIEF-P (parent) - BRIEF-P (teacher) - SB-5 (Verbal Working Memory and Non-verbal Working Memory) - NEPSY-II (Statue) - Cookie Delay Task (CDT)	OP pesticide metabolites were positively associated (i.e., worse outcomes) with parent and teacher ratings of Emotional control, Inhibition, and Working Memory on the BRIEF-P.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Thomson et al. (2023)	Barwon Infant Study (BIS) N=1074 (48.3% female)	Phthalates measures in maternal urine at GW 36	**2 and 4 years** - CBCL 1.5-5 (autism spectrum problems scale only) - SDQ (peer relationships subscale only)	No significant associations.	N/A
Torres-Olascoaga et al. (2020)	ELEMENT N=218 (53.2% female)	Phthalates in maternal urine in each trimester	48 months - MSCA	Mean phthalates (across trimesters) were negatively associated with Motor scores. Associations were strongest in the first trimester, generally significant but weak in the second trimester, and null in the third trimester.	One first trimester phthalate metabolite was negatively associated with the GCI in boys only.
Torres-Sanchez et al. (2009)	Four municipalities in Morelos, Mexico N=270 (41.1% female)	DDE in maternal blood at each trimester	**12, 18, 24, and 30 months** - BSID-II (Spanish version)	**Longitudinal analyses** show a marginally significant negative association between third trimester DDE and MDI scores.	No significant interactions with sex.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Torres-Sanchez et al. (2013)	Four municipalities in Morelos, Mexico N = 203 (42.4% female)	DDT and DDE in maternal blood at the baseline interview and/or at each trimester visit	**42, 48, 54, and 60 months** - MSCA	In a **longitudinal analysis**, third trimester DDE was associated with a lower GCI, and Quantitative, Verbal, and Memory component scores.	No significant interactions with child sex.
Tsai et al. (2023)	Taiwan Maternal and Infant Cohort Study N=408 (45.6% female)	Pb, arsenic and phthalates in maternal urine in the third trimester	4 years - CBCL 1.5-5 (ASD, ADHD, and ODD scales only)	Phthalates were associated with higher scores on the ADHD scale.	N/A
Valeri et al. (2017)	Two clinics in Dhaka Community Hospital Trust in Bangladesh Clinic 1 (Pabna): N=409 (49.6% female). Clinic 2 (Sirajdikhan): N=416 (48.7% female)	Pb, Mn, and Arsenic in cord blood	20-40 months - Bayley-III (Cognitive and Language scores only)	**Pabna**: Negative association between the metal mixture and Cognitive scores when all metals were at or above the 60th percentile (compared to the median), with the effect being driven by Mn. **Sirajdikhan**: Marginally significant negative associations between Pb and the Cognitive score and between As and the Language score.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Vejrup et al. (2022)	Norwegian Mother, Father and Child Cohort Study (MoBA) N=2936 (% female not specified)	Hg in maternal blood at GW 18	3 and 5 years - CBCL (Externalizing composite only)	No significant associations.	N/A
Vermeir et al. (2021)	FLEHS (Flemish Environment and Health Study) N=214 (50% female)	PCBs and DDE in cord blood	**12 months** - Infant Behaviour Questionnaire (IBQ) **3 years** - Snijders-Oomen nonverbal intelligence test (SON 2.5-7; Intelligence: reasoning and visuospatial abilities)	No significant associations on scales of interest.	At **12 months**, no sex differences on scales of interest. At **3 years**, PCBs were associated with lower Reasoning, Performance, and Total IQ scores on the SON in boys.
Vuong et al. (2021)	HOME N=241 (53.9% female)	PFAS in maternal serum at GW 16, 26, and/or at delivery	**5 years** - ADHD portion of the Diagnostic Interview Schedule for Children–Young Child (DISC-YC).	PFAS was associated with more total symptoms of ADHD and hyperactivity.	No sex differences.
Wang et al. (2021)	Shanghai, China N=242 (48.4% female)	DDE in cord blood	18 months - Bayley-III	Positive association between DDE and scores on the Language composite.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Wang et al. (2015)	Taiwan Maternal and Infant Cohort Study N=120 (60.8% female)	PFAS in maternal serum in the third trimester	**5 years** - WPPSI-R	One PFAS was associated with lower PIQ on the WPPSI-R.	N/A
Wang et al. (2017)	Laizhou Wan Birth Cohort N=235-237 (% female not specified)	OP pesticides in maternal urine at delivery	**12 and 24 months** - GDS	At **24 months**, OP pesticide metabolites were associated with lower Social Development scores.	**12 months**: N/A At **24 months**, OP pesticide metabolites were associated with lower Social Development in boys.
A. Wang et al. (2023)	Wuhan Women's and Children's Health Care Center N=1041 (46.9% female)	OP pesticides and pyrethroids in maternal urine samples from each trimester (averaged)	2 years - BSID Chinese Revision (BSID-CR)	No significant associations.	OP pesticides and pyrethroids were associated with lower MDI scores in boys only.
H. Wang et al. (2023)	Shanghai Birth Cohort Study N=2031 (48.2% female)	PFAS in maternal blood between GW 9 and 16	4 years - WPPSI-IV	No significant associations.	No significant interactions with sex or sex differences.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
P. W. Wang et al. (2023)	Taipei City Hospital N=56-94 (50% female)	BPA in maternal urine at recruitment (GW 27-38)	**2-3 years** - Bailey-III **4-6 years** - WPPSI-IV	N/A	At **age 2-3 years**, BPA was associated with higher motor scores on the Bailey-III in girls. At **age 4-6 years**, BPA was associated with lower Verbal Comprehension Index scores on the WPPSI-IV in girls.
Watkins et al. (2016)	ELEMENT N=159-187 (51-52% female)	Pyrethroids (3-PBA) in maternal urine in the third trimester	**24 and 36 months** - BSID-II Spanish version	At **24 months**, pyrethroids were associated with marginally lower MDI scores.	At **24 months**, pyrethroids were marginally associated with lower MDI scores in girls only.
Wei et al. (2023)	Nanjing Maternity and Child Health Care Hospital N=138-172 (53.5-57.3% female)	OP pesticides in maternal blood at enrollment (GW 13-26)	**12 and 18 months** - ASQ	At **12 months**, OP pesticides were associated with lower scores for communication, gross motor, and fine motor subscales. At **18 months**, OP pesticides were associated with lower scores for communication and problem-solving subscales.	In **12-month-old** boys, OP pesticides were associated with better problem-solving scores. In **18-month-old boys**, OP pesticides were associated with lower problem solving and better communication scores.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
					In **12-month-old** girls, OP pesticides were associated with lower problem solving and personal- social scores. OP pesticides were also associated with lower communication scores in girls at both **12 and 18 months old**.
Whyatt et al. (2012)	CCCEH N=319 (52.7% female)	Phthalates in maternal urine in the third trimester	3 years - BSID-II - CBCL	Some phthalate metabolites were associated with significantly lower PDI scores on the BSID-II as well as greater odds of having a psychomotor delay.	Significant negative association between one phthalate metabolite and MDI on the BSID-II in girls only.
Xie et al. (2022)	Shanghai-Minhang Birth Cohort Study N=614 (44.4% female)	PFAS in maternal blood between GW 12 and 16	**2 and 4 years** - CBCL 1.5-5	N/A	In sex-stratified models, PFAS were associated with more aggressive behaviour, attention problems, and externalizing problems in both boys and girls.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Yamamoto et al. (2022)	Japan Environment and Children's Study (JECS) N=3,787 (49.5% female)	Mn in maternal blood in the second and third trimesters and in cord blood	**12, 18, 24, 30, and 36 months** - ASQ, 3rd edition, Japanese version (J-ASQ-3)	Cord blood Mn was associated with lower Gross Motor skills at **12 months.** Maternal blood Mn was also associated with lower scores for Gross Motor and Personal-social at **12 months**, Fine Motor at **18 months**, Gross Motor and Fine Motor at **24 months**, Communication, Gross Motor, and Problem Solving at **30 months**, as well as Communication, Gross Motor, and Problem Solving at **36 months**.	At **36 months**, maternal blood Mn was associated with lower Fine Motor skills in girls only.
Yamazaki et al. (2018)	Hokkaido Study N=115-164 (51.8-55.7% female)	DDE in maternal blood after the second trimester	**18 months** - BSID-II	No significant associations.	N/A
Yao et al. (2022)	Laizhou Wan Birth Cohort N=274 (49% female)	PFAS in cord blood	1 year - GDS	Negative association between PFAS and the developmental quotient (DQ) for the Gross Motor and Adaptive domains.	PFAS were related to lower DQs in the Gross Motor, Adaptive, and Social domains in boys only.
Yu et al. (2022)	Wuhan, China N=961 (47.5% female)	Phthalates in maternal urine in the first trimester	2 years - BSID-Chinese Revision	Phthalates were negatively associated with PDI scores.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Yu et al. (2016)	Laizhou Wan Birth Cohort N=774 (48.6% female)	Mn in cord serum	1 year - Gesell Developmental Inventory (GDI)	Significant negative association between Mn and the Gross Motor score. Marginally significant negative association between Mn and the Personal-Social score.	N/A
Zhang et al. (2019)	Sheyang Mini Birth Cohort Study N=377 (51.2% female)	Carbamates in maternal urine prior to delivery	2 years - GDS	Significant negative associations between carbamates and the Adaptive, Social, and Total scores.	In girls, carbamates were significantly associated with lower Adaptive scores and marginally associated with lower Total scores.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Zhang et al. (2023)	Sheyang Mini Birth Cohort Study N=352-565 (45.1% female)	PFAS in cord blood	**1 year** - Developmental Screen Test for Children ages 0-6 years (DST) **2 and 3 years** - GDS	At **age 1**, PFAS were associated with lower motor function and marginally higher overall developmental quotient. One PFAS was associated with significantly higher mental function while another PFAS was associated with marginally lower mental function. At **age 2**, PFAS were associated with lower Motor, Social, Adaptive, Language, and Average DQs. At **age 3**, PFAS were associated with lower Social and Adaptive DQs.	At **age 1**, PFAS were associated with higher mental function scores in boys. In girls, PFAS were associated with lower motor function and marginally lower overall DQ. At **age 2**, PFAS were associated with lower Motor, Adaptive, and Average DQs in girls. At **age 3**, there were no significant associations in either boys or girls in stratified models.
Zheng et al. (2022)	Guangxi Birth Cohort Study (GBCS) N=750 (37.6% female)	Phthalates in maternal blood in the first, second, or third trimester	2-3 years - GDS	N/A	In boys, one phthalate was associated with lower scores for gross motor while another phthalate was associated with higher gross motor, social, and total scores.
Zhou et al. (2023)	Shanghai Maternal-Child Pairs Study	PFAS in cord serum	**12 and 24 months** - ASQ-3	No significant associations at either age.	No sex differences at either age.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
	N =1285 (47.2% female)				
Zhu et al. (2020)	Ma'anshan Birth Cohort (MABC) N=2128 (48.0% female)	Phthalates in maternal urine samples from each trimester	3-6 years - WPPSI-IV Chinese version	In analyses with repeated measures for exposure, there was a significant negative association between phthalates and the Visual Spatial Index (VSI), and positive associations with the Fluid Reasoning Index (FRI) and Working Memory Index (WMI). There were both positive and negative associations (depending on the phthalate metabolite) with the Verbal Comprehension Index (VCI) and FSIQ scores.	In boys, there was a negative association between phthalates and the VSI, and positive associations with the VCI, FRI, and Processing Speed Index (PSI). There were both positive and negative associations with the FSIQ depending on the specific phthalate metabolite. In girls, there was a significant positive association between phthalates and the PSI.

Table A3

Result Summary for Studies in School-Age (6-12 Years)

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Bashash et al. (2017)	ELEMENT N=211-287 (55.0-55.7% female)	Fluoride in maternal urine in each trimester	6-12 years - Wechsler Abbreviated Scale of Intelligence (WASI)	Fluoride was associated with lower FSIQ scores.	N/A
Bashash et al. (2018)	ELEMENT N=210 (55.2% female)	Fluoride in maternal urine between GW 10 and 38	6-12 years - Conners Rating Scales Revised (CRS-R) - Conners CPT-II	Significant positive associations between fluoride and CRS-R scores for inattention and total ADHD symptoms.	N/A
Bauer et al. (2017)	PHIME N=136 (58.1% female)	Mn in child deciduous teeth	10-14 years - Virtual Radial Arm Maze (VRAM)	No significant associations.	Mn was positively associated with distance and working memory errors in girls only.
Bauer et al. (2021)	PHIME N=190 (53.8% female)	Mn in child deciduous teeth	10-14 years - WISC-III	Significant positive associations between Mn and two subtests of the WISC-III (Digits Backward and Block Design).	Significant interaction with sex on the Picture Completion subtest, where the association with Mn was positive in boys only.
Beck et al. (2023)	Odense Child Cohort (N=967; 47% female)	PFAS in maternal serum at GW 8-16	6-7 years - WISC-V (FSIQ and VCI only)	Maternal PFAS were associated with significantly lower FSIQ and VCI scores.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Beranger et al. (2017)	PELAGIE N=204 (53.4% female)	Glycol ether (solvent) metabolites in maternal urine before GW 19	6 years - WISC-IV (Verbal Comprehension and Working Memory Indices only) - NEPSY Design Copying and Arrows subtests	Concentrations of one metabolite in the highest tertile were associated with lower WISC-IV Verbal Comprehension scores. Concentrations of another metabolite in the highest tertile were associated with lower NEPSY Design Copying scores.	N/A
Binter et al. (2019)	PELAGIE N=73 (61.6% female)	Glycol ether (solvent) in maternal urine before GW 19	10-12 years - Go/No-Go Task	Glycol ether metabolites were associated with longer reaction times and lower performance scores.	N/A
Binter et al. (2020)	PELAGIE N=95 (56.8% female)	OP pesticides in maternal urine before GW 19	10-12 years - Go/No-Go task	Moderate OP pesticide metabolite levels were associated with fewer commission errors and marginally associated with lower performance scores and longer response latency.	In girls, moderate levels of one type of metabolite were associated with fewer commission errors while moderate levels of another metabolite were associated with more commission errors.
Bornehag et al. (2021)	Swedish Environmental Longitudinal Mother and Child, Asthma	BPA in maternal urine in the first trimester	7 years - WISC-IV	No significant associations.	No significant sex differences.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
	And Allergy (SELMA) N=803 (50.4% female)				
Bouchard et al. (2011)	CHAMACOS N=329 (53.2% female)	OP pesticides in maternal urine at GW 5-27 and 18-39	7 years - WISC-IV	OP pesticide metabolites were associated with lower Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed, and FSIQ scores.	No significant interactions with sex.
Boucher et al. (2016)	QC Inuit, N=265 (51.7% female)	Hg, Pb, and PCBs measured in cord blood	11 years - Santa Ana Form Board - NES3 Finger Tapping Test - SB Copying subtest	Hg was associated with lower scores on the Santa Ana Form Board and the NES3 Finger Tapping. Pb was associated with lower scores on the NES3 Finger Tapping Test.	N/A
Boucher, Burden, et al. (2012)	Cord Blood Monitoring Program N=196 (55.1% female)	Hg, Pb, and PCBs in cord blood	9-13 years - Go/No-Go task	Pb was associated with fewer correct responses on Go and No-Go trials.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Boucher, Jacobson, et al. (2012)	Cord Blood Monitoring Program N=279 (50.5% female)	Hg, Pb, and PCBs in cord blood	8-14 years - CBCL (Teacher; Externalizing and Attention Problems) - Disruptive Behaviour Disorders Rating Scale (Teacher)	Hg was associated with more teacher-reported Attention Problems on the CBCL and greater odds of being classified as having ADHD-Inattentive type and ADHD-Hyperactive-Impulsive type on the DBD.	N/A
Braun, Bellinger, et al. (2017)	HOME N=198 (54% female)	Phthalates and BPA in maternal urine at GW 16 and 26	8 years - Virtual Morris Water Maze	Phthalate metabolites were associated with a reduced distance to complete the maze.	Phthalate metabolites were associated with longer latency, shorter distance, and slower speed in girls, but shorter latency, faster speed, and more time in the correct quadrant in boys.
Carrizosa et al. (2021)	INMA N=1240 (48.5% female)	PFAS in maternal plasma in the first trimester (around GW 13)	7 years - Attention Network Test (ANT) - N-back task	No significant associations.	No significant sex differences.
Cartier et al. (2016)	PELAGIE N=231 (49.4% female)	OP pesticides in maternal urine before GW 19	6 years - WISC-IV (Verbal Comprehension and Working Memory only)	Significant positive association between the highest tertile of OP metabolites and Verbal Comprehension score.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Casas et al. (2015)	INMA N=438 (47% female)	BPA in maternal urine in the first and third trimesters (averaged)	7 years - SDQ - Conners Parent Rating Scales (CPRS)	No significant associations.	Interaction with sex for parent-reported Hyperactivity, but results were null for both sexes.
Chevrier et al. (2016)	PELAGIE N=159 (approx. 52.4% female)	PBDEs in cord serum	6 years - WISC-IV (Verbal Comprehension and Working Memory only)	No significant associations.	N/A
Choi et al. (2014)	Faroe Islands N=182 (50% female)	Hg in cord blood and PCBs in maternal serum at GW 34	7 years - BNT - NES Finger Tapping - NES CPT - WISC-R Digit Span Forward and Block Design subtests - SB Copying and Recall subtests - CVLT	Hg was associated with lower CVLT scores on the Short Delay trial. Hg was also marginally associated with lower scores on the CVLT Learning trial and the SB Immediate Recall subtest.	N/A
Claus Henn et al. (2018)	ELEMENT N=138 (53.6% female)	Mn in child deciduous teeth	6-16 years - WRAVMA	No significant associations.	No significant sex differences.
Cowell et al. (2015)	WTC N=107-109 (47-48% female)	PBDEs in cord plasma	**6 years** - CBCL (Attention subscale only)	No significant associations.	No significant sex differences.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Cowell et al. (2018)	CCCEH N=212 (56% female)	PBDEs in cord plasma	9-14 years - Children's Memory Scale (CMS)	No significant associations.	PBDEs were associated with lower Auditory Working Memory in girls.
Dai et al. (2023)	Sheyang Mini Birth Cohort Study N=389 (44.5% female)	Arsenic in maternal urine prior to delivery	6 years - CBCL	No significant associations.	No significant sex differences.
Daniel, Balalian, Insel, et al. (2020)	CCCEH N=322 (52.5% female)	Phthalates in maternal urine in the third trimester	7 years - Conners Parent Rating Scale (CPRS) - CBCL	No significant associations.	Phthalate metabolites were associated with more Social Problems on the CPRS and more Externalizing Problems on the CBCL in boys. In girls, phthalate metabolites were associated with lower Hyperactivity and Impulsivity and ADHD Index scores on the CPRS.
Daniel, Balalian, Whyatt, et al. (2020)	CCCEH N=209 N=209 (55.5% female)	Phthalates in maternal urine in the third trimester	11 years - Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition	No significant associations.	Phthalate metabolites were associated with a decrease in Fine- and Gross Motor functions in girls.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Davidson et al. (2000)	Seychelles Pilot Cohort N=87 (45% female)	Hg in maternal hair	9 years - WISC-III Block Design, Information, Vocabulary, Digit Span, and Coding subtests - CVLT - BNT - Beery VMI - WRAML Design subtest - Grooved Pegboard - Trail Making - Finger Tapping	No significant associations.	In boys, Hg was associated with higher scores on the BNT, Grooved Pegboard, and Beery VMI. In girls, Hg was associated with lower scores on the Grooved Pegboard with the dominant hand.
Davidson, Sloane-Reeves, et al. (2008)	Seychelles Main Study N=346 (% female not specified)	Hg in maternal hair	10 years - Bender Visual Motor Gestalt Test	Hg was marginally associated with lower scores on the Reproduction task.	No significant interactions.
Deroma et al. (2013)	Friuli Venezia Giulia region N=154 (50% female)	Hg in maternal hair	7-9 years - WISC-III	Hg was marginally associated with lower FSIQ.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Engel et al. (2011)	Mount Sinai Children's Environmental Health Study N=169-276 (% female not specified)	OP pesticides in maternal urine and PCBs in maternal blood in the third trimester	**6 years** - WPPSI-III **7-9 years** - WISC-IV	No significant associations at either time point or in analyses combining both ages.	N/A
Eskenazi et al. (2013)	CHAMACOS N=212-266 (% female not specified)	PBDEs in maternal serum around GW 26	**7 years** - Conners' ADHD/DSM-IV Scales (CADS) - CADS teacher - BASC-2 (Hyperactivity and Attention Problems subscales only) - BASC teacher (same subscales as parent report) - MSCA Gross Motor skills - WRAVMA Pegboard Test - BARS Finger Tapping - WISC-IV	**At age 7**, PBDEs were associated with a higher ADHD Confidence Index, DSM-IV Total score, and Inattentive subscale score on the maternal-report CADS. PBDEs were also associated with lower nondominant hand fine motor skills on the WRAVMA Pegboard and lower Verbal Comprehension IQ on the WISC-IV.	No significant sex differences.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Ethier et al. (2015)	Nunavik Child Development Study N=27 (33.3% female)	Pb, Hg, and PCBs in cord blood	8-12 years - Posner Attention-Shift Paradigm	Pb was associated with more commission errors. PCBs were associated with more omission errors.	N/A
Evans et al. (2014)	Study for Future Families II (SFFII) N=153 (49.7% female)	BPA measured in maternal urine	6-10 years - CBCL (parent)	No significant associations.	BPA was associated with more Rule-Breaking behaviour, Externalizing problems, Oppositional/Defiant behaviour, and Conduct problems in boys.
Factor-Litvak et al. (2014)	CCCEH N=328 (52.7% female)	Phthalates in maternal urine during the third trimester (approx. GW 34)	7 years - WISC-IV	Phthalates were associated with lower FSIQ, Processing Speed, Perceptual Reasoning, Verbal Comprehension, and Working Memory.	Phthalates were associated with lower Working Memory in girls and lower Verbal Comprehension and Processing Speed in boys. Phthalates were also associated with lower FSIQ and Perceptual Reasoning scores in boys or girls depending on the specific metabolite.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Fei and Olsen (2011)	Danish National Birth Cohort (DNBC) N=526-787 (53.3-48.5% female)	PFASs in maternal blood at the first antenatal care visit (GW 8)	7 years - SDQ - Developmental Coordination Disorder Questionnaire (DCDQ)	The lowest two tertiles of PFOA had significantly lower odds of having a high Hyperactivity score on the SDQ, but the linear trend was not significant.	N/A
Forns, Torrent, Garcia-Esteban, Caceres, et al. (2012)	INMA N=393 (51% female)	DDE and PCBs in cord blood	11 years - CPT-II	No significant associations.	N/A
Fortenberry et al. (2014)	ELEMENT N=187 (47.6% female)	Chlorpyrifos in maternal urine in each trimester	6-11 years - BASC - Conners' Parental Rating Scales-Revised - Conners CPT	No significant associations.	Marginally significant positive association between chlorpyrifos and the ADHD Index of the CPT in boys. The middle tertile of chlorpyrifos was marginally associated with more BASC Attention Problems in girls.
Friedman et al. (2023)	PHIME N=140 (55.7% female)	Mn in child deciduous teeth	10-14 years - CVLT-C	Mn was associated with fewer intrusion errors.	In boys, Mn was associated with fewer intrusion errors.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Fruh et al. (2019)	Project VIVA N=1006 (49.3% female)	Pb in maternal blood in the second trimester	7 years - BRIEF (parent and teacher) - SDQ (parent and teacher)	Pb was associated with worse executive function on the Shift and Plan/Organize subscales of the parent-reported BRIEF.	Pb was associated with worse executive function on the parent-reported BRIEF Behavioral Regulation Index, Plan/Organize subscale, and General Executive Composite in girls.
Fruh et al. (2021)	Project VIVA N=1009 (49.3% female)	Pb, Hg, and Mn in maternal blood in the second trimester	6-11 years - BRIEF (parent and teacher) General Executive Composite (GEC) only	Pb was marginally associated with worse executive function (i.e., higher parent-reported GEC), while Mn and Hg were marginally associated with better executive function (i.e., lower GEC).	N/A
Furlong et al. (2014)	Mount Sinai Children's Environmental Health Study N=136 (50% female)	OP pesticides in maternal urine in GW 25-40	7-9 years - SRS	No significant associations.	OP pesticide metabolites were associated with worse SRS scores in boys only.
Gari et al. (2022)	REPRO_PL N=436 (51% female)	Pb in cord blood and Hg measured in maternal hair	7 years - SDQ - Intelligence and Development Scales (IDS)	Hg was associated with more Hyperactivity on the SDQ. Pb was marginally associated with lower Fluid and Crystallized IQ on the IDS.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Gascon et al. (2015)	INMA N=336-367 (49% female)	Phthalates in maternal urine at GW 12 and 32	**7 years** - SDQ - Conners Parent Rating Scales (CPRS)	At **age 7**, phthalates were associated with fewer parent-reported Inattention symptoms and lower ADHD Index on the CPRS.	No significant sex differences.
Gaspar et al. (2015)	CHAMACOS N=244-266 (% female not specified)	DDT and DDE in maternal blood in the second trimester	**7 and 10.5 years** - WISC-IV	**In longitudinal analyses**, DDT was associated with lower Processing Speed. In age-specific analyses, DDT was marginally associated with lower Processing Speed **at age 7**.	No significant sex differences.
Ghassabian et al. (2018)	Upstate KIDS Study N=918 (49.2% female)	PFAS and BPA in newborn dried blood spots	7 years - SDQ	PFOA and BPA were associated with lower Prosocial Behavior.	No significant interactions with sex.
Golding, Gregory, Emond, et al. (2016)	ALSPAC N=1599-2776 (% female not specified)	Hg in maternal blood in early pregnancy	**6 and 11 years** - SDQ (parent report) **7-8 and 10-11 years** - SDQ (teacher report)	**At age 6**, Hg was associated with fewer parent-reported Peer problems.	N/A
Goodman, Bashash, et al. (2022)	ELEMENT N=348 (52% female)	Fluoride in maternal urine in one or more trimesters	**6-12 years**	At **age 6-12 years**, fluoride was associated with lower FSIQ, Performance IQ, and Verbal IQ.	No significant interactions with sex.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- Wechsler Abbreviated Scale of Intelligence (WASI; Spanish version)		
Grandjean et al. (2001)	Faroe Islands N=435 (50.6% female)	Hg in cord blood and PCBs in umbilical cord tissue	7 years, - NES2 Finger Tapping Test - NES2 Hand-Eye Coordination Test - NES2 CPT - WISC-R Digit Span, Similarities, and Block Design subtests - Bender Visual Motor Gestalt Test - CVLT (Children) - BNT	PCBs were associated with longer reaction times on the NES2 CPT and lower scores on the BNT. Hg was associated with more missed responses and longer reaction time on the CPT. Hg was also associated with lower scores on the WISC-R Digit Span forward, the BNT, and the CVLT.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Grandjean et al. (2012)	Faroe Islands N=923 (% female not specified)	Hg, PCBs, and DDE in cord blood	7 years - NES2 Finger Tapping Test - NES2 Hand-Eye Coordination Test - NES2 CPT - WISC-R Digit Span, Similarities, and Block Design subtests - Bender Visual Motor Gestalt Test - CVLT (Children) - BNT	PCBs were associated with more missed responses on the CPT and lower scores on the BNT, Finger Tapping, and CVLT short-term recall. DDE and Hg were each associated with higher reaction time and more missed responses on the CPT and lower scores on the BNT.	N/A
Grandjean et al. (2014)	Faroe Islands N=675 (% female not specified)	Hg in cord blood	7 years - NES2 Finger Tapping Test - NES2 Hand-Eye Coordination Test - NES2 CPT	Hg was associated with lower scores on NES2 Finger Tapping, longer reaction time and more missed items on the NES2 CPT, lower scores on BNT, and lower scores on the CVLT-C long delay.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- WISC-R Digit Span, Similarities, and Block Design subtests - Bender Visual Motor Gestalt Test - CVLT (Children) - BNT		
Grandjean et al. (2023)	Odense Child Cohort N=837 (48.0% female)	Fluoride in maternal urine at GW 28	7 years - WISC-V (FSIQ only)	No significant associations.	No significant sex differences.
Gray et al. (2005)	Collaborative Perinatal Project N=894 (45.3-62.5% female)	PCB in maternal serum in the third trimester	7 years - WISC	No significant associations.	N/A
Guo, Wu, Zhang, Li, et al. (2020)	Sheyang Mini Birth Cohort Study N=386 (46.6% female)	BPA in maternal urine at delivery	10 years - SDQ	No significant associations.	No significant sex differences.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Guo, Wu, Zhang, Qi, et al. (2020)	Sheyang Mini Birth Cohort Study N=326 (42.9% female)	Pb, Hg, pyrethroids, chlorpyrifos, and BPA in maternal urine at delivery	7 years - WISC-IV Chinese-Revised	In single-chemical models, Pb and BPA were associated with lower FSIQ. In multi-chemical models, Pb was associated with lower FSIQ scores while the overall mixture was associated with lower FSIQ when all the chemicals' concentrations were at or above the 75th percentiles.	Pb and BPA were associated with lower FSIQ in boys only.
Harley et al. (2013)	CHAMACOS N=292 (43.5-53.4% female)	BPA in maternal urine around GW 12 and 26	**7 years** - BASC-2 (teacher and parent) - Conners ADHD DSM-IV Scales **9 years** - Conners CPT	No significant associations.	BPA was associated with greater teacher-reported Aggressive Behavior in boys only.
Harris et al. (2018)	Project VIVA N=875-986 (48% female)	PFAS in maternal plasma between GW 4 and 21	**7 years** - KBIT-2 - WRAML2 (Visual Memory Index) - WRAVMA	At **age 7**, PFAS were associated with higher scores on the WRAML Design and Picture Memory subtests, lower KBIT-2 Verbal and Non-verbal IQ, and lower WRAVMA Visual--Motor scores.	No sex differences (data not shown in paper).

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Harris et al. (2021)	Project VIVA N=1080 (48.6% female)	PFAS in maternal blood between GW 4 and 21	6-10 years - SDQ (parent and teacher) - BRIEF (parent and teacher)	No consistent pattern of associations. The third quartile of one metabolite was associated with more Metacognition problems on the BRIEF (teacher-report) and more SDQ Externalizing Problems (parent- and teacher-reports). The second quartile of another metabolite was associated with better Metacognition and Global Executive Composite of the BRIEF (teacher-report).	No consistent pattern in sex-stratified analyses. One metabolite in the 3rd and 4th quartiles was associated with more Executive Function problems on the teacher-reported BRIEF in boys.
Hartley et al. (2022)	HOME N=243 (56% female)	PBDEs in maternal serum at GW 16 or 26	12 years - Social Skills Improvement System (SSIS); self-report and parent report)	No significant associations.	PBDEs were associated with lower parent-reported Social Skills and more self- and parent-reported Problem Behaviours in boys.
Herbstman et al. (2010)	CCCEH N=96-152 (49.3% female)	PBDEs in cord blood	6 years - WPPSI-R	PBDEs were associated with lower PIQ and FSIQ at age 6.	N/A
Horton et al. (2018)	ELEMENT N=133 (51.9% female)	Mn and Pb in child deciduous teeth	8-11 years - BASC-2	Mn was associated with fewer Externalizing Problems.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Hoyer et al. (2015)	INUENDO (Biopersistent organochlorines in diet and human fertility) N=1106 (46.2% female)	PFAS in maternal blood during pregnancy (specific timing not specified)	5-9 years - SDQ - Developmental Coordination Disorder Questionnaire (DCDQ)	PFAS were associated with more Hyperactivity on the SDQ.	N/A
Hoyer et al. (2018)	INUENDO (Biopersistent organochlorines in diet and human fertility) N=1023 (46% female)	PFAS in maternal plasma around GW 23-25	5-9 years - SDQ	PFAS were associated with more Hyperactivity.	N/A
Hyland et al. (2019)	CHAMACOS N=300-322	Phthalates in maternal urine in GW 13 and 26 (averaged)	**7 years** - BRIEF parent - BRIEF teacher - WISC-IV - BASC-2 parent - Conners ADHD DSM-IV Scales (CADS) parent - CADS teacher **9 years** - BRIEF parent - NEPSY Tower subtest	Phthalates were associated with better social cognition based on ENI at **age 9** and more omission errors on the CPT-II between **ages 9 and 12**.	In **longitudinal analyses**, phthalates were associated with fewer perseverative errors on the WCST as well as lower FSIQ and Working Memory on the WISC-IV in boys. In girls, phthalates were associated with better FSIQ, Working Memory, and Processing Speed on the WISC-IV, as well as better social cognition on the ENI.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- Wisconsin Card Sorting Test (WCST) - Evaluacion neuropsicologica del nino (ENI) - CADS parent - Conners CPT-II **10.5 years** - WISC-IV - BASC-2 parent - BASC-2 self-report **12 years** - BRIEF parent - WCST - NEPSY-II Affect recognition subtest - CADS parent - Conners CPT-II		
Ibarluzea et al. (2023)	INMA N=236-255 (49.8-54.2% female)	Fluoride in maternal urine in early (around GW 13) and late (around GW 32) pregnancy	8 & 10 years - Conners Parent Rating Scale Revised Short Form (CPRS-R:S) Inattention, Impulsivity, ADHD Index	No significant associations.	No significant interactions with sex.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Itoh et al. (2022)	Hokkaido Study N=772 (47.3% female)	PFAS measured in maternal blood around GW 28-32 and in cord blood	8 years - ADHD-Rating Scale (ADHD-RS)	PFAS were associated with lower odds of obtaining a high Total score, suggesting fewer overall symptoms.	In boys, PFAS were associated with lower odds of high Total and Hyperactivity-Impulsivity scores. In girls, PFAS were associated with lower odds of a high Inattention score.
Jacobson et al. (2015)	Cord Blood Monitoring Program N=282 (50.7% female)	Hg, Pb, and PCBs in cord blood	8-14 years - WISC-IV - BNT - Verbal Fluency Test (VFT)	Hg was associated with lower FSIQ, Verbal comprehension, and Perceptual Reasoning. Pb was marginally associated with lower FSIQ and significantly associated with lower Working Memory.	N/A
Jankowska et al. (2019)	REPRO_PL N=134 (% female not specified)	Phthalates in maternal urine in the third trimester	7 years - SDQ - Intelligence and Development Scales (IDS)	One phthalate metabolite was associated with Higher Fluid intelligence and Cognition on the IDS.	N/A
Julvez et al. (2013)	ALSPAC N=1311 (47.2% female)	Hg in umbilical cord tissue	8 years - WISC-III	No significant associations.	N/A
Julvez et al. (2019)	ALSPAC N=1723	Hg in umbilical cord tissue	8 years - WISC-III	No significant associations.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Julvez et al. (2021)	HELIX N=1298 (45.3% female)	Exposome DDT, DDE, PCBs, PBDEs, PFAS, Arsenic, Hg, Mn, and Pb in maternal blood. Phthalates, BPA, and OP pesticides in maternal urine.	6-11 years - Raven Coloured Progressive Matrices Test (CMP) - Attention Network Test (ANT) - N-back task	Hg was associated with better scores on the Raven CPM Test. One OP pesticide metabolite was marginally associated with poorer ANT scores.	N/A
Jusko et al. (2019)	Generation R N=708 (48.7% female)	OP pesticides in maternal urine before GW 18, between GW 18-25, and after GW 25	6 years - Snijders-Oomen Nonverbal Intelligence Test-Revised; Mosaics and Categories subtest	OP pesticides measured after GW 25 were associated with lower nonverbal IQ.	OP pesticides measured after GW 25 were associated with lower nonverbal IQ in girls only.
Jusko et al. (2012)	Collaborative Perinatal Project N=1042-1142 (49-51% female	DDT and DDE in maternal serum in the third trimester	**7 years** - WISC (FSIQ only)	No significant associations.	N/A
Kalloo et al. (2021)	HOME N=253 (55% female)	Exposome	**8 years** - WISC-IV (working memory only)	Several PFAS were associated with better Working Memory.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
		BPA, phthalates, OP pesticides, pyrethroids, and arsenic in maternal urine. PFAS, PBDEs, PCBs, and DDE in maternal serum. Hg in maternal blood. Samples collected at GW 16 and/or 26			
Kim et al. (2017)	Environment and Development of Children N=175 (48% female)	Phthalates in maternal urine between GW 14 and 27	6 years - Korean Educational Developmental Institute's WISC - Comprehensive Attention Test	No significant associations.	N/A
Kim et al. (2021)	Environment and Development of Children (Korea)	Phthalates in maternal urine in the second trimester	**6 and 8 years** - SCQ	No significant associations.	At **6 years**, phthalates were associated with worse SCQ scores in boys.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
	N=344-477 (46.4-46.8% female)				
Kobrosly et al. (2014)	Study for Future Families N=153 (49.7% female)	Phthalates in maternal urine in GW 10-39	6-10 years - CBCL	Phthalates were associated with more Aggressive Behavior, Attention Problems, Oppositional/Defiant Problems and Conduct Problems.	Individual metabolites were associated with more Attention Problems, Aggressive Behaviour, Rule-Breaking Behaviour, Externalizing Problems, Conduct Problems, and Oppositional/Defiant Problems in boys.
Lam et al. (2013)	Prince of Wales Hospital in Hong Kong N=608 (46.1% female)	Hg in cord blood	7-8 years - Hong Kong WISC (HK-WISC) - Honk Kong List Learning Test (HKLLT) - Grooved Pegboard Test - TEA-Ch - BNT	Hg was associated with lower scores on the Picture Arrangement subtest of the HK-WISC and the Short and Long delay recall test of the HKLLT.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Lane et al. (2023)	PROGRESS N=559 (49.4% female)	Mn in maternal blood and urine in the second and third trimesters and in cord blood (combined to form a multi-media biomarker mixture)	6-8 years - CANTAB Spatial Working Memory test	Mn mixture was associated with better spatial working memory and worse executive functioning skills.	Significant interaction between the Mn mixture and sex for working memory (Mn would be associated with worse working memory in girls and better working memory in boys) and for executive function (Mn would be associated with worse performance in boys).
Lee et al. (2022)	Environment and Development of Children N=414-449 (47.0-47.1% female)	Pyrethroids in maternal urine between GW 14 and 27	**6 and 8 years** - ADHD Rating Scale-IV	Pyrethroids were associated with a higher Total score at **age 6**.	The association between pyrethroids and ADHD scores at age 6 was significant in boys only.
Lee et al. (2021)	Environment and Development of Children N=502 (49.4% female)	Pb, Hg and Mn in maternal blood in the second trimester	6 years - Korean Educational Developmental Institute WISC (KEDI-WISC; FSIQ only)	The metal mixture was associated with lower FSIQ. No significant associations with between individual metals and FSIQ.	No significant sex differences.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Lien et al. (2016)	Taiwan Birth Panel Study (TBPS) and Taiwan Birth Cohort Study (TBCS) N=282 (48.6% female)	PFAS in cord blood	7 years - SNAP-IV (Swanson, Nolan, and Pelham IV scale) - CBCL - SDQ	PFAS were associated with greater symptoms of Inattention and Oppositional-Defiant Disorder on the SNAP-IV and more Hyperactivity/Impulsivity on the SDQ.	PFAS were associated with greater symptoms of Inattention and Hyperactivity/Impulsivity on the SNAP-IV in boys. PFAS were also associated with more ODD symptoms on the SNAP-IV, Externalizing Problems on the CBCL, and Peer problems on the SDQ in girls.
Lien et al. (2015)	Taiwan Maternal and Infant Cohort Study N=122 (% female not specified)	Phthalates in maternal urine in the third trimester	8 years - CBCL	Phthalate metabolites were associated with more Externalizing Problems, Social Problems, Delinquent Behavior, and Aggressive Behavior.	N/A
Lin et al. (2017)	Taiwan Birth Panel Study (TPBS) N=148-208 (43.8-47.3% female)	BPA in cord plasma	**7 years** - WISC-IV	At **age 7**, BPA was associated with lower FSIQ, Verbal Comprehension Index (VCI), and Perceptual Reasoning Index (PRI).	At **age 7**, BPA was associated with lower FSIQ and VCI in boys and lower FSIQ, PRI, and Working Memory Index in girls.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Lize et al. (2022)	PELAGIE N=185 (48.6% female)	OP pesticides (including chlorpyrifos) in maternal urine before GW 19	11 years - Childhood Autism Spectrum Test (CAST)	Chlorpyrifos (but not other OP pesticide metabolites) were associated with higher CAST scores.	Chlorpyrifos and its metabolites chlorpyrifos-oxon and TCPY were associated with higher CAST scores in boys only.
Luo et al. (2020)	Danish National Birth Cohort (DNBC) N=2832 (44.9% female)	PFASs in maternal plasma in GW 8	7-11 years - SDQ	PFAS were associated with more Externalizing problems.	No significant interactions with sex.
Maitre et al. (2021)	HELIX N=1286 (45.1% female)	Exposome: DDE, PCBs, PBDEs, PFAS, Arsenic, Hg, Mn, Pb, phthalates, BPA, and OP pesticides	6-11 years - Conners Rating Scale - CBCL	OP pesticide metabolites were marginally associated with more Externalizing Problems on the CBCL.	N/A
Millenson et al. (2017)	HOME N=224 (56.7% female)	OP pesticides in maternal urine in GW 16 and 26 (averaged)	8 years - SRS	No significant associations.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Miodovnik et al. (2011)	Mount Sinai Children's Environmental Health Study N=137 (% female not specified)	BPA and phthalates in maternal urine in the third trimester	7-9 years - SRS	Phthalate metabolites were associated with lower scores on Social Cognition, Social Communication, and Social Awareness.	N/A
Mora et al. (2015)	CHAMACOS N=248 (56.5% female)	Mn in child deciduous teeth shed starting at age 7	**7 years** - BASC-2 parent - BASC-2 teacher - Conners ADHD DSM-IV Scales (CADS) parent - CADS teacher - WISC-IV - Finger Tapping test (Reitan Neuropsychology Laboratory) - WRAVMA Pegboard **9 years** - CADS parent - Conners CPT-II - NEPSY-II Memory for Designs - Luria-Nebraska Motor Battery	**7 years** Mn was associated with marginally less parent-reported Inattention on the CADS. Mn was also associated with marginally better performance on the WISC-IV Perceptual Reasoning and the Finger Tap Dominant hand task. **9 years** Mn was associated with marginally fewer commission errors on the CPT-II and marginally better Delayed Recall on the NEPSY-II. **10.5 years**	**7 years** In girls, Mn was associated with marginally less parent-reported Inattention on the CADS. In boys, Mn was associated with better performance on the Finger Tap Dominant hand task. **9 years** In boys, Mn was associated with a lower ADHD Confidence Index on the CPT-II and better Immediate and Delayed recall scores on the NEPSY-II. **10.5 years**

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			10.5 years - BASC-2 parent - BASC-2 Self-Report (Hyperactivity and Attention Problems subscales) - WISC-IV - CAVLT-2 - Luria-Nebraska Motor Battery	Mn was associated with higher Learning and marginally better Delayed Recall on the CAVLT-2 as well as marginally better performance on the Luria-Nebraska Motor Scale.	In boys, Mn was associated with better performance on the CAVLT-2 Delayed Recall, and Luria-Nebraska Motor Scale as well as more parent-reported Hyperactivity on the BASC-2.
Myers et al. (2003)	Seychelles Child Development Study N=643 (% female not specified)	Hg in maternal hair	9 years - WISC-III (FSIQ only) - CVLT - WRAML Visual-Memory - Finger tapping - Trail Making - Grooved pegboard - Bruininks-Oseretsky Test of Motor Proficiency - BNT - Beery VMI	Hg was associated with a lower Hyperactivity Index on the Connors Teacher Rating Scale.	Hg was associated with worse performance on the Grooved Pegboard nondominant hand test in boys.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- Test of haptic matching - Connor's CPT - Connor's Teacher Rating Scale - CBCL		
Myers et al. (2020)	Seychelles Child Development Study, N=643 (% female not specified)	Hg in maternal hair	8-9 years - CBCL	Hg was associated with fewer Social Problems.	N/A
Nakamura et al. (2023)	Wakayama prefecture region, Japan N=113-128 (52.3-53.1% female)	Hg in umbilical cord tissue	6 years - WISC-III - BNT	N/A	No significant associations in either boys or girls.
Neugebauer et al. (2015)	Duisburg Birth Cohort Study N=117 (46.2% female)	Pb and PCBs in maternal blood in GW 32	8-9 years - Computerized Test Battery for Attentional Performance for Children (KITAP)	PCBs were associated with more omission errors on the KITAP Divided Attention subtest as well as less parent-reported Hyperactivity and a lower ADHD Index on the FBB-ADHD.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- Diagnostic System for Mental Diseases in Children and Adolescents (DISYPS II) parent rating scale for ADHD (FBB-ADHD)	Pb was associated with more omission errors on the KITAP Distractibility and Divided Attention subtests, longer reaction times on the KITAP Flexibility subtest and more parent-reported Impulsivity and a higher ADHD Index on the FBB-ADHD.	
Nowack et al. (2015)	Duisburg Birth Cohort Study N=116 (46.6% female)	PCBs in maternal blood between GW 28 and 42	**8-11 years** - Empathy-Systemizing Quotient (EQ-SQ, German version) **9-12 years** - SRS	PCBs were associated with fewer SRS Autism Mannerisms and marginally lower SRS Total scores at **age 9**.	PCBs were associated with lower scores on the SRS Total, Social Cognition and Autism Mannerism scales in girls.
Oken et al. (2016)	Project VIVA N=872 (49% female)	Hg in maternal blood erythrocytes in the second trimester	7-8 years - KBIT-2 - WRAVMA (Drawing subtest) - WRAML	No significant associations.	N/A
Orenstein et al. (2014)	New Bedford Cohort N=393 (50.1% female)	PCBs and DDE in cord serum. Hg in maternal hair	8 years - WRAML	Hg was associated with lower scores on the Visual Memory Index.	Hg was associated with lower scores on the Learning Index in boys.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Oulhote et al. (2016)	Faroe Islands N=539 (47.9% female)	PFASs in maternal serum at GW 32	7 years - SDQ	No significant associations.	No significant interactions with sex.
Oulhote et al. (2019)	Faroe Islands N=449 (49.4% female)	Hg, PCBs and PFAS in maternal blood at GW 32	7 years - BNT	Hg and PFAS were each associated with lower scores on the BNT Without cues. Hg, PFAS, and the chemical mixture each predicted lower scores on the BNT With cues.	N/A
Rauh et al. (2011)	CCCEH N=265 (55.8% female)	OP pesticide (chlorpyrifos) in cord blood	7 years - WISC-IV	Chlorpyrifos was associated with lower FSIQ and Working Memory Index scores.	N/A
Reilhac et al. (2020)	PELAGIE N=169 (50.9% female)	Glycol ether (solvent) in maternal urine before GW 19	6 years - Rhythmic CPT 90 (R-CPT90)	One glycol ether metabolite was associated with lower Inhibition scores.	N/A
Reyes Sánchez et al. (2022)	ELEMENT N=743 (48.7% female)	Pb in maternal patella measured using a K X-ray Fluorescence instrument in the first year postpartum	8-14 years - BASC-2 (Conduct Problems and Aggression subscales only)	Pb was associated with more conduct problems on the BASC-2.	No significant interactions with sex.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Roen et al. (2015)	CCCEH N=250 (54% female)	BPA in maternal urine in the third trimester	7-9 years - CBCL	N/A	In girls, BPA was marginally associated with fewer Social Problems. In boys, BPA was associated with more Externalizing, Rule-breaking behaviour, and Aggressive behaviour.
Rosenquist et al. (2017)	INUENDO N=1018 (46% female)	DDE and PCBs in maternal serum in GW 23-25	5-9 years - SDQ (parent report)	DDE was associated with more Hyperactivity.	N/A
Sagiv et al. (2010)	New Bedford Cohort N=590 (48.8% female)	DDE and PCBs in cord blood	8 years - Conners Rating Scale (teacher report)	PCBs and DDE were associated with a higher ADHD Index, Hyperactive-Impulsive subscale score, and Total score.	N/A
Sagiv, Thurston, Bellinger, Amarasiriwardena, et al. (2012)	New Bedford Cohort N=421 (49.6% female)	Hg in maternal hair	8 years - Conners Rating Scale (teacher report; CRS-T) - NES2 CPT	Hg was associated with more teacher-reported Inattentiveness, Impulsivity-Hyperactivity, and Total ADHD symptoms, more commission errors on the CPT, and lower Processing Speed on the WISC-III.	In girls, low Hg was associated with slower reaction time and less reaction time variability on the CPT while high Hg was associated with more teacher-reported ADHD symptoms.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- WISC-III Processing Speed Index and Freedom from Distractibility score		In boys, Hg was associated with more teacher-reported Impulsivity-Hyperactivity on the CRS-T, more omission errors on the CPT, and lower scores on both WISC-III indices.
Sagiv, Thurston, Bellinger, Altshul, et al. (2012)	New Bedford Cohort N=512 (49.6% female)	DDE and PCBs in cord blood	8 years - NES2 CPT - WISC-III Processing Speed Index	No significant associations.	In girls, PCBs were associated with faster reaction times on the CPT, and PCBs and DDE were associated with lower reaction time variability. In boys, PCBs were associated with more omission errors and more reaction time variability on the CPT and lower scores on the WISC-III Processing Speed.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Sagiv et al. (2015)	CHAMACOS N=230-262 with measured prenatal exposure (% female not specified)	PBDEs in maternal blood around GW 26 or at delivery	**9 years** - Conners CPT-II - CADS - WCST - Balloon Analogue Risk Test (BART) - NEPSY Tower - BRIEF **10.5 years** - WISC-IV Processing Speed - WISC-IV Working Memory - BASC-2 parent report (Hyperactivity and Attention Problems subscales) - BASC-2 self-report (Hyperactivity and Attention Problems subscales) - Luria-Nebraska Motor Scales	In **longitudinal analyses**, PBDEs were positively associated with Hit Rate SE by Block on the CPT-II, indicating worse vigilance. PBDEs were also associated with fewer errors and fewer perseverative errors on the WCST as well as worse executive function on the BRIEF Emotional Control subscale, Working Memory subscale, Metacognition Index, and Global Executive Composite. At **9 years**, PBDEs were associated with fewer errors and perseverative errors on the WCST, and worse executive function on the BRIEF Working Memory subscale, Metacognition Index, and Global Executive Composite.	No significant interactions with sex.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			12 years - Conners CPT-II - CADS - WCST - BART - BRIEF	At **12 years**, PBDEs were associated with fewer perseverative errors on the WCST.	
Sagiv et al. (2018)	CHAMACOS N=248-354 (% female not specified)	OP pesticides in maternal urine in GW 13 and 26	**7 years** - BASC-2 parent (Social Skills only) - BASC-2 teacher (Social Skills only) **9 years** - Evaluación Neuropsicológica Infantil (ENI) Facial Expression Recognition Test **10.5 years** - BASC-2 (Social Skills) **12 years** - NEPSY-II Affect Recognition subtest	At **7 years**, OP pesticide metabolites were associated with worse teacher-rated Social Skills on the BASC-2.	No sex differences.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Sagiv et al. (2021)	CHAMACOS N=351 (53.0% female)	OP pesticides in maternal urine at GWs 13 and 26, averaged	**7 years** - BRIEF teacher - CADS teacher - BASC-2 teacher **7 and 10.5 years** - BASC-2 self-report - WISC-IV (Working Memory Index and Processing Speed Index) **7, 9, and 12 years** - BRIEF parent - CADS parent - BASC-2 parent **9 and 12 years** - WCST Computer Version 2 Research Edition - Conners CPT-II	In **longitudinal analyses**, OP pesticide metabolites were associated with a lower WISC-IV Working Memory Index and a marginally lower Processing Speed Index. OP pesticide metabolites were also associated with more Errors and Perseverative Errors on the WCST, worse executive function on the BRIEF Global Executive Composite (GEC), Behavior Regulation Index (BRI), and Metacognition Index (MI), as well as more parent-reported symptoms of ADHD on the CADS (Total Scale, Inattentive, Hyperactive/Impulsive, and ADHD Index).	In **longitudinal analyses**, OP pesticides were associated with worse executive function based on the BRIEF BRI and GEC in boys. In girls, OP pesticide metabolites were associated with more commission errors on the CPT-II. In teacher-reported outcomes at **age 7**, OP pesticide metabolites were associated with worse BRIEF MI and GEC scores and marginally worse BRIEF BRI score in girls.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
				In teacher-reported outcomes at **age 7**, OP pesticide metabolites were associated with a higher ADHD-Index on the CADS and more Attention Problems on the BASC-2.	
Signes-Pastor et al. (2022)	HOME N=260 (54% female)	Arsenic in maternal urine at GW 16 and 26	**8 years** - WISC-IV (FSIQ only)	No significant associations.	N/A
Sioen et al. (2013)	FLEHS (Flemish Environment and Health Study) N=260 (53.8% female)	Pb in cord blood, PCBs and DDE in cord plasma	7-8 years - SDQ	Pb was associated with more Hyperactivity.	No significant sex differences.
Solazzo et al. (2021)	GEStation and Environment (GESTE) cohort N=355 (45% female)	PBDEs in maternal blood at early pregnancy and delivery	6-8 years - WISC-IV Vocabulary, Information, Digit Span, and Coding subtests - NEPSY-II Design Copying and Trail Making subtests	One PBDE congener measured at delivery was associated with higher WISC-IV Digit Span scores. Another congener measured at delivery was associated with lower WISC-IV Block Design scores.	Average prenatal PBDEs were associated with lower scores on the TEA-Ch Score subtest (suggesting lower sustained attention) in boys only.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- TEA-Ch Sky Search, Score, and Score DT subtests - Developmental Coordination Disorder Questionnaire (DCD-Q)		
Spratlen et al. (2020)	WTC N=302 (49.7% female)	PFAS in maternal blood at delivery and cord blood	**6 years** - WPPSI-R	No significant associations	No significant sex differences.
Stacy et al. (2017)	HOME N=228 (55.7% female)	BPA in maternal urine at GW 16 and 26	8 years - BASC-2 - BRIEF - WISC-IV	No significant associations.	BPA were associated with more Externalizing Problems on the BASC-2 in girls.
Stewart et al. (2005)	Oswego Study N=174-183 (% female not specified)	PCBs in cord blood (exposure divided into 4 groups: non-detected, low, middle, upper tertiles)	**8 years** - NES2 CPT **9.5 years** - Extended CPT (E-CPT)	At **8 years,** PCBs were associated with more commission errors.	No significant interactions with sex at either age.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
				At **9.5 years**, there was no main effect of PCBs, but a significant interaction of PCBs and CPT Condition, whereby PCBs were associated with more commission errors in task blocks with high inhibition demands, but not in blocks with low inhibition demands.	
Stewart et al. (2008)	Oswego Study N=187 (51% female)	PCBs in placental tissue	9 years - WISC-III	PCBs were associated with lower FSIQ, Verbal IQ and Freedom from Distractibility Index.	N/A
Strain et al. (2021)	Seychelles Child Development Study Nutrition Cohort 2 (NC2) N=1237 (48% female)	Hg in maternal hair)	7 years - KBIT-2 - BNT - Trail Making A - Finger Tapping - SRS-2 - Social Communication Questionnaire (SCQ)	No significant associations.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Sussman et al. (2022)	GEStation and Environment (GESTE) cohort N=63 (36.5% female)	PCBs and PBDEs in maternal plasma at delivery	9-11 years - Computerized Simon task - BASC-3	PCBs and PBDEs were each associated with lower accuracy scores on congruent trials of the Simon task. PCBs were associated with higher ADHD Index and Hyperactivity scores on the BASC-3. PBDEs were associated with lower Executive Function scores on the BASC-3.	N/A
Takser et al. (2003)	Robert Debré Maternity (Paris, France) N=247 (45% female)	Mn in maternal blood, cord blood, maternal hair, newborn hair, and placental tissue (all collected at delivery/birth)	**6 years** - MSCA (GCI, nonverbal memory, attention, and hand skills composites)	No significant associations.	No significant sex differences
Tatsuta et al. (2020)	Tohoku Study of Child Development (TSCD) N=289 (48.8% female)	Pb and Hg in cord blood	12 years - WISC-IV (Japanese version) - BNT (Japanese version)	N/A	Significant negative association between cord blood Pb and BNT scores With and Without cues in boys.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Taylor et al. (2017)	ALSPAC N=404-2217 (43.3-49.3% female)	Pb in maternal blood in early pregnancy (approx. GW 9-13)	**8 years** - WISC-III	No significant associations.	Pb was associated with better VIQ and FSIQ as well as marginally better PIQ in girls.
Tillaut et al. (2023)	PELAGIE N=444 (49.5% female)	PFAS in cord blood	12 years - SDQ (externalizing composite and hyperactivity subscale) - Dominic Interactive for Adolescents (self-report; Externalizing composite and ADHD subscale)	PFAS was associated with higher scores on the parent-report SDQ for externalizing and hyperactivity and for the self-report DIA externalizing and ADHD scales.	No significant interactions with sex or sex differences.
Thilakaratne et al. (2023)	Project VIVA N=900 (48.4% female)	Arsenic, Hg, Pb, and Mn in maternal blood in early pregnancy	**8 years** - WRAML2 (overall, design memory, & picture memory) - WRAVMA (visual motor) - KBIT-II (fluid & crystallized)	Mn was associated with higher fluid (non-verbal) intelligence scores on the KBIT-II as age 8.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Vahter et al. (2020)	Matlab area in Bangladesh N=1467 (47% female)	Arsenic in maternal urine at GW 8 (early pregnancy) and 30 (late pregnancy) weeks gestation and in maternal plasma at GW 14	10 years - WISC-IV	Arsenic in early pregnancy maternal urine and maternal plasma were each associated with lower Perceptual Reasoning. Early pregnancy urinary arsenic was also marginally associated with a lower Full Developmental Score (i.e., the sum of the 10 primary subtests).	Early pregnancy urinary arsenic was associated with lower Perceptual Reasoning and Total scores in girls only.
van den Dries et al. (2019)	Generation R N=622-781 (48.6-49.4% female)	OP pesticide metabolites measured 3 times in pregnancy (approximately once per trimester)	6 years - SRS	No significant associations.	No significant interactions with sex.
van den Dries et al. (2020)	Generation R N=1282 (49.5% female)	BPA and phthalates in maternal urine in early (before GW 18), mid (GW 18-25), and late (after GW 25) pregnancy	6 years - Snijders-Oomen Nonverbal Intelligence Test-Revised	Early pregnancy phthalates were negatively associated with nonverbal IQ scores.	No significant interactions with sex.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
van den Dries et al. (2021)	Generation R N=782 (49.1% female)	OP pesticides, phthalates, and BPA in maternal urine in early (before GW 18), mid (GW 18-25), and late (after GW 25) pregnancy	6-7 years - Snijders-Oomen Nonverbal Intelligence Test-Revised (SON-R) - CBCL 1.5-5 - SRS	The chemical mixture and phthalates were each associated with lower nonverbal IQ.	No significant sex differences in sex-stratified analyses.
Viel et al. (2015)	PELAGIE N=287 (51.6% female)	Pyrethroids in maternal urine in early pregnancy (GW 6-19)	6 years - WISC-IV (Verbal Comprehension and Working Memory only)	No significant associations.	N/A
Viel et al. (2017)	PELAGIE N=287 (51.6% female)	Pyrethroids in maternal urine in early pregnancy (GW 6-19)	6 years - SDQ (French version)	No significant associations.	No significant interactions or sex differences.
Vilmand et al. (2023)	Odense Child Cohort N=585 (48% female)	Phthalates in maternal urine at GW 28	7 years - WISC-V (FSIQ only)	Phthalates were associated with lower FSIQ.	No significant interactions with sex or sex differences.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Vreugdenhil et al. (2002)	Rotterdam and Groningen, The Netherlands N=372 (48.9% female)	PCBs in maternal plasma in the last month of pregnancy	6.5 years - MSCA (Dutch version)	Marginally significant negative association between PCBs and the MSCA Motor subscale.	N/A
Vreugdenhil et al. (2004)	Rotterdam, The Netherlands N=83 (47.0% female)	PCBs in maternal plasma in the last month of pregnancy (stratified as High- and Low0 PCB groups)	9 years - Rey Complex Figure Test (memory) - Simple Reaction Time Test (SRTT; attention) - Auditory-Verbal Learning Test Dutch Version (verbal memory) - Tower of London (TOL; planning; executive function).	Compared to the Low-PCB group, those in the High-PCB group had significantly longer reaction time and more reaction time variability on the SRTT and scored lower on the TOL.	N/A
Vuong et al. (2019)	HOME N=221 (54.8% female)	PFAS in maternal serum at GW 16 and 26	8 years - WISC-IV	Certain PFAS were associated with higher Working Memory scores.	Significant interaction of sex in the association between PFOA and Full-Scale IQ, where a positive association was found in girls only.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Vuong et al. (2018)	HOME N=204 (54.9% female)	PFAS in maternal serum at GW 16 and 26 weeks	8 years - Conners CPT-II - Virtual Morris Water Maze (VMWM)	PFAS were associated with fewer commission errors on the CPT-II and greater distance travelled in the correct quadrant in the VMWM (suggesting better visual-spatial working memory).	Certain significant interactions with sex, but associations were null for both sexes in sex-stratified analyses.
Vuong, Braun, et al. (2017)	HOME N=162 (54.3% female)	PBDEs in maternal serum at GW 16	8 years - Virtual Morris Water Maze (VMWM)	PBDEs were associated with more time spent and distance travelled in the correct quadrant during the probe trial (suggesting better visual-spatial memory).	PBDEs were associated with longer completion distances (i.e., worse performance) in boys.
Vuong, Yolton, et al. (2017)	HOME (Ohio) N=214 (55.6% female)	PBDEs in maternal serum at 16 weeks gestation	8 years - Conners' Continuous Performance Test, 2nd edition (CPT-II)	No significant associations.	Significant interaction with sex for one PBDE congener, where PBDEs were associated with fewer omission errors in girls only.
Wang et al. (2015)	Taiwan Maternal and Infant Cohort Study N=120 (60.8% female)	PFAS in maternal serum in the third trimester	**8 years** - WISC-III	One PFAS was associated with lower VIQ on the WISC-III.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Wang et al. (2022)	Wujiang, China N=148 (52.0% female	Pb, Mn, and arsenic in cord blood	7-8 years - WISC-Chinese Revision	Pb was associated with lower Performance IQ.	No significant sex interactions.
Xie et al. (2023)	Shanghai-Minhang Birth Cohort Study N=449 (42.5% female)	PFAS in maternal blood between GW 12 and 16	**6 years** - WISC-IV (FSIQ, Verbal Comprehension Index and Perceptual Reasoning Index only) - CBCL	PFAS were associated with marginally higher scores on the WISC FSIQ, VCI, and PRI. PFAS were also associated with more attention problems, aggressive behaviour, and externalizing problems on the CBCL.	N/A
Yorifuji et al. (2011)	Faroe Islands N=808-896 (50.1% female at age 7 years; % female not specified at age 14 years)	Pb in cord blood	**7 years** - WISC-R (Digit Span, Similarities, Block design - BNT - CVLT-Children's Version (CVLT-C)	At **7 years**, Pb was associated with higher scores on the BNT (With and Without cues) and higher Learning scores on the CVLT-C.	N/A
Zhang et al. (2017)	HOME N=239 (55.0% female)	PBDEs and PCBs in maternal serum at GW 16	8 years - WISC-IV (FSIQ only) - BASC-2 (Externalizing Problems subscale only)	PBDEs were associated with lower FSIQ scores on the WISC-IV and marginally more Externalizing Problems on the BASC-2.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Zhang et al. (2020)	Sheyang Mini Birth Cohort Study N=303 (43.2% female)	Carbamates in maternal urine at delivery	7 years - WISC Chinese Revision	No significant associations.	No significant interactions with sex.

Table A4

Result Summary for Studies in Adolescence (13-17 Years)

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Berghuis et al. (2018)	Development at Adolescence and Chemical Exposure (DACE) study N=101 (45.5% female)	PCBs, PBDEs, and DDE in maternal serum in the second or third trimester	13-15 years - WISC-III-NL (Dutch version) - Auditory Verbal Learning Test (AVLT) - TEA-Ch, Dutch version (TEA-Ch-NL) - Movement-ABC	PCBs were marginally associated with lower FSIQ on the WISC-III. PBDEs and DDE were not associated with any cognitive or motor outcomes.	On the Movement-ABC, there were marginally significant negative associations between one PBDE congener and Fine Motor Skills in girls and between DDE and Motor Performance in boys.
Davidson et al. (2011)	Seychelles Main Study N=371-462 (% female not specified)	Hg in maternal hair	15-18 years - CVLT - WCST - CANTAB Intra-Extra Dimensional Shift Set - CANTAB Paired Associates Learning	Hg was negatively associated with number of trials on the CANTAB Intra-Extra Dimensional Shift Set task, reflecting better performance.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- CANTAB Delayed Match to Sample - CANTAB Pattern Recognition Memory - CANTAB Spatial Recognition Memory - CANTAB Spatial Working Memory - CANTAB Reaction Time - CANTAB Rapid Visual Information Processing		

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Debes et al. (2006)	Faroe Islands N=838 (50.2% female)	Hg and PCBs measured in cord blood, cord tissue and maternal hair	14 years - NES2 CPT - NES2 Finger Tapping - Catsys Simple Reaction Time (RT) - WISC-R Block Design - Stanford-Binet Copying - Children's Category Test - Wechsler Memory Scale III (WMS-III) Spatial Span - BNT	Specific associations with Hg varied based on the tissue (cord blood, cord tissue, and maternal hair). Overall, Hg was associated with worse scores on the NES2 Finger Tapping, BNT With/Without cues, and CVLT Learning trial, slower reaction time on the CPT, and better scores on the WMS Spatial Span. No significant associations for PCBs in any tissue.	N/A
Ghassabian et al. (2023)	Generation R N=671 (49.7% female)	Phthalates in maternal urine in early (< GW18), mid (GW 18-25), and late (> GW25) pregnancy	14 years - WISC-V (estimated the FSIQ based on the Vocabulary, Matrix Reasoning, Digit Span, and Coding subtests)	Phthalates were associated with lower scores on the Vocabulary and Matrix Reasoning subtests.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Golding, Gregory, Emond, et al. (2016)	ALSPAC N=1599-2776 (% female not specified)	Hg in maternal blood in early pregnancy	**13 and 16 years** - SDQ	**At age 13**, Hg was associated with fewer parent-reported Peer problems.	N/A
Hyland et al. (2019)	CHAMACOS N=300-322	Phthalates in maternal urine in GW 13 and 26 (averaged)	**14 years** - SRS - BASC-2 parent - BASC-2 self-report **16 years** - BASC-2 parent - BASC-2 self-report	Phthalates were associated with more self-reported Hyperactivity and Attention problems on the BASC-2 at **age 16**.	No significant sex differences at either age.
Julvez et al. (2010)	Faroe Islands N=863 (50.2% female)	Hg in cord blood	14 years - NES2 CPT	No significant association in the first 2 minutes, but a significant positive association between Hg and reaction time emerged starting at 3 minutes until the end of the task (10 minutes), suggesting worse sustained attention.	N/A
Oppenheimer, Bellinger, Coull, Weisskopf, Zemplenyi, et al. (2021)	New Bedford Cohort N=235-373 (51.5-52.0% female)	PCBs and DDE in cord serum; Pb and Mn in cord blood; Hg in maternal hair, and Arsenic measured in maternal toenails	15 years - D-KEFS Design Fluency (Empty Dots) - D-KEFS Color-Word Interference	Mn was associated with worse performance on Color-Word Interference.	No significant sex differences (either interactions or sex-stratified analyses).

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Oppenheimer, Bellinger, Coull, Weisskopf and Korrick (2021)	New Bedford Cohort N=235-373 (51.5-52.0% female)	PCBs and DDE in cord serum; Pb and Mn in cord blood; Hg in maternal hair, and Arsenic measured in maternal toenails	15 years - D-KEFS Trail-Making (Number-Letter Switching) - D-KEFS Verbal Fluency (Category Switching) - D-KEFS Design Fluency (Filled dots and Empty dots Switching) - D-KEFS Color-Word Interference (Inhibition/Switching)	Mn was adversely associated with Trail Making and Color-Word Interference.	Pb was associated with better Verbal Fluency in boys.
Oppenheimer et al. (2022b)	New Bedford Cohort N=235-373 (51.5-52.0% female)	PCBs and DDE in cord serum; Pb and Mn in cord blood; Hg in maternal hair, and Arsenic measured in maternal toenails	15 years - WRAML2 Verbal Working Memory - WRAML2 Symbolic Working Memory	Mn was associated with worse scores on both subtests while PCBs were associated with better Verbal Working Memory scores.	In sex-stratified analysis, Mn was associated with significantly lower Verbal Working Memory in boys only.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Oppenheimer et al. (2022a)	New Bedford Cohort N=410 (52.2% female)	Mn in cord blood	15 years - D-KEFS Trail-Making - D-KEFS Verbal Fluency - D-KEFS Design Fluency - D-KEFS Color-Word Interference - D-KEFS Sorting - D-KEFS Tower - WRAML2 Verbal Working Memory - WRAML2 Symbolic Working Memory	Mn was associated with lower scores on the Sorting task (measure of problem-solving) and Verbal Working Memory.	No sex differences.
Sagiv et al. (2018)	CHAMACOS N=248-354 (% female not specified)	OP pesticides in maternal urine in GW 13 and 26	**14 years** - SRS-2 - BASC-2 (Social Skills)	At **14 years**, OP pesticides were associated with worse SRS scores, especially on the Social Communication and Interaction scale.	No significant sex differences.
Yorifuji et al. (2011)	Faroe Islands	Pb in cord blood	**14 years** - WISC-R (Digit Span, Similarities, Block design	No significant associations.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
	N=808-896 (50.1% female at age 7 years; % female not specified at age 14 years)		- BNT - CVLT-Children's Version (CVLT-C)		

Table A5

Result Summary for Studies with Multiple Timepoints Over Multiple Age Groups

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Braun, Yolton, et al. (2017)	HOME (Ohio), N=346 (54% female)	BPA in maternal urine at GW 16 and 26. PBDEs in maternal serum at GW 16	**2, 3, 4, 5, and 8 years** - BASC-2 (BPA in girls only and PBDEs) **1, 2, 3 years** - BSID-II (MDI and PBDEs only) **5 years** - WPPSI-III (FSIQ and PBDEs only) **8 years** - WISC-IV (FSIQ and PBDEs only)	**Repeated measures analyses.** PBDEs were associated with more Externalizing Problems on the BASC-2 **between ages 2 and 8**, lower MDI on the BSID-II at **ages 2 and 3**, and lower FSIQ from **ages 5 to 8**. N/A for BPA (tested in girls only).	BPA was associated with more Externalizing Problems on the BASC-2 between **ages 2 and 8** in girls only. N/A for PBDEs.
Davidson et al. (2006)	Seychelles Child Development Study N=643-738 (% female not specified)	Hg in maternal hair	**19 and 29 months** - BSID (MDI only) **66 months** - MSCA (GCI and Memory subscale only) **107 months** - WISC-III (FSIQ only)	Repeated measures analyses. No significant associations.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- WRAML (Memory scale only)		
Engel et al. (2010)	Mount Sinai Children's Environmental Health Study N=188 (46% female)	Phthalates in maternal urine in the third trimester	**4-5, 6, and 7-9 years** - BRIEF - BASC	**Repeated measures analyses.** Phthalate metabolites were associated with more Aggression, Conduct Problems, Attention Problems, and Externalizing Problems and poorer Adaptive skills on the BASC. Phthalates were also associated with poorer executive function based on the Global Executive Composite and the Emotional Control subscale on the BRIEF.	Phthalate metabolites were associated with more Aggression and Externalizing Problems in boys only. There was a significant interaction with sex for Conduct problems (phthalates were associated with more Conduct problems in both sexes, but the effect size was larger in boys than in girls) and for Hyperactivity (associations were null in both sexes, but the effect size was larger in boys than in girls).

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Furlong, Barr, et al. (2017)	Mount Sinai Children's Environmental Health Study N=162 (45.1% female)	Pyrethroids in maternal urine in the third trimester	**4, 6, and 7-9 years** - BASC - BRIEF	**Repeated measures analyses.** Pyrethroid metabolites were associated with worse scores on the BRIEF Monitoring subscale (part of the Metacognition Index) as well as the Behaviour Regulation Index and its subscales (Emotional Control, Shifting, and Inhibitory Control). Pyrethroid metabolites were also associated with more Conduct and Externalizing Problems on the BASC.	No significant interactions with sex.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Furlong, Herring, et al. (2017)	Mount Sinai Children's Environmental Health Study N=141 (49% female)	OP pesticides in maternal urine between GW 25 and 40	**4, 6, and 7-9 years** - BRIEF - BASC **6 years** - WPPSI-III **7-9 years:** - WISC-IV	**Repeated measures analyses**. OP pesticide metabolites were associated with lower Working Memory Index scores on the WPPSI-III/WISC-IV and better scores on an Executive Functioning Factor (composed of the BRIEF as well as the BASC Attention scale, Hyperactivity scale, Atypicality scale, and Behavioral Regulation Index).	No significant interactions with sex.
Golding et al. (2018)	ALSPAC N=2249- 3885 (% female not specified)	Hg in maternal blood in early pregnancy	**3 years** - Emotionality, Activity, Sociability (EAS) Temperament Traits **5 years** - Repetitive behaviour (derived measure) **7 years**	**Repeated measures analyses.** No significant associations.	N/A

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			- Social and Communication Disorders Checklist **9 years** - Child Communication Checklist		
Goodman, Bashash, et al. (2022)	ELEMENT N=348 (52% female)	Fluoride in maternal urine in one or more trimesters	**4 and 5 years** - MSCA (Spanish version) **6-12 years** - Wechsler Abbreviated Scale of Intelligence (WASI; Spanish version)	In **repeated measures analyses**, fluoride was associated with lower overall cognitive functioning and Performance IQ.	No significant interactions with sex.
Huang et al. (2019)	Taiwan Maternal and Infant Cohort Study N=153 (52.3% female)	Phthalates in maternal urine in the third trimester	**8-9, 11-12, and 14-15 years** - CBCL	**Repeated measures analyses**. Phthalates were associated with more Attention and Externalizing problems.	No significant sex differences.
Huang et al. (2015)	Taiwan Maternal and Infant Cohort Study N=110 (47.3% female)	Phthalates in maternal urine in the third trimester	**2 years** - BSID-II (MDI only) **5 years** - WPPSI-R (FSIQ)	**Repeated measures analyses**. No significant associations.	No significant interactions (data not shown).

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
			8 years - WISC-III (FSIQ) **11 years** - WISC-IV (FSIQ)		
Hyland et al. (2019)	CHAMACOS N=300-322	Phthalates in maternal urine in GW 13 and 26 (averaged)	**7, 10.5, 12, and 16 years** - BASC-2 parent **14 and 16 years** - BASC-2 self-report	**Repeated measures analyses.** No significant associations.	No significant sex differences.
Kalloo et al. (2021)	HOME N=253 (55% female)	Exposome BPA, phthalates, OP pesticides, pyrethroids, and arsenic in maternal urine. PFAS, PBDEs, PCBs, and DDE in maternal serum. Hg in maternal blood. Samples collected at GW 16 and/or 26	**5 years** - WPPSI-III **8 years** - WISC-IV	**Repeated measures analyses.** Phthalates were associated with higher PIQ while PCBs were associated with higher VIQ and PFAS were associated with faster Processing Speed.	N/A
Kim et al. (2021)	Environment and Development of Children (Korea)	Phthalates in maternal urine in the second trimester	**4, 6, and 8 years** - Social Communication Questionnaire (SCQ)	**Repeated measures analyses.** No significant association.	No significant sex differences.

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
	N=344-477 (46.4-46.8% female)				
Li et al. (2019)	HOME N=202 (56.9% female)	Phthalates in maternal urine at GW 16 and 26	**5 years** - WPPSI-III **8 years** - WISC-IV	**Repeated measures analyses.** Phthalate metabolites were associated with lower FSIQ.	No significant sex differences.
(Li et al., 2023)	Maoming Birth Cohort Study N=718 (44.6% female)	PFAS in maternal serum in the third trimester	**3, 6, 12, 18, 24, and 36 months** - ASQ-3	PFAS were associated with greater odds of having consistently low scores on the communication, gross motor, and problem solving scales and lower odds of consistently low scores on the fine motor scale.	In girls, PFAS were associated with higher odds of persistently low scores for communication. In boys, PFAS were associated with higher odds of persistently low scores for problem solving and lower odds of persistently low score for fine motor function.
Oh et al. (2022)	Hamamatsu Birth Cohort (HBC) Study N=598 (48.2% female)	PFAS (PFOA and PFOS only) in cord blood	**4, 6, 10, 14, 18, 24, 32, and 40 months** - Mullen Scales of Early Learning (MSEL)	**Repeated measures analyses.** PFAS were positively associated with the Composite score and the Receptive and Expressive language subscales.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Patel et al. (2019)	HOME N=320 (54.7% female)	Hg in maternal blood at GW 16 and 26, at delivery, and in cord blood (averaged)	**2, 3, 4, 5, and 8 years** - BASC-2	No significant associations (Externalizing, Adaptive skills, Aggression, Hyperactivity, and Attention) in **repeated measures analyses**.	N/A
Sagiv et al. (2018)	CHAMACOS N=248-354 (% female not specified)	OP pesticides in maternal urine in GW 13 and 26	**7, 10.5 and 14 years** - BASC-2 parent (Social Skills only)	In r**epeated measures analyses**, OP pesticide metabolites were associated with worse parent-rated Social Skills on the BASC-2.	No significant sex differences.
Shah-Kulkarni et al. (2016)	MOCEH N=965 (48% female) at 6 months	Pb in maternal blood in early pregnancy (before GW 20) and at delivery (representing late pregnancy) and in cord blood	**6, 12, 24, and 36 months** - Korean version of the Bayley-II (K-BSID-II)	No significant associations in longitudinal analyses.	N/A
van den Dries et al. (2019)	Generation R N=622-781 (48.6-49.4% female)	OP pesticide metabolites measured 3 times in pregnancy (approximately once per trimester)	**3, 6, and 10 years** - CBCL (ADHD scale)	No significant associations in **longitudinal analyses**.	No significant interactions with child sex.

Author (year)	Cohort, sample size, % female	Exposure (chemical, matrix, timing)	Outcome measures and ages	Main results	Sex differences
Vuong et al. (2016)	HOME N=201-246 (54.1-55.7% female)	PBDEs and PFAS in maternal serum at GW 16	**5 and/or 8 years** - BRIEF	**Repeated measures analyses.** PBDEs were associated with greater odds of scoring in the "at risk" range on the Behaviour Regulation Index (BRI) and Global Executive Composite (GEC). PFAS were associated with greater odds of scoring in the "at risk" range on the Metacognition Index (MI), BRI, and GEC.	PBDEs were associated with worse scores on the BRI and GEC in boys. PFAS were associated with worse scores on the MI and the GEC in girls.
Vuong et al. (2021)	HOME N=241 (53.9% female)	PFAS in maternal serum at GW 16, 26, and/or at delivery	**5 and 8 years** - BASC-2	In r**epeated measures analyses**, PFAS were associated with more externalizing problems and hyperactivity.	PFAS were associated with more Conduct Problems in girls only.
Wasserman et al. (2000)	Kosovo, Yugoslavia N=289-390 (47.9-48.2% female)	Pb in maternal blood in mid-pregnancy and at delivery (averaged)	**3 and 4 years** - MSCA (GCI only) **5 years** - WPPSI-R (FSIQ) **7 years** - WISC-III (FSIQ)	**Repeated measures analyses only.** Pb was associated with lower global cognitive functioning.	N/A

Author (year)	**Cohort, sample size, % female**	**Exposure (chemical, matrix, timing)**	**Outcome measures and ages**	**Main results**	**Sex differences**
Yamamoto et al. (2022)	Japan Environment and Children's Study (JECS) N=3,787 (49.5% female)	Mn in maternal blood in the second and third trimesters and in cord blood	**6, 12, 18, 24, 30, and 36 months** - ASQ, 3rd edition, Japanese version (J-ASQ-3)	Cord blood Mn was associated with lower Gross Motor skills while maternal blood Mn was associated with lower ASQ scores for all domains (i.e., Communication, Gross Motor, Fine Motor, Problem solving, and Personal-social) in **repeated measures analyses.**	No significant sex differences.
Yu et al. (2024)	HOME N=271 (55% female)	Phthalates in maternal urine around GW 16 and 26	4-8 years - SRS (Total score only)	No significant associations.	No significant sex differences.

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Appendix B: Chapter 3 Supplementary Tables

Table B1

Description of the initial MIREC cohort, the sample in the six largest sites, and the sample that participated in the neurodevelopmental follow-up

	Initial MIREC Cohort (n = 1862 singleton live births)	Sample of the MIREC Cohort in the 6 largest study sites (n = 1537 singleton live births)	Sample that participated in the neurodevelopmental follow-up (n = 610)
Study site			
Site 1	141 (7.6%)	141 (9.2%)	55 (9.0%)
Site 2	19 (1.0)	--	--
Site 3	87 (4.7%)	--	--
Site 4	303 (16.3)	303 (19.7%)	69 (11.3%)
Site 5	257 (13.8%)	257 (16.7%)	85 (13.9%)
Site 6	112 (6.0%)	--	--
Site 7	249 (13.4%)	249 (16.2%)	130 (21.3%)
Site 8	107 (5.7%)	--	--
Site 9	311 (16.7%)	311 (20.2%)	154 (25.2%)
Site 10	276 (14.8%)	276 (18.0%)	117 (19.2%)
Maternal education[2]			
High school or less	161 (8.6%)	128 (8.3%)	31 (5.1%)
College or trade school	538 (28.9%)	428 (27.8%)	170 (27.9%)
Undergraduate diploma	684 (36.7%)	590 (38.4%)	243 (39.8%)
Graduate diploma	477 (25.6%)	389 (25.3%)	164 (26.9%)
Missing	2 (0.1%)	2 (0.1%)	2 (0.3%)
Maternal age[2]			
18-29 years	573 (30.8%)	454 (29.5%)	151 (24.8%)
30-34 years	657 (35.3%)	562 (36.6%)	251 (41.1%)
35-39 years	503 (27.0%)	408 (26.5%)	173 (28.4%)
40+ years	129 (6.9%)	113 (7.4%)	35 (5.7%)
Household annual income[2,4]			
< 50k	318 (17.1%)	262 (17.0%)	92 (15.1%)
50 – 80k	382 (20.5%)	331 (21.5%)	145 (23.8%)
80 – 100k	359 (19.3%)	289 (18.8%)	118 (19.3%)
> 100k	717 (38.5%)	591 (38.5%)	235 (38.5%)
Missing	86 (4.6%)	64 (4.2%)	20 (3.3%)

	Initial MIREC Cohort (n = 1862 singleton live births)	Sample of the MIREC Cohort in the 6 largest study sites (n = 1537 singleton live births)	Sample that participated in the neurodevelopmental follow-up (n = 610)
Maternal birth country[2]			
Canada	1507 (80.9%)	1224 (79.6%)	503 (82.5%)
Other	355 (19.1%)	313 (20.4%)	107 (17.5%)
Parity[2]			
Nulliparous	814 (43.7%)	667 (43.4%)	266 (43.6%)
1	754 (40.5%)	632 (41.1%)	252 (41.3%)
2 or more	294 (15.8%)	238 (15.5%)	92 (15.1%)
Smoking during pregnancy[3]			
Non smoker	1493 (80.2%)	1249 (81.3%)	536 (87.9%)
Quit during pregnancy	113 (6.1%)	91 (5.9%)	34 (5.6%)
Current smoker	80 (4.3%)	57 (3.7%)	15 (2.5%)
Missing	176 (9.5%)	140 (9.1%)	25 (4.1%)
Maternal pre-pregnancy BMI[2]			
Underweight (< 18.5)	49 (2.6%)	39 (2.5%)	14 (2.3%)
Normal (18.51 – 25)	1044 (56.1%)	870 (56.6%)	342 (56.1%)
Overweight (25.1 – 30)	373 (20.0%)	312 (20.3%)	115 (18.9%)
Obese (>=30)	258 (13.9%)	207 (13.5%)	93 (15.2%)
Missing	138 (7.4%)	109 (7.1%)	46 (7.5%)

[1] As participants from each site were not representative samples from each city, the cities have not been identified; [2] Variables assessed in the first trimester of pregnancy; [3] Variable assessed in the third trimester of pregnancy; [4] Canadian dollars.

Table B2

Difference in IQ scores (95% Cis) for a tenfold increase in maternal plasma concentrations of Σ_4PBDEs, BDE-47, and BDE-153, unadjusted for confounders

	FSIQ	VIQ	PIQ
Log10 Σ_4PBDEs	-2.2 (-4.4, -0.1)	-1.7 (-3.8, 0.4)	-2.1 (-4.5, 0.2)
Log10 BDE-47	-2.8 (-5.0, -0.6)	-2.7 (-4.8, -0.5)	-2.3 (-4.7, 0.2)
Log10 BDE-153	-0.8 (-2.3, 0.8)	-0.3 (-1.8, 1.1)	-0.9 (-2.6, 0.7)

Abbreviations. VIQ : Verbal Intelligence Quotient; PIQ : Performance Intelligence Quotient; FSIQ : Full Scale Intelligence Quotient; Σ_4PBDEs : Sum of BDE-47, BDE-153, BDE-99, and BDE-100.

Table B3

Difference in IQ scores (95% Cis) for a tenfold increase in maternal plasma concentrations of Σ_4PBDEs, BDE-47, and BDE-153, from boys and girls, unadjusted for confounders

	FSIQ	VIQ	PIQ
Log10 Σ_4PBDEs			
Boys	-3.7 (-7.2, -0.3)	-3.3 (-6.6, 0.1)	-3.2 (-6.9, 0.5)
Girls	0.0 (-2.6, 2.6)	0.5 (-2.1, 3.1)	-0.7 (-3.7, 2.4)
Log10 BDE-47			
Boys	-4.0 (-7.5, -0.6)	-4.4 (-7.7, -1.0)	-2.6 (-6.3, 1.1)
Girls	-0.8 (-3.6, 1.9)	-0.2 (-2.9, 2.5)	-1.4 (-4.6, 1.8)
Log10 BDE-153			
Boys	-1.5 (-3.8, 0.9)	-0.9 (-3.2, 1.3)	-1.5 (-4.0, 1.1)
Girls	0.4 (-1.5, 2.2)	0.7 (-1.1, 2.5)	-0.2 (-2.3, 2.0)

Abbreviations. VIQ : Verbal Intelligence Quotient; PIQ : Performance Intelligence Quotient; FSIQ : Full Scale Intelligence Quotient; Σ_4PBDEs : Sum of BDE-47, BDE-153, BDE-99, and BDE-100.

Appendix C: Lay Article Written for a UQAM Knowledge Translation Platform

Azar, N. (2022, May). *Doit-on s'inquiéter des effets des retardateurs de flammes sur nos enfants?* Faire à sa tête : Pollution et santé du cerveau. https://faireasatete.uqam.ca/doit-on-sinquieter-des-effets-des-retardateurs-de-flammes-pour-nos-enfants/

Doit-on s'inquiéter des effets des retardateurs de flammes sur nos enfants?

Les polybromodiphényléthers (PBDEs) sont des retardateurs de flammes qui peuvent se détacher des objets auxquels ils sont ajoutés et se retrouver dans notre environnement. Les enfants ont une plus grande exposition aux PBDEs que les adultes et des études démontrent que leur développement en est affecté, incluant la cognition. Cet effet n'est pas nécessairement observable chez les enfants exposés, mais il est important à l'échelle de la population.

On estime que les enfants sont exposés aux PBDEs de 3 à 9 fois plus que les adultes (Linares et al., 2015). Les plus grandes concentrations de PBDEs observées dans le corps des jeunes enfants s'expliquent en grande partie par leur plus petite taille, mais aussi à cause de certains comportements propres aux enfants, tels que jouer au sol et porter les objets à leur bouche. La recherche suggère que l'exposition aux PBDEs pourrait être associée négativement au développement cognitif et au comportement des enfants (Lam et al., 2017). Bien que les PBDEs ont été bannis progressivement entre 2006 and 2012, on sait que l'exposition va perdurer pour les années et décennies à venir puisque les PBDEs sont des polluants organiques persistants (Linares et al., 2015).

Les PBDEs : c'est quoi au juste?

Les polybromodiphényléthers (ou plus communément, les PBDEs) sont des retardateurs de flammes ajoutés à des biens de consommation et objets ménagers, tels que les meubles rembourrés, vêtements et électroménagers (Frederiksen et al., 2009; Linares et al., 2015). Leur utilisation visait à diminuer le risque de propagation de flammes dans ces objets.

Comment est-on exposés aux PBDEs?

Les PBDEs peuvent s'échapper des objets auxquels ils sont ajoutés puisque leur liaison chimique est faible. Ainsi, des particules de PBDEs peuvent se retrouver dans notre

environnement quotidien (Costa & Giordano, 2007). L'exposition survient principalement à travers des particules qui se sont déposées dans la poussière à la maison, qu'on peut ensuite inhaler ou ingérer accidentellement (Frederiksen et al., 2009). C'est pourquoi les jeunes enfants, qui passent beaucoup de temps au sol et portent souvent leurs mains à leur bouche, ont une plus grande exposition que les adultes (Klinčić et al. 2020).

Bien que moins importante, l'exposition aux PBDEs se produit aussi par l'alimentation. Les PBDEs s'accumulent dans les tissus adipeux. On les retrouve donc surtout dans les aliments riches en gras (p. ex., les produits laitiers, la viande ou le poisson). Pour la même raison, les PBDEs sont aussi présents dans le lait humain, ce qui explique la grande concentration de PBDEs dans le corps des bébés allaités (Klinčić et al. 2020).

L'exposition aux PBDEs peut également se produire pendant la grossesse puisque ces polluants peuvent traverser le placenta (Frederiksen et al., 2009; Klinčić et al. 2020).

Comment les PBDEs affectent-ils le développement cognitif des enfants?

Les chercheurs sont particulièrement intéressés aux effets des PBDEs sur le développement des tout-petits. En effet, les bébés et les jeunes enfants sont plus à risque que les adultes puisqu'ils sont en développement. Leur cerveau est en pleine croissance et donc plus facilement affecté par leur environnement. Celui-ci peut être positif (p. ex., les bienfaits d'un milieu riche en stimulations sociales) ou négatif dans le cas de l'exposition aux substances chimiques, rendant ainsi les enfants plus vulnérables aux risques associés aux PBDEs (Grandjean & Landrigan, 2014).

Des études ont notamment cherché à déterminer l'impact de l'exposition aux PBDEs pendant la grossesse ou la petite enfance sur le développement cognitif des enfants. Pour ce faire, des scientifiques de différentes équipes (principalement en Amérique du Nord et en Europe) ont

recruté des cohortes de femmes enceintes, puis ont suivi leurs enfants au fil des années. Ces études montrent que l'exposition aux PBDEs pendant la grossesse ou pendant la petite enfance est associée à une légère réduction du score de quotient intellectuel chez les enfants (Lam et al., 2017; Gibson et al., 2018). De plus, certaines études indiquent une légère augmentation de problèmes d'organisation, d'attention, et d'hyperactivité, soit des symptômes du trouble du déficit de l'attention avec/sans hyperactivité ou TDAH. Ces résultats sont cependant peu consistants d'une étude à l'autre (Lam et al., 2017; Gibson et al., 2018).

Les contaminants tels que les PBDEs peuvent affecter le développement par différents moyens. Dans le cas des PBDEs, leur structure chimique ressemble aux hormones thyroïdiennes, lesquelles jouent un rôle clé dans le développement du cerveau pendant la grossesse. Les PBDEs peuvent ainsi déstabiliser les niveaux d'hormones thyroïdiennes maternelles en s'attachant à ses récepteurs. Cela viendrait perturber le développement du cerveau pendant la grossesse et mènerait ensuite aux problèmes de développement cognitif et de comportement observés dans plusieurs études (Gibson et al., 2018; Costa & Giordano, 2007).

Faut-il s'inquiéter de la situation?

Tout d'abord, tel que mentionné plus tôt, les PBDE sont bannis depuis plusieurs années au Canada. On ne les retrouve donc plus dans des objets neufs. Par contre, les PBDEs sont des contaminants persistants et peuvent donc être relâchés dans nos environnements pour plusieurs années (Linares et al., 2015).

Il est aussi important de mentionner que la diminution de la fonction cognitive ou l'augmentation de problèmes du comportement dans les études n'est pas nécessairement visible d'un enfant à l'autre. Il est très difficile, voire impossible, de distinguer un enfant exposé d'un enfant non-exposé sur la base de leur quotient intellectuel si celui-ci diffère seulement de

quelques points. En effet, pour une concentration corporelle de PBDEs 10 fois plus grande, on parle d'une diminution de quotient intellectuel de 3.7 points en moyenne (Lam et al., 2017) alors qu'une différence notable se situerait plutôt dans l'ordre de 15 points et plus ! Là où il y a lieu de s'interroger, c'est plutôt par rapport à l'impact de ces changements au niveau populationnel. En effet, même si l'effet est petit au niveau individuel, il est important à l'échelle de la société.

Comprendre l'effet populationnel d'un contaminant

À l'échelle de la population, même un petit changement peut avoir un effet significatif (Grandjean & Landrigan, 2014; Lanphear, 2015). Voici deux exemples pour illustrer ce principe. Une étude américaine sur l'exposition des enfants au plomb a estimé qu'une diminution de 5 points du QI moyen de la population pourrait augmenter le nombre d'enfants ayant une déficience intellectuelle de 57%, c'est-à-dire passant de 6 millions à 9.3 millions (Lanphear, 2015).

De manière similaire, certaines études indiquent que le nombre moyen de symptômes de trouble du déficit de l'attention avec/sans hyperactivité (TDAH) dans la population générale est de 1 ou 2 (Lanphear, 2015) alors qu'il en faut au moins 6 pour recevoir un diagnostic de TDAH (APA, 2013). Selon des études américaines portant sur l'exposition au plomb ou au tabac, si le nombre moyen de symptômes dans la population passait de 1-2 à 3-4, le pourcentage d'enfants ayant suffisamment de symptômes pour recevoir un diagnostic de TDAH pourrait doubler, passant de 5-7% à 13-16% (Lanphear, 2015).

Malgré que ces exemples soient tirés d'études portant sur d'autres contaminants, le principe reste le même : un changement qui semble petit au niveau individuel peut avoir un effet majeur lorsqu'il est appliqué à l'échelle de la population.

Conclusion

En somme, l'exposition aux PBDEs a un effet néfaste sur la capacité intellectuelle à l'échelle de la population, mais ne mène pas nécessairement à une différence significative au niveau individuel. C'est d'ailleurs le cas pour plusieurs contaminants communs (Lanphear, 2015). En tant que société, on se doit donc de prendre une approche plus proactive en effectuant une meilleure évaluation des risques amenés par un contaminant potentiel AVANT qu'il soit intégré dans des produits d'usage quotidien.

Conseils ou recommandations pour réduire l'exposition aux PBDEs mais également à d'autres contaminants comme le plomb présent dans les poussières (https://littlethingsmatter.ca/pbdes-pfcs/)

1. Passer une vadrouille humide plutôt que l'aspirateur.
2. Utiliser un aspirateur avec un filtre de type HEPA (High Efficiency Particulate Air).
3. Éviter les produits contenant de la mousse de polyuréthane et favoriser les rembourrures de coton, laine, ou polyester.
4. Laver ses mains (et celles de ses enfants) fréquemment pour réduire l'ingestion accidentelle de poussière lors de contacts main-à-bouche.

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Pour en savoir +

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