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Developmental neurotoxicants and the vulnerable male brain: a systematic review of suspected neurotoxicants that disproportionally affect males

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The prevalence of neurodevelopmental disorders (NDs), including autism spectrum disorder, attention-deficit/hyperactivity disorder, tic disorder, obsessive-compulsive disorder, and emotional disturbances, has increased notably in the past few decades. To date, debate continues as to the origins of NDs. Increases in widespread exposure to and bioaccumulation of chemical neurotoxicants have paralleled the upsurge in NDs, and are suggested to be causal agents for NDs. One consistent aspect of NDs is the male preponderance. This review considers the issue of male preponderance by reviewing the gender-specific neurotoxic effects of recognized neurotoxicant chemicals to assess their possible etiology in NDs. This investigation consisted of a systematic literature review of original studies published from 1970–2016 on suspected neurotoxicant, to examine whether they have a disproportionate adverse effect based on gender. Based on that review, the neurotoxicants exhibiting consistent gender-specific effects, with exposed males being more affected (than similarly exposed females), were: lead, Thimerosal/ethylmercury, some organochlorine pesticides (e.g., dieldrin, endosulfan, and heptachlor), and air pollution. The next group identified were neurotoxicants exhibiting gender-specific neurotoxic effects, with males being somewhat (but not consistently) more affected than females: mercury vapor, polychlorinated biphenyls (PCBs), and organophosphate pesticides. Finally, there was a group of studies in which the neurotoxicants exhibited apparent gender-related neurotoxic effects but failed to show whether exposed males were consistently more affected than females: inorganic mercury salts, methylmercury species, and certain endocrine disruptors (e.g., phthalates and BPA). The overall conclusion from the studies reviewed was that the brain in males is more vulnerable to many toxic exposures than it is in females. Evidence suggests that the reasons for the male brain being more vulnerable include: (1) greater glutathione availability in females; (2) greater sulfate-based detoxification capacity in females; (3) potentiating effects of co-exposure to neurotoxicants and testosterone; (4) greater neuroinflammatory response in males; (5) reduced vulnerability to oxidative stress in females; and (6) neuroprotective effects of female hormones (estrogen and progesterone), especially in the reduction of inflammation and oxidative stress.

Key words: neurodevelopmental disorders; mercury; metals; autism; neurotoxicants; autism spectrum disorder, attention deficit hyperactivity disorder, tic disorder, obsessive-compulsive disorder, and emotional disturbances

INTRODUCTION

The incidence and prevalence of neurodevelopmental disorders has increased notably in the past few decades. In the United States of America (US) in 1976, the ratio of children diagnosed with learning disability to the total population of children was 1 in 30; in 2013, that ratio was 1 in 6 (Boyle at al., 2011; Campbell, 2015). In 1988, that ratio for those diagnosed with an autism spectrum disorder (ASD) was 1 in 1000 children; in 2013, that ratio was 1 in 45 children (Bryson et al., 1988; Sugiyama and Abe, 1989; Zablotsky et al., 2015). For children diagnosed with an attention deficit hyperactivity disorder (ADHD), that ratio was 1 in 18 children in 1996; in 2012, that ratio was 1 in 8 children – an increase of about 75 percent (Child Trends, 2014). Tic disorder was once considered to be rare, but, by 2012, up to 46% of school-aged children experienced tics during

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their lifetime, making tic disorder the most common movement disorder (Cubo, 2012). Also, obsessive-compulsive disorder (OCD), once thought to be rare, now affects one in 50–100 children (Beyond OCD, 2015). The number of children considered emotionally disturbed in 1980 was 1 in 50 children (US Department of Education, 1980); in 2004, that ratio had increased to 1 in 11 children (Wagner et al., 2005) (Table I).

Based on a large study conducted in 2011 by the US Centers for Disease Control and Prevention (CDC), roughly one child in six in the US is now diagnosed with a neurodevelopmental disorder (Boyle et al. 2011). This represents a dramatic increase in the last few decades. Those increases in neurodevelopmental disorders have, in turn, led to today's crises in our educational, medical, parental, and custodial care systems. Many of those children are teens who are now aging out of the education systems (Autism Speaks 2012). A greater care crisis will occur when their aging parents become unable to care for their children.

Whether these reported increases reflect true increases in the rates of neurodevelopmental disorders has been questioned. The non-etiological factors associated with an increased rate of neurodevelopmental disorders may include changes in diagnostic criteria, the inclusion of milder cases, and earlier age at diagnosis. However, several studies have specifically examined this issue and determined that these parameters, at most, can explain only a portion of the increase in neurodevelopmental disorders.

For instance, in a study of increasing ASD rates in California from 1990 to 2006, Hertz-Picciotto and Delwiche (2009) reported that the California ASD rate increased by 600%. They explained 200% of that 600% increase: 120% was from changes in diagnostic criteria (a 2.2-fold increase); 56% was from the inclusion of milder cases (a 1.56-fold increase), and 24% was from the earlier age at diagnosis (a 1.24-fold increase). They concluded that, given the uncertainties in their analyses, their explanations only accounted for between 200 and 400% of the 600% increase. They reported that there were other possible, but as yet unquantified, artifacts in the dataset that their study used. Based on the absence of values for those artifacts, they declined to claim that the reported increase represents a true increase. However, the reported residual (of 200–400%) would be hard to explain without true etiological factors.

Similarly, a study by King and Bearman (2011), using a large and representative dataset that spanned the California birth cohorts from 1992 through 2000, examined individual and community resources associated with the likelihood of an ASD diagnosis over time. Their study objective was to identify key social factors that have contributed to the numerical increase in ASD prevalence. However, they found that their study was unable to explain about half of the observed time-related increases.

For decades, the USDepartment of Education has regularly provided independent reports on the numbers of children identified as having developmental disabilities in the US school system; and those reports have consistently shown nation-wide average increases in neurodevelopmental disorders (U.S. Department of Education 1980, 2016). For example, the number of children and youths 3–21 years of age who received special education services increased from 4.7 million (11 percent of total public school enrollment) from school years 1990–91 through 2004–05 to 6.7 million (14 percent of total public school enrollment) in the last reported school year – a 27% relative net increase

Table I. The prevalence (male/female ratio) and average annual increases in neurodevelopmental disorders in the US for males

Neurodevelopmental disorder	Male / female ratio	Incidence Rate for Diagnosis (in year)		Average annual rate increase
Learning disabled	2 to 1	1 in 30 (1976)	1 in 6 (2013)	4.45%
Autism spectrum disorder (ASD)	4 to 1	1 in 1000 (1988)	1 in 45 (2013)	13.2%
Attention deficit hyperactivity disorder (ADHD)	5 to 1	1 in 18 (1996)	1 in 8 (2012)	5.2%
Tic disorder	3–4 to 1	rare* (1980)	1 in 2 (2012)	extremely high
Obsessive-compulsive disorder (childhood)	3 to 2	rare* (1980)	1 in 100 to 50 (2015)	extremely high
Emotionally disturbed	3 to 1	1 in 50 (1980)	1 in 11 (2004)	6.5%
Neurodevelopmental disorders in general	—		1 in 6 (2011)	—

* "rare" is estimated as less than (<) 1 in 10,000.

during the 14 year period (National Center for Education Statistics 2016). Those findings were reflected in a growing need for and an increase in the California financial support level for special-accommodation - programs which many high-functioning autistics (who are allegedly driving up the reported ASD rates) would not need. The "special-ed" stigma may offset the "special-ed" benefits such that the Department of Education data is likely to represent a true increase in neurodevelopmental disorders.

A study by Geier et al. (2015) examined prospective longitudinal medical records to evaluate whether diagnostic substitution from other diagnoses such as mental retardation (MR) and/or cerebral palsy (CP) to an ASD diagnosis was the driving factor behind increased ASD diagnoses in the US. The results observed were inconsistent with diagnostic substitution as a significant driving force in the increase in ASD diagnosis, and, in fact, revealed significant important clinical differences in the features associated in those with an ASD diagnosis in comparison to those with a CP or MR diagnosis. Specifically, it was observed that those with an ASD diagnosis had a significant increase in male/female ratio, delayed mean age of initial diagnosis, and a lack of significant problems at birth in comparison to those with an MR or CP diagnosis. By contrast, those with an MR or CP diagnosis in comparison to those with an ASD diagnosis had a roughly equal male/female ratio, early mean age of initial diagnosis, and significant problems at birth.

Regardless of the explanations or lack thereof, today's reported overall rate (roughly one child in six is being diagnosed with a neurodevelopmental disorder) is a crisis that deserves scrutiny.

One aspect that many neurodevelopmental disorders have in common is male preponderance. In those diagnosed with an ASD, today's male to female ratio is about 4 to 1 (Zablotsky et al. 2015). In those having an ADHD diagnosis, today's male to female ratio is roughly 5 to 1 (Joelsson et al. 2016). For learning delay, that ratio is roughly two males to one female. For developmental delay, it is also about two males to one female (Liao et al. 2015). For tic disorder, that ratio is less certain — roughly 3–4 males to one female (Cubo 2012). Emotional disturbances reflect a similar approximate three to one ratio (Wagner et al. 2005). For OCD, although it levels out in adults, the ratio in childhood is about three males to two females (Hanna 1995; Beyond OCD 2015).

In general, many researchers have not recognized the importance of finding the most probable causal factors for male preponderance in neurodevelopmental disorders. When the issue of etiology is addressed, the federal and state governmental and the medical-pharmaceutical industry researchers often cite "genetics" as the underlying cause for neurodevelopmental dis-

orders. However, that reason is improbable because genetically-based disorders typically show consistent levels or slow growth rates across generations, not dramatic generational increases. Further, the potential for sex-related genetic alterations to explain the observed male/female ratio is not supported by the perceived inheritance pattern. Finally, in those families with one or more children diagnosed with an ASD (the neurodevelopmental disorder which has shown the greatest increase (Boyle et al. 2011) including identical twins, genetic investigations have not identified consistent genetic changes. Instead, chromosomal microarray testing has shown that about 80% of ASD children have a normal genome (Shen et al. 2010; Geier et al. 2016a). The remaining 20% who have an abnormal genome have shown little to no commonality in their genetic abnormalities (Shen et al. 2010, Geier et al. 2016, Stessman et al. 2017, Yuen et al. 2017).

Instead, a genetic susceptibility to the risk of developing a neurodevelopmental disorder diagnosis is suggested, in part, because some of these disorders show a higher occurrence rate among siblings (Schendel et al. 2014). Genetic susceptiblity among families to environmentally caused diseases (e.g., acrodynia [also called "Pink disease"]) have been described previously (Bjørklund 1995, Dally 1997). Specifically, the the main cause of Pink disease was children's exposure to inorganic-mercury-containing compounds, particularly teething powders (marketed mainly in the US, the United Kindom (UK) and other English-speaking countries that were former UK colonies). Those teething powders, which were the main cause of the childhood Pink disease cases, contained high levels of mercurous chloride (Hg_2Cl_2), were rubbed on children's gums to lessen their teething pain (Bjørklund 1995, Dally 1997).

Also, as mentioned previously, if genes were a major causal factor for neurodevelopmental disorders, it would most probably require involvement of sex-related genes on the X chromosome. As a result of X chromosome involvement, female affected children would have to have affected fathers. However, this pattern is not found in neurodevelopmental disorders. Thus, the male preponderances observed indicate that neurodevelopmental disorders have environmental causes rather than specific genetic abnormalities acting in isolation.

The developing male has long been considered more fragile than the developing female (Kraemer 2000). In many instances, recent research has reported that males are more vulnerable to environmental toxicants than females. As discussed in Section 3 below, multiple studies examining the effects of neurotoxicants on neurodevelopmental disorders have found gender-dependent neurotoxicity, with males often being significantly more vulnerable than females (Kishi et al. 2013,

Allen et al. 2014a, b). Thus, male preponderance has often been reported in research studying environmental toxicants regardless of whether human cohorts, animal models, or tissue culture studies were examined.

In regard to male susceptibility in those diagnosed with an ASD, Schaafsma and Paff (2014) described many genetic, epigenetic, hormonal, and environmental mechanisms that might explain the observed male preponderance in ASD, including early exposure to an-

drogenic hormones and early maternal immune activation. Robinson et al. (2013) analyzed two separate, large studies of twins and found that the females in those studies were more protected from autistic impairments relative to the males, indicating that females may require larger etiologic loads than males to manifest the autistic phenotype. Jacquemont et al. (2014) found that females with an ASD diagnosis have a higher mutational burden, meaning that it takes more mutations

Table II. The results of the current examination of gender-specific neurotoxic effects of the neurotoxicants suspected of playing a role in the increase in neurodevelopmental disorders

Developmental neurotoxicants documented in human epidemiology studies	Grandjean and Landrigan 2006 (formal list of 5)	Landrigan et al. 2012 (informal list of 13)	Workshop described by Landrigan et al. 2012 (formal list of 10)	Grandjean and Landrigan 2014 (formal list of 11)	Project TENDR	Sealey et al. 2016	Score assigned by current review
Lead (Pb)	X	X	X	X	X	X	1
Methylmercury (Me-Hg-)	X	X	X	X	X	X	3
Polychlorinated biphenyls	X	X	X	X	X		2
Arsenic (As)	X	X		X		X	5
Toluene or other solvents	X			X		X	—
Organophosphate pesticides (e.g., chlorpyrifos)		X	X	X	X	X	2
Organochlorine pesticides		X	X			X	1
Endocrine disruptors (e.g., phthalates)		X	X			X	3
Automotive exhaust		X	X				1
Polycyclic aromatic hydrocarbons (PAHs) or combustion-related air pollutants		X	X		X	X	5
Bisphenol A (BPA)		X					3
Polybrominated diphenyl ethers (PBDE flame retardants)		X	X	X	X		6
Perfluorinated compounds		X	X				5
Manganese		X		X			—
Fluoride				X			—
Dichlorodiphenyl-trichloroethane (DDT)				X			—
Tetrachloroethylene				X			—
Glyphosate						X	5
Aluminum adjuvants						X	5
Fragrances						X	—
Thimerosal / Other ethyl-Hg-based compounds							1

1 = Consistent gender-specific neurotoxic effects with males more affected; 2 = Gender-specific neurotoxic effects, with males being somewhat more affected, but not consistently; 3 = Gender-specific neurotoxic effects, but it is not clear whether males or females are more affected; 4 = Gender-specific neurotoxic effects, with females being more affected; 5 = Insufficient research on gender-specific neurotoxic effects; and 6 = No gender-specific neurotoxic effects reported.

to trigger an ASD diagnosis in females than it does for males, indicating that females have greater resistance to the etiologies of an ASD diagnosis than males.

Moreover, the rise in the incidence and prevalence of neurodevelopmental disorders has paralleled the increase in the widespread exposure to and the bio-accumulation of chemical neurotoxicants (Genuis and Kelln 2015). Various environmental neurotoxicants or xenobiotics have been suggested as causal agents in neurodevelopmental disorders (Table II). For example, in a widely-read 2006 study, Grandjean and Landrigan identified five industrial chemicals as neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Grandjean and Landrigan et al. (2014) in afollow-up study stated that neurodevelopmental disabilities affect over 10% of children born in the US each year. Additionally, they listed the top ten environmental compounds suspected of triggering neurodevelopmental disorders in the affected children: lead, methylmercury, polychlorinated biphenyls, organophosphate pesticides, organochlorine pesticides, endocrine disruptors such as phthalates, automotive exhaust, polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers (PBDEs; brominated flame retardants), and perfluorinated compounds. Grandjean and Landrigan (2014) postulated that these toxic chemicals may be responsible for the increase in some neurodevelopmental disorders in the past few decades. Overall, this theory seems biologically plausible since we are living in an increasingly toxic world, and fetuses, infants, and children are the most vulnerable (Schettler 2001, Laks 2009, Grandjean and Landrigan, 2014).

A recent consensus statement by Project TENDR: Targeting Environmental Neuro-Developmental Risks, a collaboration of health professionals and children's advocates, also provided examples of toxic chemicals that can contribute to learning, behavioral, or intellectual impairment, as well as to specific neurodevelopmental disorders, such as ADHD and ASD (Bennett et al. 2016). Like the list provided by Grandjean and Landrigan (2014), their list included organophosphate pesticides; PBDE flame retardants;; lead; mercury; and polychlorinated biphenyls; combustion-related air pollutants, which include polycyclic aromatic hydrocarbons, nitrogen dioxide and particulate matter (Bennett et al. 2016).

Sealey et al. (2016) also presented a list of neurotoxicants suspected to play a role in the increase in neurodevelopmental disorders. That list added two more neurotoxicants in addition to those previously mentioned: glyphosate (a chemical used as the "active" ingredient in the herbicide Roundup) and aluminum adjuvants (annealed polymeric hydroxyaluminum III "salts" usually used in vaccines to "indiscriminately ac-

tivate" the immune systems in the recipients of certain vaccines) (Nevison 2014; Sealey at al. 2016).

In this systematic review, we considered male preponderance as an important feature to help elucidate potential environmental etiological risk factors related to neurodevelopmental disorders. We analyzed the gender-specific neurotoxic effects of specific neurotoxicants to assess their role in and the level of contribution to neurodevelopmental disorders. Thus, on the premise that male preponderance is an important clue to the etiology of neurodevelopmental disorders, this investigation examined a list of known neurodevelopmental toxicants to evaluate the evidence regarding their gender-dependent neurotoxicity. This critical review also rated the magnitude of gender-specific effects of the neurotoxicants evaluated based on available research. Finally, possible biological mechanisms that may explain the heightened vulnerabilities of the male brain in comparison to the female brain were examined.

Although two of the reviewed listings of suspected causal agents only mentioned the organic mercury compound, "methylmercury", this investigation reviewed "mercury species", a broader category that includes methylmercury. Also, even though one of the preceding lists of neurotoxicants only included "automotive exhaust", this review evaluated "air pollution", a broader category that includes "automotive exhaust", because, in some instances, air pollution includes airborne toxic metal species (both particulate [e.g., aluminum and lead oxides] and gaseous [e.g., elemental mercury vapor and nickel tetracarbonyl]).

METHODS

This investigation comprised a systematic literature search of original studies on these suspected neurotoxicants to examine whether they have a disproportionate adverse effect based on gender. The literature search from 1970 to August 2016 included published original research from PubMed and Google Scholar. In addition, the references cited in the identified publications were searched to find additional studies. Search terms included: neurotoxin, neurotoxicant, toxin, toxicant, gender, gender specific, gender bias, sex, sex bias, sex selective, gender selective, gender effects, sex effects, boys more affected, girls more affected, boys, girls, lead, Pb, methylmercury, mercury, mercury vapor, Hg, Thimerosal, metals, methyl-mercury, ethyl-mercury, inorganic-Hg, mercury chloride, polychlorinated biphenyls, organophosphate pesticides, glyphosate, Round-up, organochlorine pesticides, pyrethrins, endocrine disruptors such as phthalates, automotive exhaust, air pollution, particulates, polycyclic aromatic

hydrocarbons, polybrominated diphenyl ethers (brominated flame retardants), perfluorinated compounds, and aluminum adjuvant.

The neurotoxicants were then rated on the extent and consistency of gender-specific neurotoxic effects based on the available research, using the following scoring system:

Scoring system

- Score 1 = Consistent gender-specific neurotoxic effects with males more affected;
- Score 2 = Gender-specific neurotoxic effects, with males being somewhat more affected, but not consistently;
- Score 3 = Gender-specific neurotoxic effects, but it is not clear whether males or females are more affected;
- Score 4 = Gender-specific neurotoxic effects, with females being more affected;
- Score 5 = Insufficient research on gender-specific neurotoxic effects; and
- Score 6 = No gender-specific neurotoxic effects reported.

EXAMINATION OF SUSPECTED NEUROTOXICANTS

Lead (Pb)

Low-level Lead (Pb from Latin plumbium) exposure has negative behavioral and cognitive consequences in humans and animals. Even brief Pb exposure during development produces behavioral changes that last well beyond the exposure period (Stewart et al. 1998), and neurobehavioral deficits from early developmental exposure to Pb can extend into adulthood (Winneke et al. 1996). A decrease in the Intelligence Quotient (IQ) score of those exposed is typically reported. A Meta-analysis of studies in Pb-exposed children have found that a typical doubling of blood Pb levels from 100 to 200 micrograms/l is associated with an average IQ-loss of 1-3 points (Winneke et al. 1996).

Several studies suggest that Pb exposure affects boys more than girls (Llop et al. 2013). For example, Khanna et al. (2015) found behavioral evidence that boys experience the negative cognitive effects of Pb more than girls. In that study, the investigators tested executive function and reading readiness skills in 40 young children, 3–6 years of age (23 children with elevated blood Pb levels, 17 children without elevated blood Pb levels). Ele-

vated blood levels of Pb adversely affected male executive function performance much more than it decreased female executive function performance. Males with elevated blood Pb levels also showed deficits in reading readiness compared to males with normal lead levels. However, reading readiness scores for females were not adversely affected by their observed blood Pb levels.

Using magnetic resonance imaging (MRI), Cecil et al. (2008) reported finding, for the 157 subjects evaluated, that significant decreases in brain volume were associated with elevation in their childhood blood Pb concentrations. The areas of Pb-associated losses in gray-matter volume were much larger and more significant in the men than the women.

In a follow-up study of that same cohort of 157 adults, these researchers (Brubaker et al. 2010) examined associations between adult gray matter volume loss measured using high resolution volumetric MRI and the yearly mean blood Pb levels reported when the individuals in the cohort were 1 to 6 years of age. When the researchers looked at the data by gender, they found that males exposed to Pb during childhood and adolescence showed significantly more gray matter volume loss in adulthood than the adult females exposed to Pb when they were young (Khanna et al. 2015, Brubaker et al. 2010).

Studying a cohort of 457 three-year-old children, Jedrychowski et al. (2009) reported on the gender-specific differences in the neurodevelopmental effects of prenatal exposure to very-low-Pb levels. They measured accumulated Pb dose in infants over the pregnancy period using cord blood lead level (BLL). They used the Bayley Mental Development Index (MDI) to assess cognitive deficits. Their study results suggested that there might be no threshold below which Pb is not toxic in children and that the 3-year old boys were more susceptible to prenatal very-low-Pb exposure than the girls in the study.

Several other studies find greater adverse neurocognitive outcomes in Pb-exposed males than Pb-exposed females. Froehlich et al. (2007) found that adverse effects of Pb on planning and rule-learning and reversal were seen primarily in boys. As early as 1987, a study found that the inverse relationship between increasing Pb exposure and decreasing IQ scores was much more pronounced in boys (Pocock et al. 1987). Ris et al. (2004) reported that, for males, increased Pb exposure led to increased deficits in both Attention and Visuoconstruction (ability to organize and manually manipulate spatial information to make a design).

However, one study by Sioen et al. (2013) found similar effects in girls and boys exposed to Pb. They examined the association between prenatal exposure to Pb and other toxic chemicals and behavioral prob-

lems in 7–8-year-old children. When the children were 7–8 years of age, 270 of their mothers completed the Strengths and Difficulties Questionnaire assessing their children's behavioral health. They found that doubling the prenatal Pb exposure (cord blood lead levels) was associated with a 3.4 times higher risk for hyperactivity in both boys and girls.

In conclusion, the preceding studies clearly support assigning Pb a Rating Score of 1, showing consistent gender-specific neurotoxic effects with males more affected except for hyperactivity, in which both sexes were equally adversely affected.

Mercury (Hg)

Mercury (Hg) toxicity can be complex and nonlinear (Berlin et al. 2015). Its molecular mechanism of toxicity is unusually broad. Since it binds sulfhydryls, which are ubiquitously found in the proteins and peptides distributed throughout the body, its toxic effects can affect any organ system (Berlin et al. 2015). Many studies have shown that Hg is a developmental neurotoxicant in both humans and animals. Some studies suggest that developing males are more sensitive to Hg exposure than developing females (Khan et al. 2012; Woods et al 2014). However, upon further investigation, the magnitude of the gender effects appear to vary somewhat according to the speciation of the Hg, e.g., elemental mercury vapor (Hg^0); inorganic mercury salts (mostly Hg^{2+} [e.g., $HgCl_2$] and a few Hg^{1+} [e.g., Hg_2Cl_2 {Calomel}]); methylmercury-based compounds (principally methylmercury species [$H_3C–Hg–X$, where X is chloride {Cl} or hydroxide {OH}] and where methylmercury may also be represented as Me-Hg—]; or ethylmercury-based compounds or Et-Hg— (mainly sodium [Na^{1+}] Et-Hg–thiosalicylate [$H_3C–(H_2C)–Hg–thiosalicylate^{1-}$]). The toxicokinetics of Hg vary depending on the form of Hg. This section will examine elemental mercury vapor (Hg^0); inorganic mercury salts (Hg^{2+} and Hg^{1+}); methylmercury chloride ($H_3C–Hg–Cl$ [Me-Hg-Cl]) and methylmercury hydroxide [Me-Hg-OH]); and the sodium salt of ethylmercury thiosalicylic acid ([Na^+ $H_3C–(H_2C)–Hg–thiosalicylate^-$ or Na^+ Et–Hg–thiosalicylate$^-$], which is known by various tradenames including, but not limited to, Thimerosal, Thiomersal, Timerosal, Tiomersal, and Merthiolate).

Elemental Mercury Vapor (Hg^0)

Elemental mercury vapor (Hg^0), such as that which is released from dental amalgams, which are roughly 50: 50 mixtures of elemental Hg and elemental silver (Ag) containing minor amounts of other metals (e.g., Copper [Cu]) is uncharged and is thus lipophilic. Hg^0 is rapidly distributed throughout the body, passing easily through cell membranes, and is then oxidized into the divalently charged form of mercury (Hg^{2+}), which can be trapped inside cells (Berlin et al. 2015).

The Casa Pia Clinical Trial of Dental Amalgams in Children provided valuable human epidemiological evidence for the hypothesis that boys tend to retain Hg more than girls. Woods et al. (2007) found that mean urinary Hg excretion for boys and girls were similar at baseline. However, at about two years after amalgam placement, urinary Hg excretion declined for both genders. The decrease in urinary Hg excretion was much larger for the boys than for the girls. This finding suggests that Hg toxicity is nonlinear and that chronic Hg exposure may impair excretion and increase retention. Based on the preceding findings, the study's boys retained and accumulated significantly higher levels of Hg than the study's girls over the course of comparable Hg exposures from Hg-amalgam dental fillings (Woods et al. 2007).

Furthermore, a detailed reanalysis of the Casa Pia data, which controlled for certain genetic variants, provided remarkable human epidemiological evidence that boys with at least one of a dozen common genetic variants experienced greater adverse effects in many different neurobehavioral outcomes than did the girls with the same genetic variants and similar Hg exposures. Specifically, Woods et al. (2014) investigated the effects on susceptibility to Hg toxicity of 27 common variants of 13 genes and found that boys with at least 1 of 12 key variants were significantly affected across a broad range of neurobehavioral outcomes, whereas girls were much less affected. Their report focused on the role of common genetic variants in modifying susceptibility to Hg toxicity. However, given that the susceptibility genes are numerous and common, the alarming subtext of the report is that children, boys in particular, get neurobehavioral toxicity from routine exposures to Hg, ostensibly from Hg-amalgam dental fillings, which have hitherto been presumed safe. The authors noted that their exposure metric, urinary Hg levels, may include other Hg sources besides amalgam; however, an earlier study by the same team found that urinary Hg levels were correlated with amalgam (Woods et al. 2007), and another study found that exposure to fish Hg in this cohort was insignificant (Evens et al. 2001); therefore, it is reasonable to conclude that the neurobehavioral impairments are correlated with amalgam exposure. For the boys with the variant(s), significant dose-dependent impairments were found in most of the 23 neurobehavioral tests administered, and the domains most affected were attention, learning and memory, visual spatial acuity, and motor function. The remaining domain, executive function, was less affect-

ed. On the other hand, among the girls evaluated with the same genetic variants, modification of the effects of Hg on neurobehavioral functions was substantially more limited. This study is remarkable not only for its indication of both significant adverse effects and gender differences in susceptible children from routine exposures, but also because it was a more detailed analysis of the Casa Pia Clinical Trial of Dental Amalgams in Children. The original (2006) results, which found no significant difference in the group-average neurobehavioral outcomes between the Hg-amalgam group and the non-amalgam group, were widely cited as evidence for the safety of Hg-amalgam fillings, which, in retrospect, appears naive (Homme et al. 2014).

In contrast to this compelling human evidence that Hg exposure affects boys significantly more than girls in terms of both Hg retention and the resulting neurobehavioral impairments, the findings from two rodent studies by Yoshida et al. (2005, 2011) suggest that female rodents with a certain genetic varient may be more susceptible. In the most recent study, the investigators found that brain concentrations of Hg were significantly higher and total locomotor activity was lower in the metallothionein-null, Hg^0-vapor-exposed female mice than in their male counterparts, although for the wild-type mice, the gender difference were much less pronounced (Yoshida et al. 2011). (Metallothionein is a metal storage protein that protects against the toxicities of various metals.) Similarly, in the earlier study, the investigators found that the brain concentrations of Hg were significantly higher in the Hg^0-exposed, metallothionein-null female mice than in their male counterparts (Yoshida et al. 2005). However, gender differences in neurobehavioral testing were mixed; Hg^0-exposed metallothionein-null male mice showed a significant decrease in total locomotor activity as compared to controls, and Hg^0-exposed metallothionein-null female mice showed a learning disability in the passive avoidance response and a retarded acquisition in the Morris water maze as compared with controls (Yoshida et al. 2005).

In conclusion, elemental mercury vapor (Hg^0) was assigned a Rating Score of 2, showing gender-specific neurotoxic effects, with the males likely being more affected, but not consistently so. Some recognition of the inconsistent and incomplete data is acknowledged.

Inorganic mercury salts

The overall neurotoxic effects of inorganic Hg salts do not appear to be as potent as organic alkyl Hg compounds or elemental Hg vapor. Because of, in part, the hydrophilic nature of inorganic Hg salts, the kidney is the main target organ for this form of Hg. For example,

Khan et al. (2001) examined the uptake and distribution of orally gavaged $HgCl_2$ in rats. The organs examined were: brain, gonads, heart, kidneys, liver, lungs, pancreas, and spleen. They found that both male and female rats accumulated significantly more Hg in their kidneys than their other organs. In regard to the gender-selective neurotoxic effects of inorganic Hg salts, the evidence appears to be mixed.

For example, Zhang et al. (2013) examined $HgCl_2$ exposure in the offspring of unsociable dams with high susceptibility to Hg-induced autoimmunity (SFvF1) and from highly sociable dams with lower susceptibility to Hg-induced autoimmunity (FvSF1). Cytokine levels were elevated in the brain regions of the Hg-treated susceptible mice but not in the lower susceptibility mice. Moreover, in the high susceptibility mice, the females had more brain regions expressing cytokines than the males. The social behaviors of high susceptibility mice were significantly impaired, with the females showing more of a decline in social behaviors than males. The greater the Hg-induced neuroinflammation found in the high susceptibility female mice, the worse their sociability outcome.

In a 1997 rodent study, Pamphlett et al. also found greater neurotoxic effects in females from exposure to inorganic Hg salts. The investigators examined whether the uptake of low-dose $HgCl_2$ into motor neurons differs between male and female mice. They found that female mice accumulated more inorganic Hg in motor neuron axons than did male mice. They theorized that these findings might have been because the females accumulated less Hg in their kidneys than the males, leaving more circulating Hg species available to be taken up by motor neuron axons.

In a 1986 rodent study, Thomas et al. reported that exposure to inorganic Hg 98 days after one subcutaneous dose of CH_3-Hg-Cl in rats resulted in greater accumulation or retention of inorganic Hg in the nervous system in females than in males. The cumulative exposure of the brain of female rats to $HgCl_2$ was 2.19 times that of the male rats.

Curtis et al. (2010) treated prairie voles with chronic ingestion of inorganic Hg salt ($HgCl_2$) and compared their behavior to controls. The behavioral effects of $HgCl_2$ ingestion were observed as social avoidance and were specific to the males. No adverse effects of inorganic Hg exposure were observed in the females.

In a rodent study, Hultman and Nielsen (2001) found significantly higher renal Hg concentrations and whole-body Hg retention in the male mice as compared to those parameters in the female mice following prolonged exposure to $HgCl_2$ dissolved in drinking water.

In conclusion, inorganic mercury salts have been assigned a Rating Score of 3, showing gender-specific

neurotoxic effects, even though it is not clear whether males or females are more affected. Inorganic Hg salts also appear to be less toxic than organic alkyl-Hg compounds and elemental Hg^0 vapor.

Methylmercury (CH₃–Hg– [i.e., Me-Hg-])

Several studies using animal models have shown greater susceptibility in males on neuropathological and behavioral parameters from Me–Hg exposure (primarily from Me–Hg–Cl solutions or, less often, Me–Hg–OH solutions or Me–Hg– exposure via dietary fish [Me–Hg–"cysteine"]). However, some earlier studies found that the treated females were more vulnerable than the like-treated males.

Beginning with studies that show males as more susceptible, one example is Biamonte et al. (2014), who studied the interactions between three risk factors: genetic status, gender, and exposure to methylmercury, in heterozygous reeler (rl$^{+/-}$) mice. Mice were exposed to Me-Hg during the prenatal and early postnatal period, either at a subtoxic dose (2 ppm in Dams' drinking water), or at a toxic dose (6 ppm in Dams' drinking water). They reported that higher doses (predominately aqueous 6ppm-Hg solutions of Me-Hg) caused loss of Purkinje cells in both sexes; however, the "autism-like" features (loss of sociability, preference for sameness) were noted only in the dosed rl$^{+/-}$ male mice.

In a study of 2-day-old mice receiving a single oral dose of 4 mg Hg/kg from Me-Hg and sacrificed 24 hours or 19 days later, scientists found that the proliferating granule cells of the developing cerebellum underwent a remarkable inhibition of division, as indicated by the decrease in late mitotic cells. Importantly, at this lower dose, there was a sex difference in sensitivity, with the dosed male mice being considerably more sensitive than the dosed females (Sager et al. 1984). Examining the cerebellar cortex, they found that the number of cells in the molecular layer and the thicknesses of the molecular layer and the internal granular layer were significantly reduced in the dosed male neonatal mice. All measures in females remained unaltered.

Onishchenko et al. (2007) investigated the long-term effects of developmental exposure to methylmercury. Pregnant mice were exposed to 0.5 mg of Hg /kg/day from Me–Hg dissolved in their drinking water. Analysis of behavior exhibited in the offspring showed decreased exploratory activity, depression-like behavior, and learning disturbances in the exposed male mice. However, like the inorganic Hg studies discussed previously, the evidence indicated that Hg accumulation in the male offspring was greater in their kidneys than it was in the females' kidneys. In the female offspring, the Hg accumulation was greater in their brain than it was in the

males' brain. Hirayama and Yasutake (1986) examined sex and age differences in Hg distribution and Hg excretion in mice given a single 5 mg/kg dose of Me–Hg–Cl. They found that the dosed males had lower Hg levels in their brain, liver, and blood than the dosed females, but not in their kidney tissues, which showed higher values than those observed for the dosed females.

Similarly, Magos et al. (1981) also found that after identical doses of Me-Hg (dosed daily by gastric gavage four or five times with 8.0 mg/kg Hg as Me–Hg) in male and female rats, the brains of dosed females always contained more Hg than those of the identically dosed males. In accordance with the brain levels, the female rats showed greater coordination disorders and more extensive damage to the granular layer of the cerebellum than the male rats.

Likewise, Tagashira et al. (1980) also found that when mice were fed Me–Hg–Cl in food containing 50 and 100 ppm of Me–Hg–Cl for 30 days, the females were more sensitive to the compound both in the onset and the severity of the toxic signs, particularly motor incoordination. The Hg content in the brain of the dosed female mice tended to reach the toxicity threshold earlier than that in the brain of the males. However, when a single dose of Me–Hg–Cl of 50.6 mg/kg was given orally only once, the males started to die several days sooner than the females.

Inouye et al. (1986) orally fed Me–Hg–Cl to pregnant mice on day 13 of pregnancy at doses of 2.5, 5, 10, and 20 mg/kg and examined maternal and fetal brain mercury levels. First, they found that the level of Hg was 1.6-4.9 times higher in the fetal brain than in the maternal brain. They also reported that a sex difference in Hg levels was observed in the fetal brain after a single Hg dose of 2.5 mg/kg was given to the pregnant mice. Specifically, the Hg concentration was higher in the females' brain than it was in the brain of the males. Goulet et al. (2003) also found that chronic exposure to Me-Hg-Cl during fetal and postnatal development had sex-dependent effects in mice. They found negative effects on horizontal exploration and on working memory in the modified T-maze, with the treated females being more affected than the treated males.

In conclusion, Me-Hg-compounds were assigned a Rating Score of 3, showing gender-specific neurotoxic effects, but it is not clear whether males or females are more affected.

Ethylmercury or Thimerosal [Na+ Et-Hg-salicylate–]

Ethylmercury (H_3C-(CH_2)-Hg- [Et-Hg-]) is the form of Hg present in Thimerosal (the sodium salt (Na^+) of Et-Hg-"thiosalicylate"$^-$), a compound still used as a preservative in many vaccines and other medical and

cosmetic preparations (Ni et al. 2016). Many studies show gender-selective effects in the neurological system from exposure to Thimerosal, with males consistently found to be more vulnerable.

In the research by Branch (2009), the discovery of the gender-selective effects of Thimerosal began with a serendipitous observation. Branch originally undertook a study to determine the maximum tolerated dose of Thimerosal in male and female CD1 mice. However, he found that Thimerosal has a differential maximum tolerated dose depending on whether the mouse was male or female. At doses of 38.4–76.8 mg/kg (using 10% aqueous DMSO as the diluent), all the male mice succumbed to the exposure while none of the female mice succumbed. That study reported that Thimerosal has a 3-fold increased toxicity in males compared to females (the maximum tolerated dose of Thimerosal in males was 25.6 mg/kg; the maximum tolerated dose in females was 76.8 mg/kg).

Khan and colleagues (2012) examined cerebellar gene expression following perinatal Thimerosal exposure in male and female rat neonates, especially on thyroid-hormone-(TH)-dependent gene expression and other genes critical for cerebellar development. They concluded that perinatal Thimerosal exposure results in altered TH-dependent gene expression, with males being more sensitive to the effects of the Thimerosal exposure. They further stated that the genes that were activated by Thimerosal are negatively regulated by TH, supporting their hypothesis of local brain hypothyroidism's being induced by Thimerosal.

These researchers previously reported greater effects in Thimerosal-treated male neonates (Sulkowski et al. 2012). In that study, Sulkowski et al. (2012) found a greater disruption of hormones in the brain of male rats exposed to Thimerosal, where local intra-brain conversion of thyroxine to the active hormone, 3',3,5-triiodothyronine (T3), was significantly decreased (60.9%) in Thimerosal-exposed SHR male rat pups. However, cognitive deficits from Thimerosal exposure were found in both male and female rats. The researchers stated that the negative neurodevelopmental impact of perinatal Thimerosal exposure appears to be both strain- and sex-dependent.

Olczak et al. (2011) examined neonatal treatment of rats with Thimerosal on behaviors, such as locomotor activity, anxiety, social interactions, spatial learning, and on the brain's dopaminergic system. Both sexes manifested impairments of locomotor activity and increased anxiety/neophobia in the open field test. When the rats were treated with the highest dose, the frequency of prosocial interactions was reduced, while the frequency of asocial/antisocial interactions was increased in males, but decreased in females. They con-

cluded that males were more sensitive than females to the neurodisruptive/neurotoxic actions of Thimerosal.

In another animal study, Li et al. (2014) conducted a transcriptomic analysis of the neurotoxic effects after intermittent neonatal administration of Thimerosal in the mouse brain. They injected mice with Thimerosal at a dose 20× higher than that used for human infants during the first four months of life. Thimerosal exposure resulted in neural developmental delay, social interaction deficiency, and inclination for depression. Neuropathological changes were also noted in adult mice neonatally treated with Thimerosal. However, an elevation of anterior pituitary secreting hormones occurred exclusively in the males but not the females treated with Thimerosal, demonstrating the gender bias of the effects of Thimerosal on the pituitary-related endocrine system.

Recent epidemiological studies in humans have found an increased risk of neurodevelopmental disorders including autism from exposure to Thimerosal in male infants as compared to female infants. Three studies, Geier et al. (2013, 2014, 2015), found, while examining the effects of Thimerosal in the Vaccine Safety Datalink (VSD) and the Vaccine Adverse Reporting System (VAERS), that far more males are affected by Thimerosal than females. Geier et al. (2014), in particular, examined the dose-response of organic mercury exposure from Thimerosal-containing vaccines and found that males are at an increased risk of NDs at a lower exposure than females.

Studies sponsored by the US Centers for Disease Control (CDC) have also reported gender-specific neurotoxicant effects from Thimerosal. Barile et al. (2012) and Thompson et al. (2007), for example, both reported an association between Thimerosal exposure during the first seven months of life and the presence of tic disorder in boys.

In conclusion, Thimerosal (an Et-Hg- derivative) was assigned a rating of 1, because numerous studies found consistent gender-specific neurotoxic effects with males being more affected than the females.

It is important to note that epidemiological studies that examined gender-specific effects of Thimerosal in ASD, ADHD, and tic disorder, have consistently found that males are more affected than females (Geier et al. 2017). As explained by Geier et al. (2017), these disorders are abnormal brain connectivity spectrum disorders (ACSDs), which display long-range under-connectivity and short-range over-connectivity, a pathology in the developing brain that can result from Thimerosal exposure (Kern et al. 2015). In addition, studies find that the symptom severity in these ASCDs correlates with the degree of long-range under-connectivity and short-range over-connectivity (Kern et al. 2015).

Polychlorinated biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are a group of organochlorine compounds and a class of human-made organic chemicals that have been widely used as industrial coolants but have been banned in the US since 1979. According to the Stockholm Convention, the ratification of the banning of organochlorine compounds such as PCBs worldwide occurred in 2001; however, in some countries, PCBs are still used for specific situations, such as malaria vector control (Gascon et al. 2015). Despite the ban, significant levels of PCBs are still present in the environment today (Gascon et al. 2015). In a study by Gascon et al. (2015), the authors state that, even decades after the US (and to some extent worldwide) ban of organochlorine compounds, young people in western countries today are still bioaccumulating these compounds. These researchers examined total serum burdens from birth until adolescence in two birth cohorts from 1997. Gascon and colleagues reported that despite the reduction in organochlorine compound concentrations, the total serum burdens of DDE and PCBs were higher in adolescents than at birth. In other words, these chemicals were continuing to accumulate in children's bodies.

PCBs are neurotoxicants and endocrine disrupters (Boas et al. 2006). Several prospective cohort studies have found that prenatal and early postnatal exposure to PCBs is associated with a deficit or retardation of mental and/or motor development (Winneke 2011). The pathophysiology seems to involve interference with thyroid metabolism during brain development (Winneke 2011). In regard to gender-specific neurotoxicant effects, evidence suggests that, similar to Hg, the gender-specific effects seem to differ depending on the form of PCB.

Most studies suggest that males are more affected the females. For example, Nguon et al. (2005) examined gender effects of a certain mixture of PCBs (Aroclor 1254) on cerebellar development and motor functions in male and female rat neonates. They found that cerebellar mass was more reduced in male than female pups. Also, there was a greater increase in glial fibrillary acidic protein (GFAP expression, which is indicative of neuronal damage) expression in males than in the females. Impaired performance on behavioral tests was also greater in the males.

Studying ADHD, Lombardo et al. (2015) examined the effects of exposure to vapor-phase inhalation of PCBs (Aroclor 1248) on operant behavior of male and female Sprague-Dawley rats. This exposure resulted in hyperactivity and impatience in the rats, and this was more pronounced in males than females. Similarly, Reilly et al. (2015) assessed the effects of gestational exposure to PCBs (Aroclor 1221) on the social behavior later in adulthood in male and female Sprague-Dawley rat. Males were more sensitive than females to the toxic exposure, showing a greater decrease in several parameters that measured sociability.

The behavioral findings that show a greater effect in males exposed to PCBs have also been found to parallel effects on gene expression. Bell et al. (2016), for example, exposed male and female Sprague-Dawley rats to PCBs (Aroclor 1221) or vehicle (a substance without action) prenatally, during juvenile development, or both, and assessed their effects on serum hormone concentrations, gene expression, and DNA methylation in adulthood. They found that gene expression in the brains of males, but not females, was affected by two doses of the PCB solutions to which the rats were exposed, and the results observed for Aroclor 1221 solutions paralleled the negative behavioral effects of exposures to PCBs. These researchers concluded that the males were more vulnerable than the females to the treatments used.

In another study in rats, the effects of PCBs (PCB52 and PCB180) on auditory function were examined using the brainstem auditory evoked potentials (Lilienthal et al. 2011). In that study, pregnant rats received repeated oral doses of PCB52 and PCB180. Brainstem auditory evoked potentials were recorded in adult male and female offspring. The effects were more pronounced in male compared with female offspring. The authors reported that latencies of waves II and IV were prolonged in the exposed males, whereas only wave IV was affected in the exposed females.

Later, Lilienthal et al. (2015) also examined brainstem auditory evoked potentials in adult rats exposed to other PCB solutions (PCB74 and PCB95). Rat dams were orally exposed to PCB74 or PCB95 from gestational day 10 to postnatal day 7. Control dams were given the vehicle (a substance without action). They found pronounced changes in brainstem auditory evoked potentials at low frequencies in PCB74 offspring, with elevated thresholds in both sexes. However, PCB95 increased thresholds in males, but not females.

In human infants, Berghuis et al. (2014) also found that prenatal exposure to PCBs (mainly 4-OH-PCB-107) was associated with less optimal neurological functioning in boys. In their observational cohort study, they found measurable levels of 10 PCBs and 6 OH-PCBs in maternal blood samples from 98 pregnant women. They assessed the infants' neurological function using the Touwen examination at three months and calculated an Optimality Score. The exposures translated into less optimal neurological functioning in the boys.

However, some studies have found greater effects in females. Guo et al. (1994) studied Taiwanese children

born seven to twelve years after their mothers' intoxication by heat-degraded PCBs. Children of the mothers showed a delay in development on the Chinese Child Developmental Inventory and on a general development test. Girls were more affected than boys in their development.

Two studies in rats showed females to be more vulnerable to the neurotoxic effects for the PCBs tested. In a study by Chu et al. (1996a) PCB28 was investigated in rats after a 90-day dietary exposure. Again, brain biogenic amine changes were greater in the female rats. Female rats showed a decrease in dopamine concentration in the *substantia nigra* region at 0.5 ppm PCB 28 and higher dosing. The authors concluded that the females were more sensitive than the males to the neurotoxic effects of PCB28.

In another study by Chu et al. (1996b), the authors examined the toxic effects of subchronic exposures to PCB153 in rats after 13 weeks of dietary exposure. PCB153 caused changes in brain biogenic amines and intermediate products mainly in females. The authors concluded that the female rats appeared to be more sensitive to the neurotoxic effects of low-level exposures to PCB153 than the similarly exposed males.

However, looking at the same PCB (PCB 153) as Chu et al. (1996b), Dervola et al. (2015) studied gender-dependent monoaminergic changes induced by PCB153 in the rat brain and found changes in both the female and male brain with slightly more changes in the male brain. PCB-exposure led to increases in monoamine transmitter turnover in both male and female animals. However, decreases in the levels of both pre- and post-synaptic dopaminergic proteins were predominantly seen in the male rats.

Berghuis et al. (2015) reviewed the scientific literature on the relationship between PCB exposure and childhood neurodevelopmental outcomes in studies from the past ten years. The authors concluded that, as a whole, the studies reviewed found that boys were more affected than girls by exposures to PCBs.

In conclusion, PCBs were assigned a Rating Score of 2, indicating consistent gender-specific neurotoxic effects, with males being somewhat more affected, but not consistently so.

Organochlorine pesticides (e.g., dieldrin, endosulfan, heptachlor, dichlorodiphenyltrichloroethane [DDT], and dichlorodiphenyldichloroethylene [DDE])

As with PCBs (which are chlorine derivatives of the organic aryl compound biphenyl), the use of the organochlorine pesticides in this section's title were also "banned" (severely restricted) by/in the 1970s, and yet

significant levels of these organochlorine pesticides and their breakdown products are still present in the environment (Caudle et al. 2005). In the study mentioned earlier that addressed findings for PCBs, Gascon et al. (2015) reported that, in two birth cohorts from 1997, the total serum burdens of DDE, a metabolite of and impurity in DDT, and PCBs were higher in the cohorts' adolescents than their burdens at birth. This was decades after the ban in the production and use of the parent organochlorine pesticide, DDT, and the organochlorine-based PCBs.

Evidence suggests that exposure to organochlorine pesticides and their metabolites can result in impaired motor and cognitive development in newborns and infants (Saeedi Saravi and Dehpour 2016), especially in visuomotor and sensorimotor functions (Berghuis et al. 2014). The nigrostriatal dopamine pathway appears to be one of the target systems in the brain (Wilson et al. 2014). Organochlorine compound exposures are also associated with higher rates of depression (Beard et al. 2013). Their gender-specific neurotoxic effects appear to be mixed. Two classes of these compounds, with slightly different toxic mechanisms, exist: DDT-related insecticides and chlorinated alicyclic insecticides. The evidence suggests that, for the chlorinated alicyclic insecticides, endosulfan, dieldrin and heptachlor, the males were more susceptible (Wilson et al. 2014), as described below. However, for both DDT and DDE, females were more susceptible, as described below.

Chlorinated alicyclic insecticides: endosulfan, dieldrin, and heptachlor

Wilson et al. (2014) investigated dopaminergic neurotoxicity following developmental exposure to the organochlorine pesticide endosulfan in offspring of mice fed endosulfan during gestation and lactation. Exposure to endosulfan during gestation and lactation caused a reduction in dopamine transporter and in tyrosine hydroxylase (a key enzyme involved in the synthesis of dopamine, used as a marker of dopaminergic neurons) in the striatum of the male offspring.

Similarly, Richardson et al. (2006) examined perinatal exposure of mice during gestation and lactation to low levels of dieldrin (an organochloride pesticide) and dopaminergic neurochemistry in the offspring. The investigators found that the exposure altered dopaminergic neurochemistry and had greater adverse effects in the male offspring.

Later, Richardson et al. (2006) examined exposure to heptachlor (another organochlorine pesticide) and the dopamine system in an animal model. The authors stated that exposure of pregnant mice to heptachlor led to increased levels of both the dopamine transporter and the vesicular monoamine transporter 2, at both the protein

and mRNA level, in the offspring of the exposed pregnant mice. Again, the neurotoxicity observed was greater in the male offspring than in the female offspring.

This finding corroborated previous findings by Caudle et al. (2005), who also found that perinatal exposure of mice to the organochlorine pesticide heptachlor is associated with alterations of the dopamine system in male mice. Similar to heptachlor, Brosenitsch and Katz (2001) found that developmental exposure to the organochlorine pesticide dieldrin caused increased dopamine transporter and vesicular monoamine transporter 2 levels in mice, and that the observed increases in said transporter levels were more pronounced in the male offspring.

In conclusion, certain organochlorine pesticides represented by endosulfan, dieldrin, and heptachlor were assigned a Rating Score of 1, showing consistent gender-specific developmental neurotoxic effects that affected the exposed males more than the exposed females.

It is important to note that evidence suggests that damage to the nigrostriatal dopamine pathway evoked by organochlorine insecticides leads to neurodevelopmental disorders. Prospective human cohort studies link early-life exposure to organochlorine pesticides (primarily DDT) to adverse effects on neurodevelopment (Roberts et al. 2012). This includes neurodevelopmental disorders such as autism. For example, Braun et al. (2014) examined gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children (autistic-like behavior). They reported that exposure to trans-nonachlor, a constituent of Chlordane (an organochlorine insecticide), was associated with more autistic-like behaviors. Research also supports an association between low-level prenatal organochlorine exposure and ADHD-like behaviors in childhood (Sagiv et al. 2010). Damage to the nigrostriatal dopamine pathway from organochlorine insecticide exposure also appears to sensitize the dopamine neurons to additional insults that may occur later in life and thereby increase the risk of Parkinson's disease (Wilson et al. 2014).

DDT and DDE

DDT and DDE persist in the body (DDE is a breakdown product of DDT). The half-life of DDT is about seven years, and DDE has a longer half-life (Burns et al. 2013). Both have been associated with behavioral problems in childhood (Sioen et al. 2013). With regard to their observed gender-specific neurotoxic effects, the evidence suggests that females are more affected.

In a study mentioned previously, Sioen et al. (2013) also assessed the association between prenatal exposure to DDE and subsequent behavioral problems when they were 7–8 years of age. Prenatal-exposure-associated neurobehavioral problems were found in girls but not in boys. In the prenatally exposed girls, the researchers found that total neurobehavioral difficulties were 4.92 times more likely when the cord blood level of DDE doubled, while no similar significant exposure-level association was found in the prenatally exposed boys.

Similarly, Gaspar et al. (2015) observed that girls were more affected by prenatal exposure to DDT/DDE. These researchers measured maternal DDT/DEE concentrations during pregnancy and then evaluated the relationship between the prenatal maternal DDT and DDE serum concentrations and the exposed children's cognition when they were 7 and 10.5 years of age. They stated that the prenatal DDT levels were associated with delayed Processing Speed in children at 7 years of age and that the relationship between prenatal DDE levels and children's cognitive development may be gender dependent, with prenatally exposed girls being more adversely affected.

In conclusion, certain organochlorine pesticides represented by DDT and DDE were assigned a Rating Score of 4, indicating consistent gender-specific neurotoxic effects with females being more affected than the similarly exposed males.

Arsenic (As)

Arsenic is a toxic mineral or metalloid sometimes found in water and food. Long-term low-level arsenic (As) exposure is associated with poorer neuropsychological functioning (O'Bryant et al. 2011). Exposure to As is significantly related to poorer scores in language, visuospatial skills, executive functioning, global cognition, processing speed, and immediate memory (O'Bryant et al. 2011). Information about gender differences in susceptibility to As exposures is still too limited to draw any definite conclusions (Llop et al. 2013).

One study in Mexican children by Rosado et al. (2007) found that boys exposed to As were more affected neurologically than girls. In that study, Rosado et al. (2007) examined 602 children 6–8 years of age living within 3.5 km of a metallurgic smelter complex. Urinary As levels were compared to cognitive performance tests. They reported that several cognitive tests were negatively associated with urinary As levels only in boys. A Letter Sequencing Test also adversely affected only boys. However, the results from a Digit Span subscale, which evaluated memory, were inversely correlated with the girls' urinary As levels.

In conclusion, As was assigned a Rating Score of 5, because there was insufficient research related to the topic to draw any general gender-based conclusions.

Polycyclic aromatic hydrocarbons (e.g., naphthalene, pyrene, and florene)

Polycyclic aromatic hydrocarbons (PAHs) are a group of chemicals found in coal, crude oil, and gasoline. PAHs are also made whenever various substances are burned; they can be released into the air during the burning of fossil fuels, garbage, or other organic substances. PAHs can persist in the environment for months or years. Many different PAHs exist, and they usually have at least one benzene ring as a part of their molecular structure. Examples include naphthalene, pyrene, and florene. These are present in tobacco smoke and are more commonly found in the air in urban rather than in rural areas.

PAHs have neurotoxic effects (Ryan et al. 2016). For instance, PAHs can cause long-lasting disruption in self-regulatory capacities across early and middle childhood that can result in social problems (Margolis et al. 2013). However, in regard to gender-specific neurotoxicant effects, the available evidence appears to be too limited to draw any conclusions.

In conclusion, PAHs were assigned a rating of 5, because there is insufficient research to form any gender-specific conclusions.

Organophosphate pesticides (e.g., chlorpyrifos, diazinon, malathion, parathion)

Organophosphate pesticides (OPPs) are well-known neurotoxicants that have been linked to neurobehavioral deficits in children (Marks et al. 2010). In regard to gender-specific neurotoxicant effects, evidence appears to suggest that exposed males are more affected.

Marks et al. (2010), for example, investigated organophosphate pesticide exposure in Hispanic women living in an agricultural region. They examined whether organophosphate exposure, as measured by urinary dialkyl phosphate metabolites in pregnant women and their children, was associated with attention-deficit outcomes among Mexican-American children living in an agricultural region of California. *In utero* dialkyl phosphates and postnatal urinary dialkyl phosphates were adversely associated with attention as assessed by maternal report, psychometrician observation, and direct assessment. These associations were somewhat stronger in boys.

Aldridge et al. (2005) examined the effects of developmental exposure to chlorpyrifos, a widely used organophosphate pesticide, on serotonin (5HT) systems in the rat brain. There were alterations in factors that are critical to the function of the serotonin system, and males were more affected than females. Dam et al.

(2000) found that, after prenatal exposure to chlorpyrifos, early postnatal deficits were observed in: a) reflex righting on post-natal day 3–4 and b) geotaxic (reaction to gravity) responses on post-natal day 5–8 (an effect that was specific to females). However, more complex behaviors indicated subsequent deficit selectivities in males. For example, open-field locomotor activity and rearing were markedly reduced in male rats prenatally exposed to chlorpyrifos.

In conclusion, OPPs were assigned a Rating Score of 2, gender-specific neurotoxic effects, with males being somewhat more affected, but not consistently.

Endocrine disruptors including bisphenol A, other bisphenols (e.g., bisphenol S and bisphenol A diglycidyl ether), and phthalates [e.g., diiso-nonyl phthalate (DINP), di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), di-iso-decyl phthalate (DIDP), di-n-octyl phthalate (DNOP), and butylbenzyl phthalate (BBP)]

Bisphenol A (BPA) and phthalates are used in making many plastic products in everyday commercial use, e.g., baby bottles, sippy cups, pacifiers, and teething products. Bisphenol A is used for hard, clear plastic products and phthalates help make plastics, like pacifiers, flexible. They both can leach from plastic into food, liquid, and directly into the mouths of children while sucking on pacifiers or teething products (Westchestergov.com 2016).

Both BPA and phthalates are endocrine disruptors at low levels (Wise et al. 2016). Because of their widespread use, exposures are of concern. For example, results of recent national surveys have shown a high prevalence of exposure to BPA (Arbuckle et al. 2015). Arbuckle et al. (2015), for instance, tested urine samples for BPA at multiple times during pregnancy in women and once more at 2–3 months postpartum and found widespread exposure among pregnant women and infants to environmental BPA.

Both BPA and phthalates are developmental neurotoxicants that have been shown to affect the number of neurons in multiple brain areas in animal models following exposure in perinatal development, as described below. In regard to gender-specific neurotoxic effects, the two chemicals (BPA and phthalates) appear to be somewhat different.

Bisphenol A

BPA has been shown to negatively impact the development of estrogen-dependent neural circuits, related behaviors, and endocrine functions (Palanza et

al. 2008). Neurotoxic effects appear to include impaired learning, increased anxiety, and abnormal novelty response behaviors (Negri-Cesi et al. 2015). BPA has been shown to alter the sex-specific colonization of the hippocampus and amygdala by microglia (Rebuli et al. 2016). However, in regard to which gender may be more vulnerable to the neurotoxic effects of BPA, the evidence appears to be somewhat mixed (Wise et al. 2016).

According to a review of BPA by Negri-Cesi et al. (2015), which examined behaviors in prenatally exposed rodents, females seem to be more sensitive than males to BPA. Gioiosa et al. (2015) also conducted research on the effects of early exposure to low doses of BPA on behavior. Although developmental exposure to the estrogenic pollutant BPA had a negative impact on behavior in both male and female mice, the behavioral alterations were more pronounced in females.

Similarly, in a study by Gioiosa et al. (2015), who looked at the effects of early exposure to low doses of BPA on the subsequent behavior and metabolism in CD-1 mice, the investigators found that the behavioral alterations were mainly in females. However, the males reportedly showed a significant age-related change in a number of metabolic indexes.

A study by Roen et al. (2015) investigated the association between prenatal and early childhood BPA exposure and the subsequent behavioral outcomes in 7–9-year-old minority children (n=250). Both boys and girls were affected, but the direction of the associations differed between boys and girls. High prenatal maternal urinary BPA concentration was associated with increased internalizing and externalizing composite scores, which were consistent in the boys evaluated. Internalizing behaviors reflect mood disturbance, including anxiety, depression, and social withdrawal. Externalizing behaviors reflect conflict with others and violation of social norms (Lande et al. 2009). Conversely, both negative internalizing composite and externalizing composite scores were associated with high postnatal urinary BPA concentrations, which were, in turn, associated with increased negative behaviors in girls. The authors stated that BPA exposure might affect childhood behavioral outcomes in a sex-specific manner and differently depending on the timing of exposure.

In contrast, Casas et al. (2015) examined the effects of prenatal BPA exposure on cognitive, psychomotor, and behavioral development in 438 children at one, four and seven years of age. They found that at four years of age BPA exposure was associated with an increased risk of ADHD-hyperactivity symptoms and that this association was stronger in boys than in girls. However, at age seven years, the relation between BPA exposure and increased risk of exhibiting ADHD-hyperactivity symptoms and the gender-related differences in the strength of the association were not statistically significant.

Sobolewski et al. (2014) found that exposures to four endocrine disrupting chemicals, atrazine, perfluorooctanoic acid, BPA, and 2,3,7,8-tetrachlorodibenzo-p-dioxin, caused significant adverse effects (such as reduced short-term memory in the novel object recognition paradigm test) in males but not in females.

Evans et al. (2014), who examined the link between BPA concentration in spot urine samples from women at a mean of 27 weeks of pregnancy and child behavior assessed at age 6–10 years using the parent-completed Child Behavior Checklist (CBCL), also found that BPA was associated with increased internalizing and externalizing behaviors, withdrawn/depressed behavior, somatic problems, and Oppositional/Defiant Disorder traits in boys. These authors stated that prenatal exposure to BPA might be related to increased behavior problems in school-age boys but not girls.

Similarly, examining the association between prenatal BPA exposure and child behavior in 198 children (87 boys and 111 girls), Perera et al. (2012) found that, among boys, high prenatal BPA exposure was associated with significantly higher behavioral problem scores on Emotionally Reactive and Aggressive Behavior syndrome scales. However, among girls, higher BPA exposure was associated with lower scores for all the behavioral syndromes tested and only reached statistical significance for Anxious/Depressed and Aggressive Behavior.

Studies that examine outcomes from prenatal BPA exposure generally find gender-related effects. Because gonadal hormones are known to influence the sexual differentiation of the brain it is possible that exposure to BPA, an endocrine disrupter, could affect gonadal hormone levels that may contribute to sex-specific behavioral changes (Negri-Cesi et al., 2015).

Phthalates (e.g., diiso-nonyl phthalate [DINP], di(2-ethylhexyl) phthalate [DEHP], dibutyl phthalate [DBP], di-iso-decyl phthalate [DIDP], di-n-octyl phthalate [DNOP], and butylbenzyl phthalate [BBP])

Comparing gender-specific developmental neurotoxic effects on a related class of endocrine disruptors, phthalates, the effects appear to be mixed. For example, Kobrosly et al. (2014) measured phthalate metabolite concentrations in urine samples from 153 pregnant women in the *Study for Future Families*, a multicenter cohort study. They found that exposure to certain phthalates in late pregnancy was associated with behavioral problems in boys. Specifically, urinary phthalate concentrations were associated with higher scores for inattention, rule-breaking behavior, aggression, conduct problems and somatic problems in boys. In contrast, girls were found to have reduced anxiety scores.

However, in a Korean environmental health study, urine phthalate metabolite concentrations and neurobehavioral development were examined in representative samples of 6–18-year-olds (Won et al. 2016). The younger children, aged 6–11 years, had significant positive associations between phthalate exposure and social problems and attention problems. Sex-specific effects of phthalate exposure revealed an increase in thought problems among the girls.

In conclusion, endocrine disruptors (e.g., phthalates, BPA) were assigned a score of 3, with gender-specific neurotoxic effects, but it is unclear overall whether males or females are more adversely affected.

Air pollution/automotive exhaust

The brain appears to be a target of air pollution toxicity (Allen et al. 2014a). Particles from air pollution can enter the circulation and distribute to most organs, including the brain (Costa et al. 2014). Neuroinflammation and oxidative stress are two putative biological mechanisms by which air pollutants may adversely affect the brain (Allen et al. 2014a). Evidence indicates that air pollution can induce neurotoxicity, neuroinflammation, oxidative stress, microglial activation, cerebrovascular dysfunction, and alterations in the blood-brain barrier (Davis et al. 2013, Costa et al. 2014, Genc et al. 2012). Findings from both animal models and human epidemiological studies show a relationship between air pollution (both traffic and industrial related) and neurodevelopmental disorders including ASD (Palmer et al. 2009, Windham et al. 2006, Volk et al. 2013). Furthermore, these studies suggest that males are more vulnerable.

In an animal model, for example, Allen et al. (2014a, b) conducted several studies that examined the effects of air pollution on the brain and behavior. Mouse pups were exposed postnatally to concentrated ambient ultrafine particles (CAPS; <100 nm) using the Harvard University Concentrated Ambient Particle System (HUCAPS). The authors reported negative behavioral and cognitive impacts such as increased impulsivity and impaired short-term memory, as well as structural and chemical brain changes. The brain changes included: cortical and hippocampal changes in amino acids, which raised the potential for excitotoxicity; and persistent glial activation in the frontal cortex and corpus callosum of both sexes. Both can result in brain cell (neuron) loss. They also reported evidence that suggests that males are more susceptible to neurotoxicity from air pollution (Allen et al. 2014b). CAPS induced brain region- and sex-dependent alterations in cytokines and neurotransmitters in both males and females, however,

lateral ventricle dilation (i.e., ventriculomegaly) was only observed in CAPS-exposed male mice (suggesting brain cell/neuron loss). The authors stated that, because ventriculomegaly is a neuropathology that has been associated with poor neurodevelopmental outcome, ASD, and schizophrenia, their findings suggest that alteration of developmentally important neurochemicals and lateral ventricle dilation may be mechanistically involved in the link between air pollutant exposure and adverse neurodevelopmental outcomes in humans, with males being more vulnerable.

In humans, several studies find that air pollution, including both prenatal and postnatal exposure, is a risk factor for neurodevelopmental disorders, particularly ASD. Roberts et al. (2013), for example, examining prenatal exposure at the Harvard School of Public Health, estimated associations between US-Environmental-Protection-Agency-modeled levels of hazardous air pollutants at the time and place of birth and ASD in the children of participants in the Nurses' Health Study II (325 cases, 22,101 controls). Their results revealed that perinatal exposures to diesel, lead, manganese, mercury, methylene chloride and an overall measure of metals from air pollution were significantly associated with ASD, with odds ratios ranging from 1.5 (for overall metals measure) to 2.0 (for diesel and mercury). They also reported that for most of the pollutants examined in the study, associations were stronger for boys (279 cases) than for girls (46 cases) and were significantly different according to gender (Roberts et al. 2013).

In conclusion, air pollution / automotive exhaust is assigned a rating of 1, indicating gender-specific neurotoxic effects with males more affected (as mentioned, some air-pollution studies include airborne toxic metals).

Polybrominated diphenyl ethers (brominated flame retardants; PBDE flame retardants)

Polybrominated diphenyl ethers (PBDEs) are organobromine compounds, which are used as flame retardants in many products, including plastics, furniture, upholstery, electrical equipment, electronic devices, textiles, and other household products (EPA 2009). After several decades of commercial use, PBDEs and their metabolites have become pervasive environmental contaminants and are detectable in the human body (Rice et al. 2009).

Exposure to PBDEs during pregnancy can lead to slower mental and psychomotor development in infants (Czerska et al. 2013). Additionally, postnatal exposure has been recognized as having long-term detrimental neurotoxic effects, e.g., in spatial learning and

memory (Reverte et al. 2013). Berghuis et al. (2015) reported that exposure to PBDEs results in lower mental development, psychomotor development, and IQ, and poorer attention in children. In regard to gender-specific, neurotoxic effects, evidence suggests that males and females are equally affected (Viberg et al. 2004).

Rice et al. (2009), for example, examined behavioral changes in aging but not young mice after neonatal exposure to the polybrominated flame retardant decaBDE. The exposed mice learned the task more slowly, made fewer errors on the first-response choice of a trial but more perseverative errors after an initial error, and had lower latencies to respond compared with controls. Effects were observed on various measures regardless of dose and gender.

Similarly, Buratovic et al. (2014) investigated neurotoxic effects arising from neonatal exposure to PBDE 209, including alterations in sex differences, spontaneous behavior, learning, and memory. Three-day-old NMRI mice of both sexes were exposed to PBDE 209. They reported observing, at adult age (2–7 months), similar developmental neurotoxic effects in both the dosed male and female mice, including lack of or reduced habituation to a novel home environment, as well as learning and memory deficits.

Likewise, Viberg et al. (2004) investigated both mouse strain and/or gender differences in developmental neurotoxic effects of exposure to PBDEs. They reported finding developmental neurotoxic effects in PBDE-exposed mice. Furthermore, the developmental neurotoxic effects of their exposures to PBDEs were as pronounced in the treated female mice as they were in the male mice.

In conclusion, a rating Score of 6 was assigned to PBDEs, indicating no gender-specific neurotoxic effects.

Perfluorinated compounds

Certain perfluorinated compounds, e.g., perfluorooctane sulfonate (PFOS) and perfluorooctanesulfonic acid (PFOA), have been and are still being used in numerous industrial and consumer products. Such perfluorinated compounds are now persistent environmental pollutants found in the tissues of fish, birds, and marine mammals globally (Lau et al. 2004). Their tissue concentrations are generally higher in industrialized areas than in less populated locations (Suja et al. 2009). Exposures to these chemicals induce neurobehavioral effects, indicating adverse effects on the central nervous system (Lau et al. 2004, Mariussen and Fonnum 2006). For example, in a study by Vuong et al. (2016) in school-age children, maternal serum PFOS levels were associated with poorer behavior regulation, metacog-

nition, and global executive functioning. The authors suggested that prenatal exposures to PFOS may be associated with executive function deficits observed in school-age children. However, the evidence for gender-specific neurotoxic effects is limited.

Quaak et al. (2016) measured PFOS and PFOA in cord plasma using a Dutch cohort *LINC* (Linking Maternal Nutrition to Child Health). The offspring in the cohort were followed through national registries. Those researchers looked for associations between the maternal serum concentrations and the offspring's neurodevelopmental outcomes. The investigators found that boys in the second and third tertile (any of the thirds in the observed range of cord-blood PFOA values arranged from low to high) of exposure to PFOA had significantly lower scores on the Externalizing Problem Scale than the boys with the lowest (first tertile) PFOA levels. The girls with elevated PFOA levels also had significantly lower scores on the Externalizing Problem Scale.

In conclusion, a Rating Score of 5 was assigned to the class of perfluorinated compounds, because there is insufficient research related to the topic to draw any general conclusions with regard to gender-specific neurotoxic effects.

Aluminum adjuvants (sparingly soluble to insoluble annealed polymerized inorganic hydroxy-aluminum salts)

Studies report that the aluminum adjuvants used in vaccines bioaccumulate and persist in the brain, with neurological consequences such as a higher apoptotic index, oxidative stress, neurotoxicity, and abnormal cerebral perfusion in the animal model and in some human studies (Cabus et al. 2015, Van Der Gucht et al. 2015, Crépeaux et al. 2015). According to Gherardi et al. (2015), brain translocation of aluminum particles is linked to a Trojan horse mechanism previously described for infectious particles. Once in the brain, they are associated with an inflammatory process (Gherardi et al. 2015). This current review found no studies specifically addressing the issue of gender-specific neurotoxic effects in regard to such aluminum adjuvants. In conclusion, the aluminum adjuvants used in vaccines have been assigned a rating of 5, because we found no research into their gender-specific neurotoxicity.

Glyphosate (Roundup)

Glyphosate is the active ingredient in the widely-used herbicide, Roundup. The US Environmental

Protection Agency considers glyphosate to be of relatively low oral and dermal acute toxicity (EPA 1993). However, in animal and tissue studies, adverse effects noted from glyphosate exposure include: decreased neuronal cell count, decreased cellular glutathione content, increased lipoperoxidation, excitotoxicity, oxidative damage, disrupted neurite development and maturation, and neurodegeneration (Negga et al. 2011, Cattani et al. 2014, Coullery et al. 2016). Glyphosate has been suggested to play a role in the increase in neurodevelopmental disorders, particularly ASD (Nevison 2014, Sealey at al. 2016). Nevison (2014), for example, presented an analysis that indicated that, among the neurotoxicants suspected as causal agents in those diagnosed with an ASD, increases in the exposure levels of PBDEs, aluminum adjuvants, and the herbicide glyphosate showed increasing trends that were positively correlated to the rise in patients diagnosed with an ASD.

In this current examination, no research was found on gender-specific neurotoxic effects in regard to glyphosate. Thus, glyphosate was assigned a rating of 5.

RESULTS

Table III shows the results of this current examination. The neurotoxicants that exhibited consistent gender-specific effects with exposed males being more affected than similarly exposed females are lead, Thimerosal/ethylmercury, some organochlorine pesticides (e.g., dieldrin, endosulfan, and heptachlor), and air pollution. These are followed by mercury vapor,

PCBs, and organophosphate pesticides which show gender-specific neurotoxic effects, with males being somewhat, but not consistently, more affected. The reviewed neurotoxicity studies that used simple inorganic mercury salts, methylmercury species and certain endocrine disruptors (e.g., phthalates and BPA) and found gender-specific neurotoxic effects did not clearly establish whether the exposed males or the similarly exposed females were more affected.

DISCUSSION

Based on the premise that the male preponderance in many neurodevelopmental disorders is very possibly an important clue as to the etiology of these disorders, the evidence from this current examination suggests that the neurotoxicants that may play a leading role in the recent and dramatic increase in neurodevelopmental disorders are: Pb, Thimerosal/ethylmercury (Et-Hg) compounds, some organochlorine pesticides (e.g., dieldrin, endosulfan, and heptachlor), and air pollution, all of which showed consistent gender-specific neurotoxic effects with males more affected. These are followed by mercury vapor, PCBs, and organophosphate pesticides, all of which also showed gender-specific neurotoxic effects, with males being somewhat, but not consistently, more affected. Inorganic mercury salts, methylmercury-based compounds (e.g., Me-Hg-Cl), and endocrine disruptors (e.g., phthalates and BPA) all exhibited gender-specific neurotoxic effects but did not clearly establish whether the exposed males or females were more affected.

Table III. Scoring of pollutants according to the previously described methods (see text)

Neurotoxicant	Score	Conclusion
Lead Thimerosal (Na$^+$ Et-Hg-thiosalicylate$^-$) / Ethylmercury (Et-Hg-) Certain organochlorine pesticides (dieldrin, endosul-fan, and heptachlor) Air pollution	1	Consistent gender-specific neurotoxic effects with males more affected
Elemental mercury vapor (Hg^0) PCBs Organophosphate pesticides	2	Gender-specific neurotoxic effects, with the males being somewhat more affected, but not consistently
Inorganic mercury salts (Hg^{2+}X$^-_2$, where "X" is Cl$^-$ or OH$^-$ or Hg$^+_2$Cl$^-_2$ [Calomel]) Methylmercury (Me-Hg-) Endocrine disruptors (phthalates and bisphenol A [BPA])	3	Gender-specific neurotoxic effects, but it is not clear whether males or females are more affected
Certain organochlorine pesticides (DDT and DDE)	4	Gender-specific neurotoxic effects, with the females being more affected
Arsenic (As) Polycyclic aromatic hydrocarbons (PAH) Perfluorinated compounds Aluminum adjuvants in vaccines & related liquid products Glyphosate (Roundup)	5	Insufficient research related to the topic to draw any conclusions
Brominated flame retardants (PBDEs)	6	No gender-specific neurotoxic effects

Organochlorine pesticides (DDT and DDE) showed gender-specific neurotoxic effects, but with the females being more affected. Perfluorinated compounds, As, PAHs, aluminum adjuvants in vaccines & related liquid products, and glyphosate (Roundup) did not have sufficient research related to the topic to draw any conclusions. PBDEs showed no gender-specific neurotoxic effects.

Even though there have been sociological and regulatory changes that have significantly reduced exposure to some of these neurotoxicants, such as banning the use of leaded gasoline for on-road vehicles, reduction of the use of Thimerosal in vaccines, and reduction of air pollution under the Clean Air Act, there is still considerable room for further improvements. Many sources of exposure remain and many of these exposure sources could be easily reduced or eliminated. The following sections describe some of the current sources of exposure.

Lead [Pb]

Although leaded fuel is banned for use in on-road vehicles in the US, aviation gasoline, or Avgas, still contains $(Et)_4Pb$, which is responsible for the release of about 100 tons of Pb every year in the US (Bryan 2014). Pb is still released into the air from smelting and refining activities (U.S. Environmental Protection Agency 2016). Other sources of Pb exposure include leaded crystal, dinnerware glazes, Pb water pipes and pipe joint solder, Pb ammunition/bullets, fishing weights, faucets with brass fittings, vinyl mini blinds made in China, some folk and Ayurvedic medicines, and some calcium supplements made from animal bone. Pb is still used in commercial products such as automotive batteries, bridge paint, computers, jewelry, and pewter.

Although banned in the European Union, Pb is present in 61 percent of lipsticks in the US, with levels ranging up to 0.65 parts per million (Campaign for Safe Cosmetics 2016). Similarly, Pb is banned in the use of hair colors in the European Union, but approved and used in hair colors in the US (Cosmetics Info 2016). In addition, many imported or pre-regulation products may still pose a risk because consumer products are not routinely tested for Pb (Agency for Toxic Substances and Disease Registry 2007).

Thimerosal/ethylmercury

Thimerosal is the most widely used organomercury compound in medicinal products (Choi et al. 2016). Currently, the amount of Hg present in Thimerosal-pre-

served vaccines nominally ranges from 12.5 to 25 micrograms per 0.5-mL dose (with some vaccines delivering more than 25 micrograms of Hg per dose). In the developing world, Thimerosal is still present in many of the childhood vaccines (e.g., the hepatitis B vaccines; the *Haemophilus influenzae* type b vaccines; the diphtheria, tetanus and pertussis vaccines; various inactivated-influenza and multi-dose meningococcal meningitis vaccines). Also, the tetanus toxoid vaccine (containing 25 micrograms of Hg per dose) and/or the inactivated influenza vaccine have been recommended for administration to pregnant women in some countries.

Other medical products that contain Thimerosal include ear, eye and nose drops and ointments, antiseptic sprays, topical medications and tinctures of Merthiolate, antitoxins, immune globulin preparations, and skin-prick test antigens (Geier et al. 2007, DermNet NZ 2016). Thimerosal is also used in some cosmetic and cleansing products such as eye shadows, make-up removers, mascaras, and soap-free cleansers (Geier et al. 2007, DermNet NZ 2016).

Organochlorine pesticides and PCBs

As mentioned earlier, PCB use was stopped in 1979 when the US banned PCB manufacturing, processing, distribution, and use (EIP Associates 1997). For the most part, the use of organochlorine pesticides is barred in the US, although a few products are still registered for use. For example, exposure to lindane is possible since products containing this chemical are still marketed and used, such as in treatments for lice and scabies (National Institutes of Health 2016).

Air pollution

The US EPA states that since the Clean Air Act of 1970, air pollutants have been cut by more than 41% as of 2010 in the US. However, millions of children are still exposed to hazardous air pollutants, and in particular, children who live in poverty are likely to live in areas in which the levels of pollutants are extremely high (Roppolo 2014). Even under the Clear Skies Act of 2003, the annual "State of the Air" report stated that 47% of Americans live in counties with frequently unhealthy levels of either ozone or particulate pollution (Roppolo 2014). There are also still many "big polluters" in the US (Fehling 2015), and currently there are significant inconsistencies in compliance from state to state with regard to pollution control (Fehling 2015). Industrial sites, such as refineries, chlorine plants, chemical plants, and coal-burning plants are among the many

industrial air polluters. Traffic sources have also been found to be associated with neurodevelopmental disorders (Palmer et al. 2009, Volk et al. 2011).

Why males might be more vulnerable

The current evidence suggests that males are more neurodevelopmentally vulnerable to several neurotoxicants than females. Research suggests that males may be more vulnerable for several reasons.

First, known differences in detoxification and oxidative stress amelioration may explain, in part, the gender differences. It appears that there are significant gender differences in glutathione availability. Sufficient glutathione levels are critical for detoxification. For example, studies report an association between lower glutathione levels and male gender (Lavoie and Chessex 1997, Rush and Sandiford 2003). Lavoie and Chessex (1997) examined whether human tissues derived from baby girls versus baby boys had an increased ability to stimulate glutathione reductase when faced with an oxidative stress challenge. They found that, *in vivo*, the intracellular total glutathione content was higher in female-derived cells. Because glutathione is a central element in the human antioxidant defense system, these results suggest that specific tissues derived from the baby girls are potentially better protected against an oxidative stress than those derived from the baby boys.

Second, sulfation chemistry and sulfate availability differences may also partially explain the gender-related differences (Kern et al. 2013). Sulfate is required for many physiological processes and sulfate depletion can both inhibit efficient detoxification and increase susceptibility to xenobiotics. Studies in rats revealed that males are twice as dependent on sulfate conjugation for the removal of phenolic compounds as compared to females. In a study using acetaminophen (APAP; a phenolic compound), male rats showed a two-fold greater APAP sulfotransferase activity than female rats, whereas the females were more dependent on glucuronide conjugation (Kane et al. 1990, Kern et al. 2004). In other words, males were more dependent upon the sulfation-conjugation detoxification pathway than females and, when sulfate is depleted, the males become more vulnerable to intoxication by toxic substances whose metabolism uses that pathway.

Third, there is also evidence that estrogen may provide neuroprotection, whereas testosterone may enhance neurotoxicity. As an example, Miller et al. (1998) examined striatal dopaminergic neurotoxicity induced by two different neurotoxicants, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and metham-

phetamine (METH). The authors found that both agents induced greater neurotoxicity in the exposed males than in the females as evidenced by the greater striatal dopamine depletions observed in males. However, when they observed the neurotoxicity of MPTP in ovariectomized mice, they found that it was the estrogen (not any metabolic/pharmacokinetic variables) that provided the neuroprotection. Similarly, in 2008, Schaeffer et al. found that human neuroblastoma SH-SY5Y cells, when exposed to hydrogen-peroxide-induced oxidative stress, were more likely to survive when they were pretreated with estradiol. The estradiol was protective against hydrogen peroxide-induced cell death. Estradiol was also capable of markedly rescuing neuroblastoma cells from letrozole-evoked cell death (letrozole lowers estrogen production). Haley (2005) observed that Thimerosal toxicity to neurons was significantly increased by co-exposure with testosterone, whereas estrogens significantly reduced the toxicity of Thimerosal to neurons.

Fourth, a greater neuroinflammatory response in males may also be a factor. Studies showed decreased neuroinflammatory responses in female mice as compared to male mice when exposed to toxicants (Fleiss et al. 2012). As an example, Kentner et al. (2010) examined the expression of the inflammatory molecule, cyclooxygenase-2 (COX-2), after exposure to lipopolysaccharide (LPS) in rats. They found that neonatal LPS exposure at postnatal day 14 caused elevated basal expression of hypothalamic COX-2 in the male, but not in the female rats. Similarly, Smith et al. (2011) found that estrogen or estrogen receptor agonists inhibited LPS-induced microglial activation and death in the brain in rats. Specifically, estrogen prevented cell death by attenuating the release of interleukin-1-alpha, interleukin-1-beta, tumor necrosis factor-α, and COX-2.

Several studies suggest that estrogen has protective effects. Estrogen modulates neural and inflammatory factors (Pratap et al. 2016). Findings suggest that estrogens prevent and control the inflammatory response, shortening the pro-inflammatory phase by facilitating deactivation of the inflammatory process (Villa et al. 2016). In fact, exogenous administration of estrogen has been shown to improve outcomes after cerebral ischemia and traumatic brain injury in experimental models (Roof and Hall 2000).

Fifth, neurotoxic exposure can result in neurological damage from the induction of oxidative stress (Risher and Tucker, 2017), and there is evidence to suggest that females are less vulnerable to oxidative stress (Borrás et al., 2003). Researchers report that one of the neuroprotective mechanisms of estrogen is linked to estrogen's ability to act as an electron-donating antioxidant (Roof and Hall, 2000). In addition, differential

mitochondrial oxidative stress between males and females may also be due to mitochondria from females having higher levels of reduced glutathione than those from males and that oxidative damage to mitochondrial DNA in males is 4-fold higher than that in females (Borrás et al. 2003). Borrás et al. (2003) stated that females have added protection against free-radical-mediated damage due to higher expression and activities of manganese superoxide dismutase and of glutathione peroxidase (Borrás et al. 2003).

Sixth, increasing evidence is demonstrating that progesterone (a female sex hormone) also has neuroprotective effects (Roof and Hall, 2000). Exogenous administration of progesterone, like estrogen, has been shown to improve outcomes after cerebral ischemia and traumatic brain injury in experimental models (Roof and Hall 2000, Stein 2011). This is the case in both females and males. According to Roof and Hall (2000) the neuroprotection from progesterone, like estrogen, is likely multifactorial; however, research shows that progesterone has a membrane stabilizing effect that also serves to reduce the damage caused by lipid peroxidation, and that it may also provide neuroprotection by suppressing neuronal hyperexcitability. In brain injury studies, Meffre et al. (2013) found modulatory effects of progesterone in inflammation, ion and water homeostasis, and myelin repair in the injured brain.

In considering all of the aforementioned phenomena, it is important to realize that the androgen (male hormone) synthesis pathway and transsulfuration pathways directly interact with one another (Geier and Geier 2006, 2007, Geier et al. 2010, 2012), and as a consequence, may significantly potentiate neurotoxicant exposures, especially in developing males (Geier and Geier 2005). It was previously revealed that testosterone exposure significantly down-regulated the enzyme, cystathionine beta-synthase (CBS), which catalyzes the committing step in the transsulfuration pathway, and resulted in significant decreases in intracellular glutathione and sulfate levels (Prudova et al. 2007). Furthermore, in the androgen synthesis pathway, the androgen metabolite of dehydroepiandrosterone (DHEA) is important to biochemically regulating the production of testosterone. DHEA can either be converted into the normally favored storage molecule of dehydroepiandrosterone-sulfate (DHEA-S), or it can be converted into androstenedeione or androstenediol in the biochemical pathway towards testosterone production. The enzyme hydroxysteroid sulfotransferase (HST) mediates the conversion of DHEA to DHEA-S and it is dependent upon sulfation and glutathione and is inhibited by inflammation (Ryan and Carrol 1976, Kim et al. 2004). In addition, neurotoxicant exposures were revealed to significantly reduce HST function and increase androgen and testosterone levels (Ryan and Carrol 1976, Freeman et al. 1977, Veltman et al. 1986, Barregard et al. 1994). The end result is that a cyclical pattern of continuous interaction between the androgen and transsulfuration pathways can be set into motion following neurotoxicant exposures that may increase susceptibility to neurotoxicity, particularly among developing males (Geier and Geier 2005).

In summary, the reasons for the male brain being more vulnerable include: (1) greater glutathione availability in females; (2) greater sulfate-based detoxification capacity in females; (3) potentiating effects of co-exposure to neurotoxicants and testosterone; (4) greater neuroinflammatory response in males; (5) reduced vulnerability to oxidative stress in females; and (6) neuroprotective effects of female hormones (estrogen and progesterone), especially in the reduction of inflammation and oxidative stress.

Study limitations

With a few of the neurotoxicants examined in this study, limited research was found on their gender-specific neurotoxic effects. However, the lack of findings cannot be taken as *a priori* evidence of no gender-specific neurotoxic effects.

In addition, the issue of gender-specific neurotoxic effects with combination exposures has yet to be adequately examined. Many studies have reported synergistic effects from the combination of toxicants. For example, the combination of Al and Hg as well as the combination of As and Pb have been shown to result in synergistic effects (Pohl et al. 2011, Gómez-Oliván et al. 2016). As such, the issue of multiple exposures and how they could possibly influence gender-specificity is another limitation of this current examination.

Additionally, the effects of toxic exposures are complex. The extent of the damage from exposure to toxic substances is dependent upon many factors, such as age of exposure, specific dose, exposure window, absorption into the body, transport into the affected tissue (brain) or system (innate immune system), excretion, interaction with critical molecules versus non-critical, the availability versus the depletion of detoxification systems, the availability of repair and compensation systems, stress-response systems, cellular repair, and genetic susceptibility. Most of these variables were not considered in this study.

One of the most important parameters in toxicity is the specific dose (dose per unit of body weight). This study did not fully examine the specific-dose variable, even though the evidence shows that gender-specific effects can be specific-dose-dependent. For example,

Thimerosal research has shown that males are more affected than females at lower specific doses; however, as the specific dose becomes relatively high, the gender-specific differences wane (Geier et al. 2014).

A further limitation of this study is the limited discussion of the interactions of the immune system with environmental factors and genetics. During development such interactions could very well set the stage for increased risk of specific neurodevelopmental and other neurological disorders.

CONCLUSION AND FUTURE DIRECTIONS

Over the past decade or so, several consensus papers have been published by notable scientists on the relationship between neurodevelopmental disorders and exposures to neurotoxicants (Bennett et al. 2016; Grandjean and Landrigan 2006, 2014). Each consensus paper calls for general action in regard to exposures to neurotoxicants. Unfortunately, the main response to the dramatic increase in neurodevelopmental disorders has been a general call for early screening and intervention (Siu et al. 2016). Children are being screened at younger ages and programs for early interventions are in place in each state in the US, such as Early Childhood Intervention Services and Early Childhood Programs. Although early screening and early intervention are reported in some studies to be helpful, they are not preventive. Early screening and early intervention programs simply find and discuss the disorders early in hopes of reducing the severity of the symptoms observed. A true preventive program would address the exposure-related issues by reducing or stopping the causative exposures to the identified neurotoxicants.

Not all cases of neurodevelopmental disorders are due to toxic exposures. However, as the consensus papers report, the neurotoxicants examined herein are causal and/or contributory in many cases of neurodevelopmental disorders (Bennett et al. 2016). Programs and policies are sorely needed to reduce or eliminate toxic exposures. For example, the US could ban the use of toxic metals in makeup and cosmetics, as has been done in the European Union. The US could also ban the use of Thimerosal in the manufacture of vaccines, as has been done in most developed nations. The US could ban all use of organochlorine pesticides. It is also possible to dramatically reduce air pollution using current technology. Airborne particles can be removed from a polluted airstream by using currently available equipment, such as cyclones, scrubbers, electrostatic precipitators, and baghouse filters (Nathanson 2015). Wet scrubbers, for example, can achieve efficiencies of more than 98 percent for particles larger than 0.5 μm in diameter.

Furthermore, the cost of inaction is not only personal but financial. For example, the Pb-attributable economic costs associated with childhood Pb exposure in the US were estimated to be about $50.9 billion in the year 2011 alone (Attina and Trasande 2013). In regard to air pollution, Jaramillo and Muller (2016) examined air pollution emissions data for the years 2002, 2005, 2008, and 2011 to estimate monetary damages due to air pollution exposure from electric power generation, oil and gas extraction, coal mining, and oil refineries. Just in the year 2011, damages associated with emissions from these sectors totaled $131 billion. In a recent epidemiological study conducted by Geier et al. (2016), the investigators estimated the cost of care of children with delays in development from exposure to Thimerosal in vaccines from 1991-2001 to exceed $1 trillion.

The current rates of neurodevelopmental disorders indicate that action and true preventive legislation are needed. Grandjean and Landrigan (2014) stated that to control the pandemic of developmental neurotoxicity will require a global prevention strategy.

Funding availability for studies that address environmental factors in neurodevelopmental disorders should also be improved. For example, the National Institutes of Mental Health (NIMH) states that about 20% of children with ASD have certain genetic conditions (National Institutes of Mental Health 2016). As mentioned previously, two large studies that conducted microarray examinations of the genome in ASD found that 80% of children diagnosed with an ASD have a normal genome (Shen et al. 2010, Geier et al. 2016). However, a search on the National Institutes of Health Research website using their Portfolio Online Reporting (RePORT) reflects that the total budget for studying genetics in ASD in 2013 was $291 million (Research Portfolio Online Reporting 2016). In contrast, the total budget for studying environmental aspects in ASD was $7.5 million in 2013 (National Institute of Environmental Health Sciences 2014). Thus, more than 38 times as much funding went to studying the role of genetics in ASD, which only addresses at best about 20% of the ASD population, than to studying the role of the environment, which apparently affects at least 80% of those with an ASD diagnosis.

Because the exposures are numerous and are from multiple sources, perhaps a task force of scientists, without industry ties, who study the issue of neurodevelopmental toxicity is needed. The sole mission of the task force would be to make recommendations to effect legislation that would address and reduce toxic exposures among pregnant women, infants, and children. Current research suggests that reducing exposures to Pb, Thimerosal, organochlorine pesticides (ones that are still in use), and air pollution should be given priority.

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