

The Role of Heavy Metal Pollution in Neurobehavioral Disorders: a Focus on Autism

Francesca Gorini · Filippo Muratori ·
Maria Aurora Morales

Received: 7 June 2014 / Accepted: 13 June 2014 / Published online: 27 June 2014
© Springer Science+Business Media New York 2014

Abstract An increasing evidence supports the role of industrial chemicals as contributors to the development of neurobehavioral disorders, including autism spectrum disorders, whose prevalence has progressively increased in recent years. Heavy metals, in particular, are recognized as neurodevelopmental toxins since they can be responsible of fetal damages which lead to neurological defects, developmental delays, learning disabilities and behavioral abnormalities. Most of the reviewed studies reported a relationship between exposure to metals during perinatal and early childhood periods and increased risk for autism. Moreover, the effects resulting from co-exposure to multiple metals should not be underestimated, especially in the assessment of children who live in developing countries or near heavily contaminated sites.

Keywords ASD · Neurodevelopment · Heavy metals · Pollution

Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy affect between 400,000 and 600,000 children born in the USA each year (Landrigan et al. 2012). Thus, it has been estimated that up to every six children has a developmental disability, and in most cases, the nervous system represents the main target (Bloom et al. 2010). Unfortunately, neurodevelopmental disorders are often untreatable and cause permanent brain damage (Grandjean and Landrigan 2014).

The impairment of cognitive skills results in loss of IQ points, in reduction of children's academic attainments, and at last in substantial costs for societies (Gould 2009). Over the last decades, there has been an increasing evidence towards industrial chemicals as contributors in neurobehavioral diseases (Grandjean and Landrigan 2006). Genetic factors alone account for no more than 30–40 % of all cases of neurodevelopmental disorders. US National Research Council estimated that 3 % of developmental disabilities are the direct result of exposure to environmental toxicants whereas another 25 % are the result of an interaction between environmental factors and inherited susceptibilities (National Research Council 2000a; Landrigan et al. 2012).

Heavy metal contamination is one of the most severe threats for the environment. Since the middle of the nineteenth century, the industrial use of heavy metals increased with consequent emission in the environment. Only at the end of the twentieth century that these emissions started to decrease in most developed countries (Nriagu et al. 1996), and nowadays, exceptions are still represented by highly industrialized areas with outdated technologies. The emission of heavy metals in the environment occurs via a wide range of processes and pathways impacting on air, surface water, and soil quality. Due to the multiple sources of exposure, heavy metals represent also one of the most serious threats to human health (Arita and Costa 2009; Dufault et al. 2009; Szewczyk 2013).

There is compelling evidence that heavy metals adversely affect neurodevelopment and increase risk of autism spectrum disorders (ASD) (DeSoto and Hitlan 2010; Abdullah et al. 2012). Many trace elements occurring in the body at less than 0.01 % of body weight are essential for physiological processes in the central nervous systems; however, when present at increased levels, they may produce neurodegenerative conditions such as Parkinson's disease, Down syndrome, and Alzheimer's disease (Fido and Al-Saad 2005; Lakshmi Priya and Geetha 2011). During the prenatal development, the

F. Gorini (✉) · M. A. Morales
Istituto di Fisiologia Clinica—CNR Pisa, via Moruzzi, 1,
56124 Pisa, Italy
e-mail: fgorini@ifc.cnr.it

F. Muratori
IRCCS Stella Maris Foundation, Calambrone Pisa, Italy

human brain is more vulnerable to xenobiotics than the brain of an adult. Indeed, placenta does not provide an effective protection against environmental contaminants (Andersen et al. 2000), and the blood-brain barrier is not formed up to 6 months after birth (Adinolfi 1985). Therefore, exposure to environmental chemicals during the early fetal development can cause brain injury at levels much lower than those affecting adult brain function (Grandjean and Landrigan 2006). Environmentally mediated changes in fetal programming may be limited to an individual's prenatal period of development or, alternatively, alteration in control of gene expression may appear later in adulthood (Dietert et al. 2011). Epigenetic mechanisms (e.g., DNA methylation, histone modifications, and expression of non-coding microRNAs) produce heritable modifications in gene expression without changes in DNA sequence (Chuang and Jones 2007; Cedar and Bergman 2009; Svoboda and Flemer 2010). "Environmental epigenomics" is thus defined as the constant interplay between the environment, which include both endogenous (such as hormones) and exogenous factors (such as chemicals and food) and the epigenome (Grafodatskaya et al. 2010; Gorini et al. 2014).

Children are particularly sensitive to neurotoxic effects of heavy metal exposure since they have weaker detoxifying mechanisms and poorer immune systems than adults (Landrigan and Garg 2002; Henn et al. 2014). The major windows of developmental vulnerability occur in the utero and during infancy and early childhood due to the continuing brain development after birth (Rodier 1995).

In recent years, attention has been focused on the study of potential contribution of heavy metals to the development of ASD. In particular, several lines of research have shown that autistic children display a higher body burden of toxic metals compared to neurotypical controls (Adams et al. 2009; Elsheshtawy et al. 2011; Lakshmi Priya and Geetha 2011). In addition, the impact of heavy metals seems to be more evident in subjects with moderate or severe ASD in comparison to subjects with mild ASD (Geier et al. 2009a, b, 2012). Generally, heavy metals are measured in blood, urine, hair, and nails, while recently, a few studies examined biomarkers in teeth. While blood and urine provide an assessment of contemporaneous exposure, hair and nail reflect metabolic changes of many elements over long periods of time since in these biological matrices, trace metal concentrations are not related to rapid fluctuations due to the diet, air, and water. In contrast to hair, teeth provide historical information of metal exposure. Enamel of primary teeth, in particular, reflects a record of prenatal and early postnatal exposure since it begins in the utero and is completely formed between 3 months and 1 year after birth (Abdullah et al. 2012).

Moreover, there is increasing evidence that metal mixtures may cause greater than additive effects on cognitive and motor development (Henn et al. 2014). Nevertheless, few studies have been performed on metal interactions, and the association

between exposure to multiple metals and autism remains to be explored.

This current review examines the evidence for an association between ASD and heavy metals with acknowledged neurotoxic properties (lead, mercury, and cadmium) and summarizes the recent literature on neurodevelopmental effects associated with metals co-exposures.

Lead

Neurotoxic effects of lead (Pb) have been known for centuries. Though acute Pb poisoning may even lead to death, long-term studies on children who survived the event showed a high incidence of learning and behavioral disorders (Byers and Lord 1943). Research performed mainly in the USA in the 1970s and 1980s revealed that effects on the central nervous system, such as deficits inherent concentration, memory, cognition, and behavior, occurred in asymptomatic children whose Pb concentration in blood was increased (Landrigan et al. 1975; Needleman 1988). Children are the major victims of Pb poisoning. Recent estimates of the World Health Organization show that approximately 15 to 18 million children in developing countries may suffer permanent brain damage due to acute Pb exposure and about 3.5 % of minor mental retardation is attributable to Pb poisoning worldwide (Prüss-Üstün et al. 2004).

According to the concept of plasticity, the recovery of function after damage to the young brain occurs more easily than in the adult brain (Winneke 2011), while correctly applied to the motor function, this principle is of limited importance for the cognitive activities (language, memory, and attention). Thus, brain injury occurring before the age of 7 years has a worse prognosis than a similar damage occurring later (Duval et al. 2002).

During the twentieth century, leaded gasoline was the predominant source of airborne Pb; nonetheless, in recent years, industrial emissions account for 78 % of air lead (U.S. Environmental Protection Agency 2007). In soil of urban areas, as a consequence of the past gasoline combustion and industrial emissions, Pb levels may reach concentrations up to 1,200 µg/g (Lanphear et al. 1998; Levin et al. 2008). In the USA, the main sources of Pb exposure result from deteriorated lead-based paints from renovations of hold homes and lead-contaminated soil and dust (Levin et al. 2008; Chandran and Cataldo 2010). Ingestion of lead paint and dust has been estimated to account for 70 % cases with elevated blood lead levels (BLLs) (Levin et al. 2008; Warniment et al. 2010). Dust particles that are composed of soil, paints, and industrial or automotive emissions are absorbed more easily in comparison to soil into the gastrointestinal tract of children (Schnur and John 2014). An updated list of the major sources of exposure to lead is shown in Fig. 1.

MAJOR SOURCES OF EXPOSURE TO LEAD

- petrol additives
- active industry (mining)
- lead-based paints (older homes, old toys, furniture, crafts)
- soil and dust
- drinking water systems
- ceramic glazes
- electronic waste

Fig. 1 The major sources of exposure to lead for children (from World Health Organization 2010)

Effects on Neurodevelopment

The highest BLLs occur between 15 and 24 months of age (Tong et al. 1996), where the normal hand-to-mouth behaviors result in high exposure to chemicals and, specifically, to Pb. Children who live in houses with deteriorating leaded paint may achieve lead concentrations of 20 $\mu\text{g}/\text{dL}$ due to the ingestion of dust arisen by lead paint residues. This level may further increase when a child displays pica, an eating disorder characterized by the persistent ingestion of non-nutritive substances (Charney et al. 1980). In addition to a higher risk of exposure, the fraction of Pb adsorption is 40 % in children compared to 10 % in adults (World Health Organization 2008).

Epidemiological research has linked Pb exposure during childhood to deficits in cognitive skills and IQ, behavioral problems, and attention hyperactivity disorder (ADHD) (Bellinger et al. 1994; Chen et al. 2007; Eubig et al. 2010). Prenatal and early postnatal Pb poisoning and long-term exposure to Pb low levels have been associated to an increased risk of neuropsychological outcome and aggressive behaviors in adolescence (Dietrich et al. 2001; Ris et al. 2004).

Prenatal exposure to lead is caused by the metal mobilization from maternal bones during pregnancy and its crossing the placenta. A study performed on a group of mother-newborn pairs showed a strong correlation between the BLLs in the mothers and their newborns; in particular, the blood lead concentration of infants was approximately 90 % of that of the mothers (Amitai et al. 1999). Furthermore, Pb accumulated in the mother's bones from past environmental exposures can be excreted into breast milk, and despite the low levels excreted, it may strongly influence the infant's BLLs (Ettinger et al. 2006).

The nervous system of the fetus is especially susceptible to Pb, which may penetrate the incomplete blood-brain barrier. The consequent adverse effects, known as "behavioral teratology," are not limited to the main prenatal brain development processes (e.g., neuronal proliferation,

migration, differentiation, synaptogenesis, and myelination) and extends after birth, with the progressive neuronal development and the volume increase of the brain (Winneke 2011). Therefore, the postnatal and the prenatal periods represent a critical phase for the developing brain to insults of environmental contaminants (Fig. 2).

The recent findings that no level of Pb is considered safe for children have led the Centers for Disease Control and Prevention Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) to remove the term "blood lead level of concern." Indeed, numerous studies reported negative effects on children's neurodevelopment, including reduced intelligence, attention disorders, and academic deficits at BLLs $<10 \mu\text{g}/\text{dL}$. For example, it has been showed that blood lead concentrations $<10 \mu\text{g}/\text{dL}$ are inversely associated with IQ scores at 3 to 5 years of age, and most declines in IQ are associated with an increase in lifetime mean blood lead from 1 to 10 $\mu\text{g}/\text{dL}$. Specifically, the estimated IQ loss was 4.6 points for each increase in the BLL of 10 $\mu\text{g}/\text{dL}$; in contrast, for children whose Pb concentration remained below this level, the estimated loss in IQ was 7.4 points (Canfield et al. 2003). Lanphear et al. (2005) found an inverse relationship between blood Pb concentration and IQ score; thus, the effects of Pb exposure were greater at lower lead levels. Bellinger (2008) supported the existence of adverse effects below 10 $\mu\text{g}/\text{dL}$, as well as the lack of existence of a threshold to Pb levels exposure.

ACCLPP has established the new reference value of 5 $\mu\text{g}/\text{dL}$ to identify children with elevated BLLs. This value is based on the 97.5th percentile of BLL distribution

High exposure:

- Hands-to-mouth behavior
- Pica
- Ingestion of dust from lead-paint residues

High absorption:

- Fraction of absorption in children is 4:1 ratio than in adults

High vulnerability:

- Incomplete blood-brain barrier
- Prenatal and postnatal windows of susceptibility to chemicals during brain development

Fig. 2 Summary of the properties making children at highest risk to lead exposure effects

in children aged 1–5 years of age (ACCLPP 2012). According to the Childhood Lead Poisoning Prevention Program, children at or above the reference value of 5 µg/dL (currently 450,000 in the USA) will need to be followed over time in order to prevent further Pb hazard exposure and adverse health effects of Pb in the body (Kentucky Department for Public Health, Childhood Lead Poisoning Prevention Programme 2013).

Association with Autism Spectrum Disorders

One the first reports evaluating the potential relationship between elevated blood lead and development of autism showed that children with autism and ADHD had BLLs of 42 µg/dl (Eppright et al. 1996). Previously, it was found that children affected by ASDs had BLL between 5 and 50 µg/dL (Cohen et al. 1982). Some years later, the study of Filipek et al. (1999) reported that 44 % of autistic children had BLLs greater than 2 standard deviations above the mean. Lidsky and Schneider (2005) described two cases of children that, as a consequence of Pb poisoning, developed autistic symptoms. In particular, the patient with a severe lead poisoning displayed impairment in cognitive functions and significant declines in speech and communication during periods of elevated blood lead concentrations. These results seem to suggest a temporal association between high BLLs and the emergence of autism and confirm the involvement of Pb in affecting cognitive, communication, and social function.

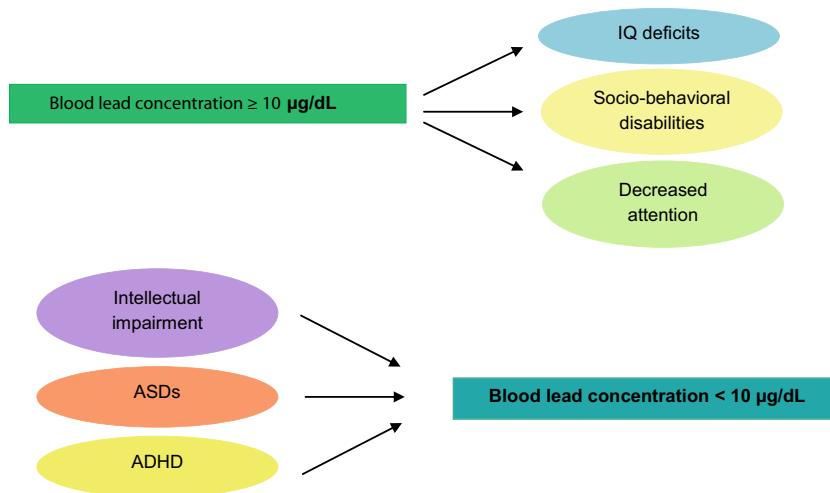
Habitual mouthing of objects and odd food preferences, typical of pica, may be potentially associated to a source of Pb. Children with autism were showed to be at increased risk for Pb exposure and intoxication due to their exploratory oral behaviors and ingestion of dangerous amounts of Pb in environments that are usually safe (Clark 2010). In the past research performed in children affected by pica, it found that mean blood lead concentration was significantly higher in the

autistic group than that in non-autistic psychotic children (Cohen et al. 1976; Kinnell 1985).

More recently, Clark (2010) showed that about 20 % of children with autism had BLLs of 2 µg/dL or greater, but none of the autistic children studied exceeded 10 µg/dL. Though the majority (65 %) of the group studied had pathological exploration of objects, the mild elevations of BLLs in these children suggested that the environment where they lived was relatively lead-free (Fig. 3).

Several studies have been reported elevated Pb levels in hair samples of autistic children. Lakshmi Priya and Geetha (2011) showed a significant increase in Pb levels in both the hair and nail samples of Indian children diagnosed with an ASD in comparison to the healthy control group. Similar results were reported in a cross-sectional study where a group of Egyptian children with ASD and a group of control were tested for Pb content in the hair, although no significant correlation was observed between the level of Pb and severity of autism (Elsheshtawy et al. 2011). One study in Kuwait (Fido and Al-Saad 2005) found that children with autism had approximately levels of lead two times higher respect to neurotypical children. Moreover, the higher toxic ratio observed between the essential metallic elements and toxic metals suggested that Pb exposure originated years later during pregnancy and may derive to Pb high levels occurring in Kuwait in the past decade when leaded gasoline was used. The comparison between a group of Arab children with ASD and an age- and sex-matched control group revealed a statistically significant difference in the hair and urine levels of Pb, suggesting that both immediate and long-term exposures were greater in autistic children (Blaurock-Busch et al. 2011). Metallomics analysis performed in Japan on hair samples of autistic children showed that especially infants aged 0–3 years suffered from high burden of Pb (Yasuda et al. 2013). In contrast, in another study, Pb was significantly lower in the hair of children with autism than in matched controls, and the

Fig. 3 Effects of lead exposure on cognitive abilities and correlations with blood lead concentrations



patients had a low ability to excrete this metal (Kern et al. 2007). Children with autism have been characterized as subjects with decreased urine levels of Pb compared to healthy children (Yorbik et al. 2010), and more recently, lead analysis in blood, urine, and hair samples has not revealed significant differences between autistic and psychotic non-autistic patients (Albizzati et al. 2012).

To date, two studies only have used deciduous teeth as biological samples for the measurement of metal exposure in autistic children. Both reports did not find any significant difference in levels of Pb between children with an ASD and typically developing children (Adams et al. 2007; Abdullah et al. 2012).

Mechanisms of Neurotoxicity

Despite the growing research, the molecular mechanisms responsible for the effect of Pb in the central nervous system are still not completely clarified (Sánchez-Martín et al. 2013). It is largely accepted that neurotoxicity of lead occurs through multiple mechanisms of action. Direct mechanisms include disruption of calcium homeostasis, damage to the mitochondria, stimulation of calcium release from the mitochondria, alteration of lipid metabolism, and accumulation in astrocytes (Lidsky and Schneider 2003). Moreover, lead has the ability to substitute for zinc that is involved in the regulation of genetic transcription through zinc-finger proteins or zinc-binding sites in receptor channels (Reddy and Zawia 2000). Changes in mechanisms that control gene expression during early neurodevelopment may lead to reduction of gray matter and alteration of myelin and consequent neurological pathologies in adults (Cecil et al. 2011). Another indirect effect of Pb on the brain involves disruption of thyroid hormone transport into the brain. Due to their critical role in the normal development of the brain, severe deficiencies of thyroid hormones may cause mental retardation (Lidsky and Schneider 2003).

It has been proposed that elevated blood lead concentrations may be correlated to autism through a deregulation of physiological levels of neurotransmitters in plasma. In the developing brain, Pb causes an inappropriate release of neurotransmitters at rest and competes with calcium in their evoked release, interfering with the correct development of synaptic connections during the first few years of life (El-Ansary et al. 2011). In particular, Pb has shown to disrupt dopamine system in mesencephalic cells, causing necrosis and apoptosis (Scortegagna and Hanbauer 1997). Increased levels of gamma-aminobutyric acid, serotonin, and dopamine have been found in the plasma of autistic patients aged 4–12 years with respect to age-matched control children (El-Ansary et al. 2011) in agreement with previous works (Singh et al. 1997; Stone et al. 2007). Thus, postnatal lead exposure might represent a risk factor in the pathogenesis of autism,

considering the implications of dopamine in mental and neurological disorders (El-Ansary et al. 2011).

Mercury

As well as lead, mercury (Hg) has also been known for its potent neurotoxicity for centuries. Still, today, mercury remains an ubiquitous element in the global environment while many industrialized countries have established procedures and policies to minimize and prevent exposure to mercury (Counter and Buchanan 2004). Most of the environmental mercury results from coal-fired stations, waste incinerators, and mining activities. Speciation of Hg includes inorganic mercury, elemental mercury, and organic mercury (e.g., methyl- and ethylmercury) (World Health Organization 2007). While common inorganic sources include air and water pollution, skin creams, and infant teething powders, elemental mercury typically comes from amalgam dental fillings and industrial exposure. Being not lipid-soluble, inorganic mercury may not cross the blood-brain barrier or blood-placenta barrier and preferentially accumulates in the kidney after ingestion (Park and Zheng 2012). Inhalation is the main exposure route of elemental mercury that, in contrast to inorganic mercury salts, is poorly adsorbed in the gastrointestinal tract. In the form of mercury vapor, elemental mercury is adsorbed in the lungs and reaches the central nervous system due to its capacity to cross the blood-brain and blood-placenta barrier as well as the lipid bilayers of cellular membranes (Park and Zheng 2012). Though no adverse health effects of elemental mercury have been ascertained, the association of mercury adsorption from dental amalgam filling and detrimental effects in the general population is still under investigation. Nonetheless, the use of dental amalgam filling is declining rapidly and risk for exposure concerns almost exclusively dentists (World Health Organization 2007).

Methylmercury (MeHg) is the most widespread source of exposure to both humans and wildlife. MeHg, a product of microbial methylation, rapidly bioaccumulates and biomagnifies in the biota (Huang et al. 2012). The general population is exposed to MeHg mainly through the diet, especially through the consumption of freshwater and marine fish and consumption of other animals that consume fish, such as marine mammals (Višnjevec et al. 2013). The major toxic effects of MeHg are on the central nervous system, and the developing fetus brain results as the most vulnerable (National Research Council 2000b).

Effects on the Central Nervous System of Children

The central nervous system is one of the major targets of MeHg. Both high- and low-dose exposures often produce

severe and long-term neurological damage though the clinical symptoms depend on the dose, pattern, time, and route of exposure (Zahir et al. 2010; Johansson et al. 2007). The effects of high dosage as well as those deriving from low-dose chronic Hg exposure are of particular concern to children during neurodevelopment stages due to their vulnerability to Hg (Counter and Buchanan 2004). The adverse effects of acute MeHg exposure in the utero have been documented for the first time following poisoning episodes that occurred in Japan (1953; 1964–1965) and Iraq (1971–1972) and include neurological symptoms and developmental delays including blindness, cerebral palsy, mental retardation, and general paralysis (Amin-Zaki et al. 1974; Tsubaki and Irukayama 1977; National Research Council 2000b). Since then, numerous epidemiological studies have evaluated the impact of early life exposure to MeHg in neurodevelopment especially in communities with high fish intakes (e.g., Cordier et al. 2002; Boucher et al. 2010; Lynch et al. 2011). Chronic moderate-level MeHg exposure, primarily through maternal consumption of fish, may also determine subtle effects, as it has been shown in New Zealand and the Faroe Islands, where offspring displayed deficits in language, IQ, memory, attention, and visual-spatial and motor skills (Grandjean et al. 1997; Crump et al. 1998; National Research Council 2000b).

Karagas et al. (2012) reviewed the epidemiological research focused on the impact of low-level MeHg exposure both in children and adults. Prospective cohort studies have reported associations of prenatal mercury exposure with impairments in neonatal motor function (Suzuki et al. 2010) and behavior (Gao et al. 2007), although dependence of toxic effects from age, sex, and timing of exposure should be evaluated. Bioindicators for prenatal MeHg exposure are maternal blood and hair collected during pregnancy or cord blood and tissue after birth, whereas postnatal exposure may be evaluated by measurement of MeHg in children's hair and blood (Julvez et al. 2012). Mercury levels in the cord blood and tissue are accepted as more useful and valid biomarkers than mercury levels in the maternal hair since it shows a better relationship with the Hg-related neurobehavioral deficits in the child (Višnjevec et al. 2013). On the other hand, breast milk is not generally used for assessing exposure due to the low concentration and variability in the proportion of mercury as MeHg (García-Esquinas et al. 2011; Miklavcic et al. 2011).

Recently, Boucher et al. (2012) reported the association between prenatal MeHg exposure and ADHD symptomatology at school age, corroborating previous results on the effects of MeHg on attention and learning skills (Grandjean et al. 1997; Debes et al. 2006). Moreover, the association with ADHD-related behaviors seem to be stronger in boys than in girls, which is consistent with the growing evidence showing differences in the impact of endocrine-disrupting chemicals (including mercury) on neurodevelopment in males and females (Sagiv et al. 2012).

Mercury and ASDs

Mercury poisoning and autism show very similar symptoms, both mental disturbances and physical disorders (Bernard et al. 2001; Geier et al. 2008). In addition, many parallels between the effects of Hg intoxication on the brain and the brain pathology found in individuals with ASD include dendritic overgrowth, neuroinflammation, brain immune response, oxidative stress and lipid peroxidation, mitochondrial dysfunction, neuronal necrosis, axonal demyelination, and gliosis (Geier et al. 2010; Kern et al. 2012) (Table 1).

Collectively, much evidence suggests the biological plausibility of mercury as an etiological agent in autism. Higher levels of mercury both in hair and urine have been reported in autistic children compared to the control group, suggesting that children with ASDs had a greater past and immediate exposure (Blaurock-Busch et al. 2011). An increased level of mercury in hair and nail of children with autism was further found in the study of Lakshmi Priya and Geetha (2011), who reported that this elevation was directly correlated with the severity degree of ASD. Geier et al. (2012) not only corroborated the relationship between hair Hg concentration and ASD severity but also observed no significant correlation between any other toxic metallic elements measured and ASD severity. On the other hand, some studies showed decreased levels of mercury in the hair of autistic children with respect to controls (Holmes et al. 2003; Adams et al. 2008; Elsheshtawy et al. 2011). Probably, the decreased ability of autistic children to excrete mercury lead to its accumulation in body tissues, including the brain (Holmes et al. 2003). Kern et al. (2007) found no statistically significant lower mercury levels in the hair of children with autism in comparison to healthy children, supporting the hypothesis that autistic subjects are poor excretors. The lowered excretion of children with ASD may explain the higher body burden and the observed association of Hg with increased Childhood Autism Rating Scale (CARS) scores and decreased IQ (Elsheshtawy et al. 2011). Unlike the others, the research of Fido and Al-Saad (2005) described a dramatic condition of Kuwaiti autistic children that showed significantly higher levels of mercury (15 times higher), which may have likely resulted from domestic bread containing methylmercury fungicide widely used in Kuwait.

In a recent study, Hg concentration was measured in the prenatal and postnatal enamel regions of teeth sampled from both autistic and neurotypical children. No differences were reported in mercury levels between the two groups of children (Abdullah et al. 2012). Previously, measurements in whole baby teeth had shown two- to threefold higher level of mercury in autistic children with respect to the control group (Adams et al. 2007). The contradictory results may derive from different deposition of mercury in the two matrices, whereas dentin is living in tissue from the origin to the lost

Table 1 Comparison of the principal effects of mercury poisoning and ASDs to human health (from Bernard et al. 2001; Geier et al. 2008; Kern et al., 2010)

	Mental symptoms	Physical symptoms	Brain pathology
Mercury poisoning	Social withdrawal	Gastrointestinal disturbances	Microtubule degeneration
Autism spectrum disorders	Abnormalities in communication	Sleep difficulties	Dendritic overgrowth
	Lack of facial expression	Excessive salivation	Neuroinflammation
	Sound sensitivity	Low muscle tone	Brain immune response
	Touch aversion	Abnormal reflexes	Oxidative stress/lipid peroxidation
	Sensitivity to light	Repetitive/stereotypic behaviors	Reduced GSH levels
	Mental retardation	Deficits in eye-hand coordination	Mitochondrial dysfunction
	Irritability/aggression	Rashes/dermatitis	Neuronal necrosis
			Axonal demyelination
			Gliosis

of tooth, enamel is completely formed only by 3–12 months of age (Ash and Nelson 2003; Adams et al. 2012). A positive relationship has been also reported between Hg levels both in whole blood and red blood cells, and the degree of severity of autism (DeSoto and Hitlan 2007; Geier et al. 2010). In contrast, results from another cohort study did not show any difference in total Hg in blood comparing children with ASD and controls (Hertz-Picciotto et al. 2010). It is important to say that blood Hg analysis is of limited evidence and is not indicative of the real levels of exposure due to the short half-life of mercury in blood (Adams et al. 2008).

Recent investigations identified atypical urinary porphyrin profiles in children with autism (Nataf et al. 2006; Geier and Geier 2007a; Austin and Shandley 2008). Porphyrins are a necessary intermediate in heme production, and metals such as mercury have been shown to inhibit the enzymes uroporphyrin decarboxylase and coproporphyrinogen oxidase, causing an excessive urinary porphyrin excretion. Porphyrinuria is not only a biomarker of Hg damage but also a concomitant biological occurrence in ASD (Austin and Shandley 2008; Garrecht and Austin 2011). In addition, children with increasingly severe ASD measured by CARS scores correlated with increasing levels of urinary porphyrins associated with Hg body burden (Geier et al. 2009a, b).

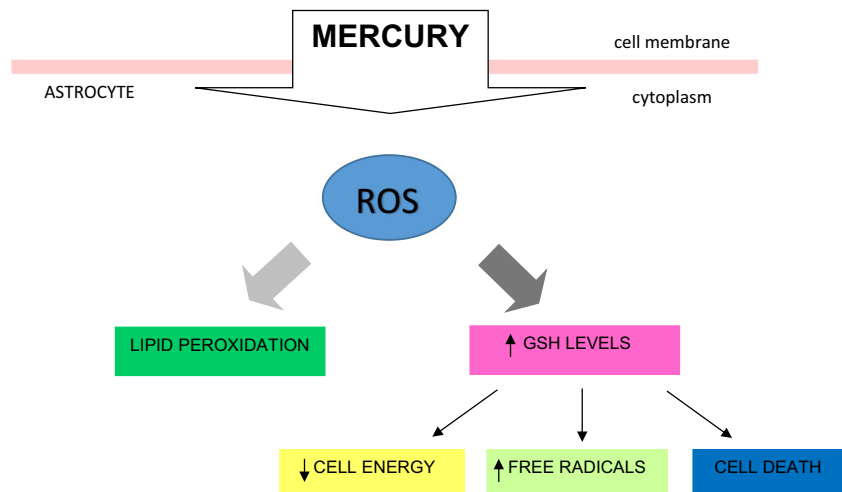
Mechanisms of Neurotoxicity

Several lines of evidence indicate that oxidative stress as well as altered mitochondrial and cell membrane permeability represent critical events related to the neurotoxic effects elicited by MeHg (Yin et al. 2007; Farina et al. 2011). MeHg has the capacity to induce the production of reactive oxygen species (ROS) both in vitro (isolated rat brain synaptosomes) and in vivo (rodent cerebellum) (Ali et al. 1992). The increased level of species such as superoxide anion, hydrogen peroxide, and nitric oxide is widely acknowledged to give rise to a multitude of lipid peroxidation products (Yin et al. 2007).

MeHg preferentially accumulates in astrocytes and, to a lesser extent, in microglial cells (Aschner 1996; Charleston

et al. 1996; Aschner et al. 2000), which, among various cell types, occupy approximately one half of the central nervous system volume (Aschner et al. 2007). Inhibition of the uptake systems for glutamate and cysteine transport, both of which compromise glutathione (GSH) synthesis and cellular redox status, is presumably one of the mechanisms involved in dysfunction of astrocytes (Allen et al. 2001; Shanker et al. 2001; Shanker and Aschner 2003). The increased oxidative stress is related to reduced intracellular GSH levels (Lee et al. 2001; Shanker et al. 2005), and GSH depletion consequently leads to impairment of mitochondrial functions and energy metabolism and increment in free radical production up to cell death (Mérard-Saidoune et al. 1999; Shenker et al. 1999; Belletti et al. 2002) (Fig. 4).

Mercury is mostly excreted through the feces, and the secretion of inorganic mercury in the bile is in large part dependent on the binding to glutathione (Ballatori and Clarkson 1984). Thus, it is primarily the Hg-GSH complex that is to be measured in the blood, urine, feces, and hair after mercury exposures (Haley 2005). Infants are especially vulnerable to Hg poisoning as a consequence of their small GSH production (Ballatori and Clarkson 1984). Relative to controls, children with autism have significantly lower baseline plasma concentrations of total glutathione (tGSH) and significantly higher concentrations of oxidized glutathione (GSSG) (James et al. 2004). In the significant increase in GSSG and the remarkable (67 %) decrease in GSH, GSSG reflects oxidative stress (James et al. 2004) that is characteristic of autism (Kern and Jones 2006; Deth et al. 2008; Chauhan et al. 2012), as well as neurodegenerative disorders such as Parkinson's and Alzheimer's diseases and amyotrophic lateral sclerosis (Kaltschmidt et al. 1993; Hunot et al. 1997; Kitamura et al. 1997; Kidd 2005). ASD seems to be associated to an impairment of glutathione-based mechanism defense in selective regions of the brain, such as the cerebellum and the temporal cortex of autistic subjects (Chauhan et al. 2012). The nervous system, including the brain, spinal cord, and peripheral nerves, is rich in polyunsaturated fatty acids. The high lipid and mitochondria content of the nervous tissue, coupled with its

Fig. 4 Possible cellular effects of Hg neurotoxicity

high oxygen demands, makes it particularly sensitive to ROS (Singh et al. 2004). Multiple studies have reported evidence of mitochondrial dysfunction in individuals with ASD (Rossignol and Bradstreet 2008; Weissman et al. 2008; Giulivi et al. 2010; Dhillon et al. 2011). Indeed, mitochondria are particularly vulnerable to damage of free radicals due to the lack of enzymes for GSH production (Enns 2003; James et al. 2009).

Overall, the scientific evidence suggests that infants with autism have a decreased ability to excrete mercury due to a combination of lowered reduced glutathione, emergence of oxidative stress, and excessive use of oral antibiotics. In rats, antibiotics prevent normal gut anaerobes to convert methylmercury to inorganic mercury that is more easily excreted (Adams et al. 2007). Thus, the elevated use of antibiotics in autistic children may further contribute to increase Hg body burden as well as partially explain the chronic gastrointestinal problems reported in approximately 50 % of children with autism (Adams et al. 2008).

Thimerosal: an Association with Autism?

In addition to seafood, the major source of Hg exposure in the USA is thiomersal (sodium ethylmercurithiosalicylate), a preservative containing 49.6 % ethylmercury used until 2003 in most childhood vaccines. Still, today, many of the influenza vaccines in the USA and childhood vaccines in developing countries contain thimerosal (TM) (Dorea 2010; Brown and Austin 2012; Golman 2013).

In the human body, TM acts as a thiol oxidizer through the binding to the sulfhydryl groups of membrane proteins, enzymes, cytoskeleton and, in many instances, render them non-functional (Farina et al. 2013). TM decreases the availability of GSH in human cells. In lymphoblastoid cells derived from autistic children and unaffected controls, James et al. (2009) measured both the cytosolic and mitochondrial tGSH/GSSG ratios as dynamic indicators of the severity of oxidative stress.

After TM exposure, the mitochondria had a significant lower GSH/GSSG ratio compared to that in the cytosol, leading to the impairment of the cellular antioxidant defense and to an increase in free radical generation (James et al. 2009).

Currently, there is much to debate about the neurotoxicity of TM in comparison to MeHg. Toxicity of TM was reported to be higher to that of other metal compounds examined, including MeHg both in human neuronal and fetal cells (Geier et al. 2009c). Indeed, TM had the ability to induce mitochondrial damage and reduce oxidation-reduction activity, cellular degeneration, and cell death even at nanomolar concentrations (Geier et al. 2009b). Previously, Ueha-Ishibashi et al. (2004) showed that both TM and MeHg exerted the same effects on cerebellar neurons, decreasing the cellular content of GSH in a concentration-dependent manner.

Both the agents are metabolized in inorganic mercury; thus, it is often difficult to discern the toxic effects of the two Hg species (Kern et al. 2013). Nonetheless, while TM enters the human body through injection, exposure to MeHg occurs by the consumption of contaminated fish or through breastfeeding; thus, the impact of MeHg may be weakened by the natural defense mechanisms of the human body (Dórea et al. 2013). Under in vivo conditions, the comparison of the two toxicokinetic profiles indicates a shorter blood half-life and a faster elimination for TM that leads to different toxicity risks of thimerosal and, specifically, ethylmercury, with respect to MeHg (Dórea et al. 2013).

Overall, the effects of TM on development of ASDs and other outcomes are still under investigation. Numerous studies by the same researchers (Geier and Geier 2003a, b, 2004, 2006, 2007b; Young et al. 2008; Geier et al. 2013) showed a relationship between exposure to TM and neurodevelopmental disorders, including autism. In contrast, other reports did not find any association between thimerosal-containing vaccines and ASD (Croen et al. 2008; Aschner and Ceccatelli 2010;

Price et al. 2010; Schultz 2010) or neuropsychological impairments (Parker et al. 2004; Marques et al. 2010; Chen et al. 2013). To date, there are no reliable data confirming thimerosal as an etiological agent in autism development; however, it cannot be excluded that individual gene profile and gene-environment interaction may play a dramatic role in modulating the individual response to TM risk exposure (Aschner and Ceccatelli 2010).

Cadmium

Cadmium (Cd) is a recognized toxic metal mainly emanating from industrial and agricultural sources (Järup and Akesson 2009). World production of cadmium amounted to 22,000 tons in 2010, while world reserves of this metal are estimated at 660,000 tons (Rodríguez-Barranco et al. 2013). Though its use in developed countries has slightly decreased, today, cadmium contamination is still a serious concern due to different human activities such as waste incineration and smelting procedures and the use of phosphate fertilizers (Bertin and Averbeck 2006; Ciesielski et al. 2012). Cadmium is listed among the top seven of the 275 most hazardous substances in the environment, and it ranks third in the metallic trace elements subdivision of the same list behind lead and mercury (Agency for Toxic Substances and Disease Registry 2013). High concentrations of Cd in the soil and water supply mean that it is readily detectable in meat, fish, vegetables, and fruits (Ishitobi et al. 2007). In addition to diet (primarily cereals and vegetables), which represents the main source of cadmium intake in the non-smoking general population, exposure to Cd may also occur through environmental tobacco smoke, house dust, and active smoking (Järup et al. 1998; Cao et al. 2009). Once it entered the body, Cd accumulates in the liver and kidney, and the highest concentrations may be observed in the renal cortex (U.S. Environmental Protection Agency 1997; Cao et al. 2009).

Neurotoxic Effects

In contrast to lead and methylmercury, the effects of cadmium exposure in neurodevelopment are still controversial (Kim et al. 2013). There is recent evidence that placenta forms only an incomplete barrier against Cd during pregnancy; thus, it is unable to protect fetal and child growth from the effects of prenatal cadmium exposure (Lin et al. 2011). In the 1970s and 1980s, both animal experiments and epidemiologic studies reported the first proofs of cadmium neurotoxicity. Prenatal Cd exposure had significantly detrimental effects on verbal IQ as well as on cognitive and visual-motor performance in children (Thatcher et al. 1982; Marlowe et al. 1985; Moon

et al. 1985; Bonithon-Kopp et al. 1986), though it was not clear whether the observed outcomes were due to a co-exposure to multiple pollutants, which included lead. It is important to say that these results were based on the hair Cd analysis in children, which may be subject to external contamination. In a more recent study, the effects of maternal exposure in the offspring were assessed by measuring cord blood Cd levels that present the absolute amount of metal that reaches the fetus through the placenta (Tian et al. 2009). Tian et al. (2009) reported an IQ full score of children in the higher cord blood cadmium group that was significantly lower with respect to the controls. Moreover, cadmium concentration in urine (that may be used as a biomarker of exposure in early pregnancy), even at low doses, was associated to decreased IQ scores in children (Kippler et al. 2012a).

Cao et al. (2009) did not observe any significant relationship between blood cadmium levels, as a result of postnatal exposure, and neurodevelopmental scores in children at 2, 5, and 7 years of age. Children 6–15 years of age who had higher urinary Cd concentrations showed an increased risk of learning disabilities; in contrast, the association with ADHD did not reach statistical significance (Ciesielski et al. 2012) as previously observed through evaluation of Cd concentration in blood of school-aged children with ADHD (Yousef et al. 2011). On the other hand, Bao et al. (2009) reported that children with increased levels of cadmium in the hair showed withdrawn, social problems and attention deficits (Table 2).

Association with ASDs: Evidence

Data inherent of the potential association between Cd exposure and the increased risk in autism development are quite poor. Lines of research reported that cadmium was significantly lower in the hair of children with autism than in matched controls (Shearer et al. 1982; Kern et al. 2007). Low levels of cadmium were also measured in hair samples of children with autistic features, classified as having childhood-onset pervasive disorder, as compared to controls (Wecker et al. 1985). In contrast, other studies reported significantly higher levels of Cd in hair samples of autistic children compared to the healthy control group (Al-Ayadhi 2005; Blaurock-Busch et al. 2011; Al-Farsi et al. 2013). Children with autism also displayed a decrease of Cd urine concentrations (Yorbik et al. 2010) that were consistent with the studies yielding decreased hair Cd levels. The reported significant decrease in urinary excretion of Cd confirms that autistic children probably have poor metal-detoxifying mechanisms, which may result in high body burden of heavy metals (Yorbik et al. 2010; Blaurock-Busch et al. 2011).

Metallomics analysis in human scalp hair in 1,967 children aged 0–15 years with autistic disorders showed that 8.5 % patients suffered from high burdens of cadmium. In particular, the highest body burden (12.1 %) was observed in the infants

Table 2 Summary of the effects of perinatal cadmium exposure on cognitive abilities in children

	Effects on children	References
Prenatal cadmium exposure	IQ deficits (4.5 years of age)	Tian et al. (2009)
	IQ deficits (5 years of age)	Kippler et al. (2012a)
Postnatal cadmium exposure	No significant effects on neurodevelopmental scores (2, 5, and 7 years of age)	Cao et al. (2009)
	Learning impairment (6–15 years of age)	Ciesielski et al. (2012); Yousef et al. (2011)
	Social problems and attention deficits (7–16 years of age)	Bao et al. (2009)

aged 0–3 years, as already observed for lead, suggesting the existence of a critical period during neurodevelopment in which mineral imbalances of environmental toxic metals may induce epigenetic alterations and neurodevelopmental disorders (Yasuda et al. 2013; Yasuda and Tsutsui 2013). Previously, the same authors had reported that not only Cd highest burden level was present in infants aged 0–3 years old but the metal mainly accumulated in females (Yasuda et al. 2012).

Mechanisms of Neurotoxicity

Cadmium has multiple effects on cells; thus, it directly or indirectly may impair brain development. It interferes with cell cycle progression, proliferation, differentiation, as well as induction of apoptosis (Dong et al. 2001; Yang et al. 2004). Though Cd is not a redox-active metal, environmental exposure to cadmium is known to induce oxidative stress and to affect antioxidative proteins (Bertin and Averbeck 2006). The affinity of the metal to thiol groups may be responsible for two events, the reduction of metallothionein expression and of glutathione levels, that both lead to the decrease of cellular activities against ROS (Bertin and Averbeck 2006). Early life low-level exposure to Cd via breast milk was found to induce oxidative stress in breast-fed infants, and the subsequent DNA damage was associated with impaired child health and development (Kippler et al. 2012b). Moreover, elevated Cd concentrations in placenta are associated with imbalances in zinc transport to the fetus (Kippler et al. 2010), and this deficiency may lead to long-term consequence for child neurodevelopment (Salgueiro et al. 2002). It is remarkable that zinc is a critical nutrient for the development of the central nervous system, being the co-factor of enzymes, proteins, and neurotransmitters involved in brain growth, brain structure, and neurotransmission and in brain memory function, respectively (Salgueiro et al. 2002). Another mechanism of developmental toxicity of Cd involves the alteration of expression of thyroid hormones that are known to be essential for brain development during the perinatal period (Ishitobi et al. 2007). Several decades ago, animal studies had shown that chronic exposure to cadmium leads to decreased

levels of norepinephrine, serotonin, and acetylcholine (Stowe et al. 1972; Singhal et al. 1976).

The Effects of Metal Co-exposure

There is growing evidence that co-exposure to heavy metals may exert adverse effects on neurodevelopment through common pathways (Kim et al. 2009; Wasserman et al. 2011; Claus Henn et al. 2012; Rodríguez-Barranco et al. 2013). Metals often co-occur in the environment, particularly in urban or industrial regions, as well as in socioeconomically disadvantaged populations or living near hazardous waste sites (Henn et al. 2014). In humans, the effects of combined exposure include birth defects (Chandra et al. 1983), reproductive outcomes (Gollenberg et al. 2010), and disabilities in cognitive and motor developments (McDermott et al. 2011; Lin et al. 2013). Furthermore, concomitant exposure to several metals may have more severe and additive effects on cognition than effects observed for each metal (Wright et al. 2006; Claus Henn et al. 2012). A recent study of Kim et al. (2013) showed a dose-dependent interaction between Pb and Cd exposure on cognitive abilities at 6 months of age. In particular, at very low levels of both Pb and Cd in maternal blood, an antagonistic interaction was observed during the early pregnancy with respect to the mental development index, and Cd had a protective effect against increasing Pb concentrations. In contrast, for concentration values of Cd above the median, there was a synergistic effect between Pb and Cd during the late pregnancy period. The ability of the two metals causing oxidative stress (Lee et al. 2006), interfering with calcium signalling (Rai et al. 2010), and/or disrupting neuroendocrine homeostasis such as thyroid hormone (Ishitobi et al. 2007) might explain their synergistic action during neurodevelopment.

Manganese (Mn) is a very common element in the environment and is present in nature in inorganic and organic forms as well as in the whole food chain and in drinking water (Rodríguez-Barranco et al. 2013). Though Mn cannot be considered an environmental pollutant, numerous evidence suggests the potential association between Mn exposure and intellectual impairment in school-aged children, who showed

deficits in IQ and verbal domain (Bouchard et al. 2007; Claus Henn et al. 2010; Bouchard et al. 2011; Menezes-Filho et al. 2011). Manganese exposure is further associated with an increased risk of behavioral disorders, including ADHD (Farias et al. 2010; Yousef et al. 2011). The neurotoxicity of Mn has been associated with deregulation of dopaminergic and cholinergic neurotransmitter release (Finkelstein et al. 2007). Kim et al. (2009) showed for the first time a possible additive interaction and effect modification of environmental Pb and Mn co-exposure on the Full-Scale IQ and verbal IQ of school-aged children. The synergism between manganese and lead on neurodevelopment was also observed during early childhood that is a potentially sensitive developmental stage. Blood levels of Mn and Pb were associated with psychomotor and mental deficits in children at 12 and 24 months, and lead toxicity was increased among children with high manganese co-exposure (Claus Henn et al. 2012). Furthermore, in the utero, co-exposure to Mn and Pb increased detrimental effects on cognitive and language development in children at 2 years of age (Lin et al. 2013). The two metals may synergistically act in neurodevelopment through common pathways including affection of mitochondrial function and alteration of neurotransmitters release and synaptic depolarization (Kim et al. 2009). Previously, rats exposed to a mixture of Pb and Mn during pre- and postnatal life showed significant alterations in the body; brain weights; content of DNA, RNA, protein; and accumulation of both metals in the brain (Chandra et al. 1983).

The evaluation of prenatal lead exposure in a Faroese birth cohort in the presence of concomitant exposure to similar molar concentration of methylmercury led to interesting results (Yorifuji et al. 2011). Cord blood Pb concentration was not associated with cognitive deficits in children at 7 and 14 years of age; nonetheless, lead-associated adverse effects on cognitive functions were observed in subjects with a low MeHg exposure. Thus, combined effects of co-exposure between Pb and MeHg were less than additive or even antagonistic, while adverse Pb effects on cognition were overlooked in the presence of high levels of MeHg exposure (Yorifuji et al. 2011; Claus Henn et al. 2014).

Arsenic (As) is a metalloid that is present in the environment both in organic and inorganic forms. The most significant sources of exposure are anthropogenic activities such as smelting, coal combustion, and waste incineration. Human exposure primarily occurs through ingestion of contaminated drinking water, as confirmed by many investigations performed in high As groundwater areas in Argentina, Chile, Mexico, and more recently in Bangladesh, Vietnam, and India (Smedley and Kinniburgh 2002). Inorganic arsenic is a known carcinogenic toxicant whose health effects in exposed adults have been largely reported in literature (Hamadani et al. 2011). One of the mechanisms of neurotoxicity from As involves an increase in oxidative stress that is the principal cause of neuronal insult (Singh et al. 2011). Associations

between arsenic exposure and oxidative stress markers were found both in the mother's urine in early pregnancy and in placenta and cord blood at delivery (Ahmed et al. 2011). Moreover, As is a potent endocrine disruptor; thus, it may interact with estrogen and thyroid hormones, both of which are essential for brain development (Davey et al. 2008). Several studies reported an association between exposure to arsenic and deleterious effects in IQ scores as well as in memory and performance domains in children aged 5–15 years (e.g., Rocha-Amador et al. 2007; Hamadani et al. 2011; Wasserman et al. 2011). On the other hand, no significant effects were found between arsenic and behavioral disorders (Roy et al. 2011; Yousef et al. 2011; Khan et al. 2012). In addition, Wasserman et al. (2011) did not report any synergistic impact of arsenic and manganese in school-aged children exposed to both metals, although each toxicant may independently be associated to a decrease of children's intelligence.

Recently, for the first time, perinatal association between air pollutants and ASD was evaluated in the children of participants in the Nurses' Health Study. Cadmium, lead, manganese, mercury, and nickel showed a roughly linear relationship between concentration and risk for autism. Moreover, for most pollutants, associations were stronger for boys than for girls (Roberts et al. 2013).

Discussion and Conclusions

Over the last few decades, the worldwide increase in prevalence rates of neurodevelopmental disorders such as autism, ADHD, and other cognitive disabilities has produced an exponential interest towards neurotoxic chemicals and, in general, environmental pollutants that potentially impact human health. The number of industrial chemicals recognized to be developmental neurotoxicants has doubled from 2006 to 2013 (Grandjean and Landrigan 2014), and numerous evidences have recognized metals such as lead, mercury, cadmium, and arsenic as important contributors to neurodevelopmental disabilities. Major windows of neurodevelopmental vulnerability occur in the utero and during infancy and early childhood when exposure to neurotoxic chemicals may cause permanent damage to the brain even at levels that would show little or no adverse effects in adults (Grandjean and Landrigan 2014). During pregnancy, toxicants reach fetal circulation by mobilization from maternal tissues, while after birth, they may be solubilized into breast milk and subsequently transferred to the infant (Rodríguez-Barranco et al. 2013).

Many of the reviewed studies have reported significant associations between prenatal exposure to toxic metals and cognitive deficits and reduced school performance in children. In particular, no safe level of exposure to lead exists (Grandjean 2010), while exposure to methylmercury in fetal

life causes diffuse and widespread neurological damage at lower doses that affect brain function in adults (Oken and Bellinger 2008). Furthermore, exposure to lead and methyl mercury has been shown to be potentially involved in autism development, while little information is available for cadmium. Many investigations indicate that autistic children have a decreased ability to excrete toxic metals and the reduced excretion combined with the relatively long half-life of these elements lead to their accumulation in tissues (Adams et al. 2012). Moreover, the level of toxic metal body burden seems to be associated with the severity of autism symptoms, as shown by Adams et al. (2009) who measured the body burden of toxic metals by giving dimercaptosuccinic acid, an oral chelator, and measuring the urinary excretions of metallic elements before and after the drug treatment. Collectively, increasing evidence suggests a significant relationship between environmental exposures in parents and children to Pb and MeHg and development of ASDs, though further investigation in this area is warranted due to the different background conditions of the studies. In particular, some of the reviewed studies relied on a limited number of subjects; others assessed toxicant exposure only during specific periods of time. Moreover, metal analysis from different samples can lead to results difficult to compare, while each measure provides specific information concerning the type and the extent of exposure.

Molecular mechanisms by which metals trigger neurobehavioral disorders and, specifically, ASDs are still not completely clear. In general, high body burden of toxic metals in autistic patients is associated with oxidative stress and increased levels of the ratio of GSSG to GSH (Adams et al. 2011). The ability of toxic metals to induce ROS production and impair the cellular mechanisms of detoxification is consistent with the reduced capacity for detoxification.

It is important to say that a 4:1 male-to-female ratio in ASD has been widely recognized; thus, male-related hormonal factors may amplify the adverse effects of metals and contribute to the higher male prevalence observed in ASD (Rossignol et al. 2014). A recent systematic review suggested gender-related differences in the susceptibility to metals, with boys generally more susceptible than girls (Llop et al. 2013). Moreover, some authors found that metals such as lead, mercury, and cadmium have the ability to interfere with physiological thyroid hormone levels (Iijima et al. 2007; Abdelouahab et al. 2008). Additionally, metals may have sex-specific effects on social behavior by interacting with central dopamine function (Curtis et al. 2010). Thus, the interaction of metals with hormones and neurotransmitters may represent one of the neurotoxicity mechanisms involved in ASDs (Hall and Kelley 2013).

Finally, several lines of evidence suggest that epigenetics plays an important role in ASD etiology, and it might integrate genetic and environmental influences to dysregulate

neurodevelopmental processes (Grafodatskaya et al. 2010; Hall and Kelley 2013). Research in this field not only provides more insight into the complex gene interactions in autism but also makes contributions to clinical aspects of ASDs.

It is well accepted that humans are normally exposed to multiple chemicals simultaneously or sequentially; thus, evaluating health effects of a single chemical exposure may underestimate the true effects (Henn et al. 2014). Effects of co-exposures should be evaluated especially in subjects who live in developing countries or near contaminated sites, where exposure to multiple toxicants may become more harmful (Kim et al. 2013). In the presence of an inefficient detoxification system which is proper of ASD children, the effects of multiple metals may be additive, despite the low levels of each metal (Blaurock-Busch et al. 2011). Although recent epidemiological studies suggest the biological interaction between metals, little information is known about developmental critical windows with respect to metal mixtures exposure. Thus, future research in this field is warranted, particularly in the context of children exposures and prevention strategies.

The reduction of exposures to environmental toxicants during the perinatal period might prevent a further increase in the prevalence rate of neurodevelopmental disorders and specifically ASDs. On one hand, future studies should focus on the exploitation of innovative clinical tests for early estimation of environmental neurotoxicity in autism development. On the other hand, analysis of biomarkers in biological tissues providing extensive pre- and postnatal exposure assessment seems to be increasingly pressing. In particular, since the brain is the major organ system affected in ASD, studies examining metal levels in the brain would give more realistic information about metals body burden of autistic subjects. A multidisciplinary approach through clinical, epidemiological, and environmental expertise could allow integrating information and ameliorating the risk assessment. Overall, new efforts should be performed in order to confirm the role of metals as etiological agents in autism and accelerate translation of science into prevention.

References

- Abdelouahab, N., Mergler, D., Takser, L., Vanier, C., St-Jean, M., Baldwin, M., et al. (2008). Gender differences in the effects of organochlorines, mercury, and lead on thyroid hormone levels in lakeside communities of Quebec (Canada). *Environmental Research*, 107(3), 380–392.
- Abdullah, M. M., Ly, A. R., Goldberg, W. A., Clarke-Stewart, K. A., Dudgeon, J. V., Mull, C. G., et al. (2012). Heavy metal in children's tooth enamel: related to autism and disruptive behaviors? *Journal of Autism and Developmental Disorders*, 42(6), 929–936.
- Adams, J. B., Romdalvik, J., Sagadopa Ramanujam, V. M., & Legator, M. S. (2007). Mercury, lead, and zinc in baby teeth of children with autism versus controls. *Journal of Toxicology and Environmental Health, Part A*, 70(12), 1046–1051.

- Adams, J. B., Blaxill, M. F., & Haley, L. W. (2008). Mercury in first-cut baby hair of children with autism versus typically developing children. *Toxicological & Environmental Chemistry*, *90*(4), 739–753.
- Adams, J. B., Baral, M., Geis, E., Mitchell, J., Ingram, J., Hensley, A., et al. (2009). The severity of autism is associated with toxic metal body burden and red blood cell glutathione levels. *Journal of Toxicology*. doi:10.1155/2009/532640.
- Adams, J. B., Audhya, T., McDonough-Means, S., Rubin, R. A., Quig, D., Geis, E., et al. (2011). Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. *Nutrition & Metabolism*. doi:10.1186/1743-7075-8-34.
- Adams, J. B., Audhya, T., McDonough-Means, S., Rubin, R. A., Quig, D., Geis, E., et al. (2012). Toxicological status of children with autism vs. neurotypical children and the association with autism severity. *Biological Trace Element Research*, *151*(2), 171–180.
- Adinolfi, M. (1985). The development of the human blood-CSF-brain barrier. *Developmental Medicine and Child Neurology*, *27*(4), 532–537.
- Advisory Committee on Childhood Lead Poisoning Prevention of the Centers for Disease Control and Prevention. (2012). *Low level lead exposure harms children: a renewed call for primary prevention* 1–54. http://www.cdc.gov/nceh/lead/acclpp/final_document_030712.pdf. Accessed 4 January 2012.
- Agency for Toxic Substances and Disease Registry. (2013). *Priority list of hazardous substances*. <http://www.atsdr.cdc.gov/sp1>. Accessed 7 May 2014.
- Ahmed, S., Mahabbat-e Khoda, S., Rekha, R. S., Gardner, R. M., Ameer, S. S., Moore, S., et al. (2011). Arsenic-associated oxidative stress, inflammation, and immune disruption in human placenta and cord blood. *Environmental Health Perspectives*, *119*(2), 258–264.
- Al-Ayadhi, L. Y. (2005). Heavy metals and trace elements in hair samples of autistic children in central Saudi Arabia. *Neurosciences (Riyadh)*, *10*(3), 213–218.
- Albizzati, A., Morè, L., Di Candia, D., Saccani, M., & Lenti, C. (2012). Normal concentrations of heavy metals in autistic spectrum disorders. *Minerva Pediatrica*, *64*(1), 27–31.
- Al-Farsi, Y. M., Waly, M. I., Al-Sharbaty, M. M., Al-Shafae, M. A., Al-Farsi, O. A., Al-Khaduri, M. M., et al. (2013). Levels of heavy metals and essential minerals in hair samples of children with autism in Oman: a case-control study. *Biological Trace Element Research*, *151*(2), 181–186.
- Ali, S. F., LeBel, C. P., & Bondy, S. C. (1992). Reactive oxygen species formation as a biomarker of methylmercury and trimethyltin neurotoxicity. *Neurotoxicology*, *13*(3), 637–648.
- Allen, J. W., El-Oqayli, H., Aschner, M., Syversen, T., & Sonnewald, U. (2001). Methylmercury has a selective effect on mitochondria in cultured astrocytes in the presence of [U-13C] glutamate. *Brain Research*, *908*(2), 149–154.
- Amin-Zaki, L., Elhassani, S., Majeed, M. A., Clarkson, T. W., Doherty, R. A., & Greenwood, M. (1974). Intra-uterine methylmercury poisoning in Iraq. *Paediatrics*, *54*(5), 587–595.
- Amitai, Y., Katz, D., Lifshitz, M., Gofin, R., Tepferberg, M., & Almog, S. (1999). Prenatal lead exposure in Israel: an international comparison. *Israel Medical Association Journal*, *1*(4), 250–253.
- Andersen, H. R., Nielsen, J. B., & Grandjean, P. (2000). Toxicologic evidence of developmental neurotoxicity of environmental chemicals. *Toxicology*, *144*(1–3), 121–127.
- Arita, A., & Costa, M. (2009). Epigenetics in metal carcinogenesis: nickel, arsenic, chromium and cadmium. *Metallomics*, *1*(3), 222–228.
- Aschner, M. (1996). Astrocytes as modulators of mercury-induced neurotoxicity. *Neurotoxicology*, *17*(3–4), 663–669.
- Aschner, M., & Ceccatelli, S. (2010). Are neuropathological conditions relevant to ethylmercury exposure? *Neurotoxicity Research*, *18*(1), 59–68.
- Aschner, M., Yao, C. P., Allen, J. W., & Tan, K. H. (2000). Methylmercury alters glutamate transport in astrocytes. *Neurochemistry International*, *37*(2–3), 199–206.
- Aschner, M., Syversen, T., Souza, D. O., Rocha, J. B. T., & Farina, M. (2007). Involvement of glutamate and reactive oxygen species in methylmercury neurotoxicity. *Brazilian Journal of Medical and Biological Research*, *40*(3), 285–291.
- Ash, M. M., & Nelson, S. J. (2003). *Wheeler's dental anatomy, physiology and occlusion* (8th ed.). St Louis: Elsevier.
- Austin, D. W., & Shandley, K. (2008). An investigation of porphyrinuria in Australian children with autism. *Journal of Toxicology and Environmental Health, Part A*, *71*(20), 1349–1351.
- Ballatori, N., & Clarkson, T. W. (1984). Dependence of biliary secretion of inorganic mercury on the biliary transport of glutathione. *Biochemical Pharmacology*, *33*(7), 1093–1098.
- Bao, Q. S., Lu, C. Y., Song, H., Wang, M., Ling, W., Chen, W. Q., et al. (2009). Behavioural development of school-aged children who live around a multi-metal sulphide mine in Guangdong province, China: a cross-sectional study. *BMC Public Health*. doi:10.1186/1471-2458-9-217.
- Belletti, S., Orlandini, G., Vettori, M. V., Mutti, A., Uggeri, J., Scandroglio, R., et al. (2002). Time course assessment of methylmercury effects on C6 glioma cells: submicromolar concentrations induce oxidative DNA damage and apoptosis. *Journal of Neuroscience Research*, *70*(5), 703–711.
- Bellinger, D. C. (2008). Very low lead exposures and children's neurodevelopment. *Current Opinion in Pediatrics*, *20*(2), 172–177.
- Bellinger, D., Leviton, A., Allred, E., & Rabinowitz, M. (1994). Pre- and postnatal lead exposure and behavior problems in school-aged children. *Environmental Research*, *66*(1), 12–30.
- Bernard, S., Enayati, A., Roger, H., & Binstock, T. (2001). Autism: a novel form of mercury poisoning. *Medicine Hypotheses*, *56*(4), 462–471.
- Bertin, G., & Averbek, D. (2006). Cadmium: cellular effects, modifications of biomolecules, modulation of DNA repair and genotoxic consequences (a review). *Biochimie*, *88*(11), 1549–1559.
- Blaurock-Busch, E., Amin, O. R., & Rabah, T. (2011). Heavy metals and trace elements in hair and urine of a sample of Arab children with autistic spectrum disorder. *Maedica*, *6*(4), 247–257.
- Bloom, B., Cohen, R. A., & Freeman, G. (2010). Summary health statistics for U.S. children: national health interview survey, 2009. *Vital and Health Statistics*, *10*(247), 1–82.
- Bonithon-Kopp, C., Huel, G., Moreau, T., & Wendling, R. (1986). Prenatal exposure to lead and cadmium and psychomotor development of the child at 6 years. *Neurobehavioral Toxicology and Teratology*, *8*(3), 307–310.
- Bouchard, M., Laforest, F., Vandelay, L., Bellinger, D., & Mergler, D. (2007). Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. *Environmental Health Perspectives*, *115*(1), 122–127.
- Bouchard, M. F., Sauvè, S., Barbeau, B., Legrand, M., Brodeur, M. E., Bouffard, T., et al. (2011). Intellectual impairment in school-age children exposed to manganese from drinking water. *Environmental Health Perspectives*, *119*(1), 138–143.
- Boucher, O., Bastien, C. H., Saint-Amour, D., Dewailly, E., Ayotte, P., Jacobson, J. L., et al. (2010). Prenatal exposure to methylmercury and PCBs affects distinct stages of information processing: an event-related potential study with Inuit children. *Neurotoxicology*, *31*(4), 373–484.
- Boucher, O., Jacobson, S. W., Plusquellec, P., Dewailly, E., Ayotte, P., Forget-Dubois, N., et al. (2012). Prenatal methylmercury, postnatal lead exposure, and evidence of attention deficit/hyperactivity

- disorder among Inuit children in Arctic Québec. *Environmental Health Perspectives*, 120(10), 1456–1461.
- Brown, I. A., & Austin, D. W. (2012). Maternal transfer of mercury to the developing embryo/fetus: is there a safe level? *Toxicological & Environmental Chemistry*, 94(8), 1610–1627.
- Byers, R. K., & Lord, E. E. (1943). Late effect of lead poisoning on mental development. *American Journal of Disease of Children*, 66(5), 471–492.
- Cao, Y., Chen, A., Radcliffe, J., Dietrich, K. N., Jones, R. L., Caldwell, K., et al. (2009). Postnatal cadmium exposure, neurodevelopment, and blood pressure in children at 2, 5, and 7 years of age. *Environmental Health Perspectives*, 117(10), 1580–1586.
- Cecil, K. M., Dietrich, K. N., Altaye, M., Egelhoff, J. C., Lindquist, D. M., Brubaker, C. J., et al. (2011). Proton magnetic resonance spectroscopy in adults with childhood lead exposure. *Environmental Health Perspectives*, 119(3), 403–408.
- Cedar, H., & Bergman, Y. (2009). DNA methylation and histone modification: pattern and paradigm. *Nature Reviews Genetics*, 10(5), 295–304.
- Chandra, S. V., Murthy, R. C., Saxena, D. K., & Lal, B. (1983). Effects of pre- and postnatal combined exposure to Pb and Mn on brain development in rats. *Industrial Health*, 21(4), 273–279.
- Chandran, L., & Cataldo, R. (2010). Lead poisoning: basics and new developments. *Pediatrics in Review*, 31(10): 399–405.
- Charleston, J. S., Body, R. L., Bolender, R. P., Mottet, N. K., Vahter, M. E., & Burbacher, T. M. (1996). Changes in the number of astrocytes and microglia in the thalamus of the monkey *Macaca fascicularis* following long-term sub clinical methylmercury exposure. *Neurotoxicology*, 17(1), 127–138.
- Charney, E., Sayre, J., & Coulter, M. (1980). Increased lead absorption in inner city children: where does the lead come from? *Pediatrics*, 65(2), 226–231.
- Chauhan, A., Audhya, T., & Chauhan, V. (2012). Brain region-specific glutathione redox imbalance in autism. *Neurochemical Research*, 37(8), 1681–1689.
- Chen, A., Cai, B., Dietrich, K. N., Radcliffe, J., & Rogan, W. J. (2007). Lead exposure, IQ, and behavior in urban 5- to 7-year-olds: does lead affect behavior only by lowering IQ? *Pediatrics*, 119(3), e650–e658.
- Chen, Y. N., Wang, J., Zhang, J., Li, S. J., He, L., Shao, D. D., et al. (2013). Effect of thimerosal on the neurodevelopment of premature rats. *World Journal of Pediatrics*, 9(4), 356–360.
- Chuang, J. C., & Jones, P. A. (2007). Epigenetics and microRNAs. *Pediatric Research*, 61(5 Pt 2), 24R–29R.
- Ciesielski, T., Weuve, J., Bellinger, D. C., Schwartz, J., Lanphear, B., & Wright, R. O. (2012). Cadmium exposure and neurodevelopmental outcomes in U.S. children. *Environmental Health Perspectives*, 120(5), 758–763.
- Clark, B. C. (2010). Is lead a concern in Canadian autistic children? *Paediatrics and Child Health*, 15(1), 17–22.
- Claus Henn, B., Ettinger, A. S., Schwartz, J., Téllez-Rojo, M. M., Lamadrid-Figueroa, H., Hernández-Avila, M., et al. (2010). Early postnatal blood manganese levels and children's neurodevelopment. *Epidemiology*, 21(4), 433–439.
- Claus Henn, B., Schnaas, L., Ettinger, A. S., Schwartz, J., Lamadrid-Figueroa, H., Hernández-Avila, M., et al. (2012). Associations of early childhood manganese and lead coexposure with neurodevelopment. *Environmental Health Perspectives*, 120(1), 126–131.
- Claus Henn, B., Coull, B. A., & Wright, R. O. (2014). Chemical mixtures and children's health. *Current Opinion in Pediatrics*, 26(2), 223–229.
- Cohen, D. J., Johnson, W. T., & Caparulo, B. K. (1976). Pica and elevated blood lead level in autistic and atypical children. *American Journal of Diseases of Children*, 130(1), 47–48.
- Cohen, D. J., Paul, R., Anderson, G. M., & Harcherik, D. F. (1982). Blood lead in autistic children. *Lancet*, 2(8289), 94–95.
- Cordier, S., Garel, M., Mandereau, L., Morcel, H., Doineau, P., Gosme-Seguret, S., et al. (2002). Neurodevelopmental investigations among methylmercury-exposed children in French Guiana. *Environmental Research*, 89(1), 1–11.
- Counter, S. A., & Buchanan, L. H. (2004a). Mercury exposure in children: a review. *Toxicology and Applied Pharmacology*, 198(2), 209–230.
- Croen, L. A., Matevia, M., Yoshida, C. K., & Grether, J. K. (2008). Maternal Rh D status, anti-D immune globulin exposure during pregnancy, and risk of autism spectrum disorders. *American Journal of Obstetrics and Gynecology*. doi:10.1016/j.jajog.2008.04.044.
- Crump, K. S., Kjellstrom, T., Shipp, A. M., Silvers, A., & Stewart, A. (1998). Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. *Risk Analysis*, 18(6), 701–713.
- Curtis, J. T., Hood, A. N., Chen, Y., Cobb, G. P., & Wallace, D. R. (2010). Chronic metals ingestion by prairie voles produces sex-specific deficits in social behavior: an animal model of autism. *Behavioral Brain Research*, 213(1), 42–49.
- Davey, J. C., Nomikos, A. P., Wungjiranirun, M., Sherman, J. R., Ingram, L., Batki, C., et al. (2008). Arsenic as an endocrine disruptor: arsenic disrupts retinoic acid receptor-and thyroid hormone receptor-mediated gene regulation and thyroid hormone-mediated amphibian tail metamorphosis. *Environmental Health Perspectives*, 116(2), 165–172.
- Debes, F., Budtz-Jørgensen, E., Weihe, P., White, R. F., & Grandjean, P. (2006). Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicology and Teratology*, 28(3), 363–375.
- DeSoto, M. C., & Hitlan, R. T. (2007). Blood levels of mercury are related to diagnosis of autism: a reanalysis of an important data set. *Journal of Child Neurology*, 22(11), 1308–1311.
- DeSoto, M. C., & Hitlan, R. T. (2010). Sorting out the spinning of autism: heavy metals and the question of incidence. *Acta Neurobiologiae Experimentalis (Warsaw)*, 70(2), 165–176.
- Deth, R., Muratore, C., Benzecry, J., Power-Charnitsky, V. A., & Waly, M. (2008). How environmental and genetic factors combine to cause autism: a redox/methylation hypothesis. *Neurotoxicology*, 29(1), 190–201.
- Dhillon, S., Hellings, J. A., & Butler, M. G. (2011). Genetics and mitochondrial abnormalities in autism spectrum disorders: a review. *Current Genomics*, 12(5), 322–332.
- Dietert, R. R., Dietert, J. M., & DeWitt, J. M. (2011). Environmental risk factors for autism. *Emerging Health Treats Journal*. doi:10.3402/ehjt.v4i0.7111.
- Dietrich, K. N., Ris, M. D., Succop, P. A., Berger, O. G., & Bornschein, R. L. (2001). Early exposure to lead and juvenile delinquency. *Neurotoxicology and Teratology*, 23(6), 511–518.
- Dong, S., Shen, H. M., & Ong, C. N. (2001). Cadmium-induced apoptosis and phenotypic changes in mouse thymocytes. *Molecular and Cellular Biochemistry*, 222(1–2), 11–20.
- Dorea, J. G. (2010). Making sense of epidemiological studies of young children exposed to thimerosal in vaccines. *Clinica Chimica Acta*, 411(21–22), 1580–1586.
- Dórea, J. G., Farina, M., & Rocha, J. B. (2013). Toxicity of ethylmercury (and Thimerosal): a comparison with methylmercury. *Journal of Applied Toxicology*, 33(8), 700–711.
- Dufault, R., Schnoll, R., Lukiw, W. J., Leblanc, B., Cornett, C., Patrick, L., et al. (2009). Mercury exposure, nutritional deficiencies and metabolic disruptions may affect learning in children. *Behavioral and Brain Functions*. doi:10.1186/1744-9081-5-44.

- Duval, J., Dumont, M., Braun, C. M., & Montour-Proulx, I. (2002). Recovery of intellectual function after brain injury: a comparison of longitudinal and cross-sectional approaches. *Brain and Cognition*, 48(2–3), 477–496.
- El-Ansary, A. K., Bacha, A. B., & Ayahdi, L. Y. (2011). Relationship between chronic lead toxicity and plasma neurotransmitters in autistic patients from Saudi Arabia. *Clinical Biochemistry*, 44(13), 1116–1120.
- Elsheshtawy, E., Tobar, S., Sherra, K., Atallah, S., & Elkasaby, R. (2011). Study of some biomarkers in hair of children with autism. *Middle East Current Psychiatry*, 18, 6–10.
- Enns, G. M. (2003). The contribution of mitochondria to common disorders. *Molecular Genetics and Metabolism*, 80(1–2), 11–26.
- Eppright, T. D., Sanfacon, J. A., & Horwitz, E. A. (1996). Attention deficit hyperactivity disorder, infantile autism, and elevated blood-lead: a possible relationship. *Missouri Medicine*, 93(3), 136–138.
- Ettinger, A. S., Tellez-Rojo, M. M., Amarasiriwardena, C., Peterson, K. E., Schwartz, J., Aro, A., et al. (2006). Influence of maternal bone lead burden and calcium intake on levels of lead in breast milk over the course of lactation. *American Journal of Epidemiology*, 163(1), 48–56.
- Eubig, P. A., Aguiar, A., & Schantz, S. L. (2010). Lead and PCBs as risk factors for attention deficit/hyperactivity disorder. *Environmental Health Perspectives*, 118(12), 1654–1667.
- Farias, A. C., Cunha, A., Benko, C. R., McCracken, J. T., Costa, M. T., Farias, L. G., et al. (2010). Manganese in children with attention-deficit/hyperactivity disorder: relationship with methylphenidate exposure. *Journal of Child and Adolescence Psychopharmacology*, 20(2), 113–118.
- Farina, M., Aschner, M., & Rocha, J. B. (2011). Oxidative stress in MeHg-induced neurotoxicity. *Toxicology and Applied Pharmacology*, 256(3), 405–417.
- Farina, M., Avila, D. S., da Rocha, J. B., & Aschner, M. (2013). Metals, oxidative stress and neurodegeneration: a focus on iron, manganese and mercury. *Neurochemistry International*, 62(5), 575–594.
- Fido, A., & Al-Saad, S. (2005). Toxic trace elements in the hair of children with autism. *Autism*, 9(3), 290–298.
- Filipek, P. A., Accardo, P. J., Baranek, G. T., Cook, E. H., Jr., Dawson, G., Gordon, B., et al. (1999). The screening and diagnosis of autistic spectrum disorders. *Journal of Autism and Developmental Disorders*, 29(6), 439–484.
- Finkelstein, Y., Milatovic, D., & Aschner, M. (2007). Modulation of cholinergic systems by manganese. *Neurotoxicology*, 28(5), 1003–1014.
- Gao, Y., Yan, C. H., Tian, Y., Wang, Y., Xie, H. F., Zhou, X., et al. (2007). Prenatal exposure to mercury and neurobehavioral development of neonates in Zhoushan City, China. *Environmental Research*, 105(3), 390–399.
- García-Esquinas, E., Pérez-Gómez, B., Fernández, M. A., Pérez-Meixeira, A. M., Gil, E., de Paz, C., et al. (2011). Mercury, lead and cadmium in human milk in relation to diet, lifestyle habits and sociodemographic variables in Madrid (Spain). *Chemosphere*, 85(2), 268–276.
- Garrecht, M., & Austin, D. W. (2011). The plausibility of a role for mercury in the etiology of autism: a cellular perspective. *Toxicological and Environmental Chemistry*, 93(5–6), 1251–1273.
- Geier, D. A., & Geier, M. R. (2003a). Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication. *Experimental Biology and Medicine (Maywood)*, 228(6), 660–664.
- Geier, D. A., & Geier, M. R. (2003b). An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. *Experimental Biology and Medicine (Maywood, N.Y.)*, 6, 97–102.
- Geier, D. A., & Geier, M. R. (2004). Neurodevelopmental disorders following thimerosal-containing childhood immunizations: a follow-up analysis. *International Journal of Toxicology*, 23(6), 369–376.
- Geier, D. A., & Geier, M. R. (2006). An evaluation of the effects of thimerosal on neurodevelopmental disorders reported following DTP and Hib vaccines in comparison to DTPH vaccine in the United States. *Journal of Toxicology and Environmental Health, Part A*, 69(15), 1481–1495.
- Geier, D. A., & Geier, M. R. (2007a). A prospective study of mercury toxicity biomarkers in autistic spectrum disorders. *Journal of Toxicology and Environmental Health, Part A*, 70(20), 1723–1730.
- Geier, D. A., & Geier, M. R. (2007b). A prospective study of thimerosal-containing Rho(D)-immune globulin administration as a risk factor for autistic disorders. *Journal of Maternal- Fetal and Neonatal Medicine*, 20(5), 385–390.
- Geier, D. A., King, P. G., Sykes, L. K., & Geier, M. R. (2008). A comprehensive review of mercury provoked autism. *Indian Journal of Medical Research*, 128(4), 383–411.
- Geier, D. A., Kern, J. K., Garver, C. R., Adams, J. B., Audhya, T., Nataf, R., et al. (2009a). Biomarkers of environmental toxicity and susceptibility in autism. *Journal of the Neurological Sciences*, 280(1–2), 101–108.
- Geier, D. A., Kern, J. K., & Geier, M. R. (2009b). A prospective blinded evaluation of urinary porphyrins versus the clinical severity of autism spectrum disorders. *Journal of Toxicology and Environmental Health, Part A*, 72(24), 1585–1591.
- Geier, D. A., King, P. G., & Geier, M. R. (2009c). Mitochondrial dysfunction, impaired oxidative-reduction activity, degeneration, and death in human neuronal and fetal cells induced by low-level exposure to thimerosal and other metal compounds. *Toxicological and Environmental Chemistry*, 91(3–4), 735–749.
- Geier, D. A., Audhya, T., Kern, J. K., & Geier, M. R. (2010). Blood mercury levels in autism spectrum disorder: is there a threshold level? *Acta Neurobiologiae Experimentalis*, 70(2), 177–186.
- Geier, D. A., Kern, J. K., King, P. G., Sykes, L. K., & Geier, M. R. (2012). Hair toxic metal concentrations and autism spectrum disorder severity in young children. *International Journal of Environmental Research and Public Health*, 9(12), 4486–4497.
- Geier, D. A., Hooker, B. S., Kern, J. K., King, P. G., Sykes, L. K., & Geier, M. R. (2013). A two-phase study evaluating the relationship between Thimerosal-containing vaccine administration and the risk for an autism spectrum disorder diagnosis in the United States. *Translational Neurodegeneration*. doi:10.1186/2047-9158-2-25.
- Giulivi, C., Zhang, Y. F., Omanska-Klusek, A., Ross-Inta, C., Wong, S., Hertz-Picciotto, I., et al. (2010). Mitochondrial dysfunction in autism. *JAMA*, 304(21), 2389–2396.
- Gollenberg, A. L., Hediger, M. L., Lee, P. A., Himes, J. H., & Louis, G. M. (2010). Association between lead and cadmium and reproductive hormones in peripubertal U.S. girls. *Environmental Health Perspectives*, 118(12), 1782–1787.
- Golman, G. (2013). Comparison of VAERS fetal-loss reports during three consecutive influenza seasons: was there a synergistic fetal toxicity associated with the two-vaccine 2009/2010 season? *Human and Experimental Toxicology*, 32(5), 464–475.
- Gorini, F., Chiappa, E., Gargani, L., & Picano, E. (2014). Potential effects of environmental chemical contamination in congenital heart disease. *Pediatric Cardiology*, 35(4), 559–568.
- Gould, E. (2009). Childhood lead poisoning: conservative estimates of the social and economic benefits of lead hazard control. *Environmental Health Perspectives*, 117(7), 1162–1167.
- Grafodatskaya, D., Chung, B., Szatmari, P., & Weksberg, R. (2010). Autism spectrum disorders and epigenetics. *Journal of the American Academy of Child & Adolescence Psychiatry*, 49(8), 794–809.
- Grandjean, P. (2010). Even low-dose lead exposure is hazardous. *The Lancet*, 376(9744), 855–856.
- Grandjean, P., & Landrigan, P. J. (2006). Developmental neurotoxicity of industrial chemicals. *The Lancet*, 368(9553), 2167–2178.

- Grandjean, P., & Landrigan, P. J. (2014). Neurobehavioural effects of developmental toxicity. *The Lancet Neurology*, *13*(3), 330–338.
- Grandjean, P., Weihe, P., White, R., Debes, F., Araki, S., Yokohama, K., et al. (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicology and Teratology*, *19*(6), 417–428.
- Haley, B. E. (2005). Mercury toxicity: genetic susceptibility and synergistic effects. *Medical Veritas*, *2*, 535–542.
- Hall, L., & Kelley, E. (2013). The contribution of epigenetics to understanding genetic factors in autism. *Autism*. doi:10.1177/1362361313503501.
- Hamadani, J. D., Tofail, F., Nermell, B., Gardner, R., Shiraji, S., Bottai, M., et al. (2011). Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study. *International Journal of Epidemiology*, *40*(6), 1593–1604.
- Henn, B. C., Coull, B. A., & Wright, R. O. (2014). Chemical mixtures and children's health. *Current Opinion in Pediatrics*. doi:10.1097/MOP.0000000000000067.
- Hertz-Picciotto, I., Green, P. G., Delwiche, L., Hansen, R., Walker, C., & Pessah, I. N. (2010). Blood mercury concentrations in charge study children with and without autism. *Environmental Health Perspectives*, *118*(1), 161–166.
- Holmes, A. S., Blaxill, M. F., & Haley, B. E. (2003). Reduced levels of mercury in first baby haircuts of autistic children. *International Journal of Toxicology*, *22*(4), 277–285.
- Huang, S. S., Strathe, A. B., Fadel, J. G., Lin, P., Liu, T. Y., & Hung, S. S. (2012). Absorption, distribution, and elimination of graded oral doses of methylmercury in juvenile white sturgeon. *Aquatic Toxicology*, *122–123*, 163–171.
- Hunot, S., Brugg, B., Ricard, D., Michel, P. P., Muriel, M. P., Ruberg, M., et al. (1997). Nuclear translocation of NF-kappaB is increased in dopaminergic neurons of patients with Parkinson disease. *Proceedings of the National Academy of Sciences of the United States of America*, *94*(14), 7531–7536.
- Iijima, K., Otake, T., Yoshinaga, J., Ikegami, M., Suzuki, E., Naruse, H., et al. (2007). Cadmium, lead, and selenium in cord blood and thyroid hormone status of newborns. *Biological Trace Element Research*, *119*(1), 10–18.
- Ishitobi, H., Mori, K., Yoshida, K., & Watanabe, C. (2007). Effects of perinatal exposure to low-dose cadmium on thyroid hormone-related and sex hormone receptor gene expressions in brain of offspring. *Neurotoxicology*, *28*(4), 790–797.
- James, S. J., Cutler, P., Melnyk, S., Jernigan, S., Janak, L., Gaylor, D. W., et al. (2004). Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *The American Journal of Clinical Nutrition*, *80*(6), 1611–1617.
- James, S. J., Rose, S., Melnyk, S., Jernigan, S., Blossom, S., Pavliv, O., et al. (2009). Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism. *The FASEB Journal*, *23*(8), 2374–2383.
- Järup, L., & Akesson, A. (2009). Current status of cadmium as an environmental health problem. *Toxicology and Applied Pharmacology*, *238*(3), 201–208.
- Järup, L., Berglund, M., Elinder, C. G., Nordberg, G., & Vahter, M. (1998). Health effects of cadmium exposure—a review of the literature and a risk estimate. *Scandinavian Journal of Work, Environmental and Health*, *24*(S1), 1–51.
- Johansson, C., Castoldi, A. F., Onishchenko, N., Manzo, L., Vahter, M., & Ceccatelli, S. (2007). Neurobehavioural and molecular changes induced by methylmercury exposure during development. *Neurotoxicity Research*, *11*(3–4), 241–260.
- Julvez, J., Yorifuji, T., Choi, A. L., Grandjean, P. (2012). Epidemiological evidence on methylmercury neurotoxicity. In: S. Ceccatelli, & M. Aschner (Eds.), *Methylmercury and Neurotoxicity* (pp. 13–35).
- Kaltschmidt, B., Baeuerle, P. A., & Kaltschmidt, C. (1993). Potential involvement of the transcription factor NF-kappa B in neurological disorders. *Molecular Aspects of Medicine*, *14*(3), 171–190.
- Karagas, M. R., Choi, A. L., Oken, E., Horvat, M., Schoeny, R., Kamai, E., et al. (2012). Evidence on the human health effects of low-level methylmercury exposure. *Environmental Health Perspectives*, *120*(6), 799–806.
- Kentucky Department of Public Health, Childhood Lead Poisoning Prevention Programme. (2013). *Guidelines on Blood Lead Screening and Management of Elevated Blood Lead Levels*. (pp. 1–18).
- Kern, J. K., & Jones, A. M. (2006). Evidence of toxicity, oxidative stress and neuronal insult in autism. *Journal of Toxicology and Environmental Health Part B*, *9*, 485–499.
- Kern, J. K., Grannemann, B. D., Trivedi, M. H., & Adams, J. B. (2007). Sulfhydryl-reactive metals in autism. *Journal of Toxicology and Environmental Health, Part A*, *70*(8), 715–721.
- Kern, J. K., Geier, D. A., Adams, J. B., Geier, M. R. (2010). A biomarker of mercury body-burden correlated with diagnostic domain specific clinical symptoms of autism spectrum disorder. *Biomaterials*, *23*(6): 1043–1051.
- Kern, J. K., Geier, D. A., Audhya, T., King, P. G., Sykes, L. K., & Geier, M. R. (2012). Evidence of parallels between mercury intoxication and the brain pathology in autism. *Acta Neurobiologiae Experimentalis (Warsaw)*, *72*(2), 113–153.
- Kern, J. K., Haley, B. E., Geier, D. A., Sykes, L. K., King, P. G., & Geier, M. R. (2013). Thimerosal exposure and the role of sulfation chemistry and thiol availability in autism. *International Journal of Environmental Research and Public Health*, *10*(8), 3771–3800.
- Khan, K., Wasserman, G. A., Liu, X., Ahmed, E., Parvez, F., Slavkovich, V., et al. (2012). Manganese exposure from drinking water and children's academic achievement. *Neurotoxicology*, *33*(1), 91–97.
- Kidd, P. M. (2005). Neurodegeneration from mitochondrial insufficiency; nutrients, stem cells, growth factors, and prospects from brain rebuilding using integrative management. *Alternative Medicine Review*, *10*(4), 268–273.
- Kim, Y., Kim, B. N., Hong, Y. C., Shin, M. S., Yoo, H. J., Kim, J. W., et al. (2009). Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. *Neurotoxicology*, *30*(4), 564–571.
- Kim, Y., Ha, E. H., Park, H., Ha, M., Kim, Y., Hong, Y. C., et al. (2013). Prenatal lead and cadmium co-exposure and infant neurodevelopment at 6 months of age: the Mothers and Children's Environmental Health (MOCEH) study. *Neurotoxicology*, *35*, 15–22.
- Kinnell, H. G. (1985). Pica as a feature of autism. *The British Journal of Psychiatry*, *147*, 80–82.
- Kippler, M., Hoque, A. M., Raqib, R., Ohrvik, H., Ekström, E. C., & Vahter, M. (2010). Accumulation of cadmium in human placenta interacts with the transport of micronutrients to the fetus. *Toxicology Letters*, *192*(2), 162–168.
- Kippler, M., Tofail, F., Hamadani, J. D., Gardner, R. M., Grantham-McGregor, S. M., Bottai, M., et al. (2012a). Early-life cadmium exposure and child development in 5-year-old girls and boys: a cohort study in rural Bangladesh. *Environmental Health Perspectives*, *120*(10), 1462–1468.
- Kippler, M., Hossain, M. B., Lindh, C., Moore, S. E., Kabir, I., Vahter, M., et al. (2012b). Early life low-level cadmium exposure is positively associated with increased oxidative stress. *Environmental Research*, *112*, 164–170.
- Kitamura, Y., Shimohama, S., Ota, T., Matsuoka, Y., Nomura, Y., & Taniguchi, T. (1997). Alteration of transcription factors NF-kappaB and STAT1 in Alzheimer's disease brains. *Neuroscience Letters*, *237*(1), 17–20.

- Lakshmi Priya, M. D., & Geetha, A. (2011). Level of trace elements (copper, zinc, magnesium and selenium) and toxic elements (lead and mercury) in the hair and nail of children with autism. *Biological Trace Element Research*, *142*(2), 148–158.
- Landrigan, P. J., & Garg, A. (2002). Chronic effects of toxic environmental exposures on children's health. *Journal of Toxicology - Clinical Toxicology*, *40*(4), 449–456.
- Landrigan, P. J., Whitworth, R. H., Baloh, R. W., Staehling, N. W., Barthel, W. F., & Rosenblum, B. F. (1975). Neuropsychological dysfunction in children with chronic low-level lead adsorption. *The Lancet*, *1*(7909), 708–712.
- Landrigan, P. J., Lambertini, L., & Birnbaum, L. (2012). A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. *Environmental Health Perspectives*, *120*(7), a258–a260.
- Lanphear, B. P., Burgoon, D. A., Rust, S. W., Eberly, S., & Galke, W. (1998). Environmental exposure to lead and urban children's blood lead levels. *Environmental Research*, *76*(2), 120–130.
- Lanphear, B. P., Hornung, R., Khoury, J., Yolton, K., Baghurst, P., Bellinger, D. C., et al. (2005). Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environmental Health Perspectives*, *113*(7), 894–899.
- Lee, Y. W., Ha, M. S., & Kim, Y. K. (2001). Role of active oxygen species and glutathione in inorganic mercury-induced injury in human glioma cells. *Neurochemical Research*, *26*(11), 1187–1193.
- Lee, D. H., Lim, J. S., Song, K., Boo, Y., & Jacobs, D. R., Jr. (2006). Graded associations of blood lead and urinary cadmium concentrations with oxidative-stress-related markers in the U.S. population: results from the third national health and nutrition examination survey. *Environmental Health Perspectives*, *114*(3), 350–354.
- Levin, R., Brown, M. J., Kashtock, M. E., Jacobs, D. E., Whelan, E. A., Rodman, J., et al. (2008). Lead exposures in U.S. children, 2008: implications for prevention. *Environmental Health Perspectives*, *116*(10), 1285–1293.
- Lidsky, T. I., & Schneider, J. S. (2003). Lead neurotoxicity in children: basic mechanisms and clinical correlates. *Brain*, *126*(Pt 1), 5–19.
- Lidsky, T. I., & Schneider, J. S. (2005). Autism and autistic symptoms associated with childhood lead poisoning. *The Journal of Applied Research*, *5*(1), 80–87.
- Lin, C. M., Doyle, P., Wang, D., Hwang, Y. H., & Chen, P. C. (2011). Does prenatal cadmium exposure affect fetal and child growth? *Occupational and Environmental Medicine*, *68*(9), 641–646.
- Lin, C. C., Chen, Y. C., Su, F. C., Lin, C. M., Liao, H. F., Hwang, Y. H., et al. (2013). In utero exposure to environmental lead and manganese and neurodevelopment at 2 years of age. *Environmental Research*, *123*, 52–57.
- Llop, S., Lopez-Espinosa, M. J., Rebagliato, M., & Ballester, F. (2013). Gender differences in the neurotoxicity of metals in children. *Toxicology*, *311*(1–2), 3–12.
- Lynch, M. L., Huang, L. S., Cox, C., Strain, J. J., Myers, G. J., Bonham, M. P., et al. (2011). Varying coefficient function models to explore interactions between maternal nutritional status and prenatal methylmercury toxicity in the Seychelles child development nutrition study. *Environmental Research*, *111*(1), 75–80.
- Marlowe, M., Stellern, J., Errera, J., & Moon, C. (1985). Main and interaction effects of metal pollutants on visual-motor performance. *Archives of Environmental Health*, *40*(4), 221–225.
- Marques, R. C., Dórea, J. G., & Bernardi, J. V. (2010). Thimerosal exposure (from tetanus-diphtheria vaccine) during pregnancy and neurodevelopment of breastfed infants at 6 months. *Acta Paediatrica*, *99*(6), 934–939.
- McDermott, S., Wu, J., Cai, B., Lawson, A., & Marjorie Aelion, C. (2011). Probability of intellectual disability is associated with soil concentrations of arsenic and lead. *Chemosphere*, *84*(1), 31–38.
- Menezes-Filho, J. A., Novaes Cde, O., Moreira, J. C., Sarcinelli, P. N., & Mergler, D. (2011). Elevated manganese and cognitive performance in school-aged children and their mothers. *Environmental Research*, *111*(1), 156–163.
- Mérad-Saidoune, M., Boitier, E., Nicole, A., Marsac, C., Martinou, J. C., Sola, B., et al. (1999). Overproduction of Cu/Zn-superoxide dismutase or Bcl-2 prevents the brain mitochondrial respiratory dysfunction induced by glutathione depletion. *Experimental Neurology*, *158*(2), 428–436.
- Miklavcic, A., Cuderman, P., Mazej, D., Snoj Tratnik, J., Krsnik, M., Planinšek, P., et al. (2011). Biomarkers of low-level mercury exposure through fish consumption in pregnant and lactating Slovenian women. *Environmental Research*, *111*(8), 1201–1207.
- Moon, C., Marlowe, M., Stellern, J., & Errera, J. (1985). Main and interaction effects of metallic pollutants on cognitive functioning. *Journal of Learning Disabilities*, *18*(4), 217–221.
- Nataf, R., Skorupka, C., Amet, L., Lam, A., Springbett, A., & Lathe, R. (2006). Porphyrinuria in childhood autistic disorder: implications for environmental toxicity. *Toxicology and Applied Pharmacology*, *214*(2), 99–108.
- National Research Council. (2000a). *Scientific frontiers in developmental toxicology and risk assessment*. Washington: National Academy.
- National Research Council, & Committee on the Toxicological Effects of Methylmercury. (2000b). *Toxicological Effects of Methylmercury*. Washington: National Academy.
- Needleman, H. L. (1988). The persistent threat of lead: medical and sociological issues. *Current Problems in Pediatrics*, *18*(12), 697–744.
- Nriagu, J. O., Blankson, M. L., & Ocran, K. (1996). Childhood lead poisoning in Africa: a growing public health problem. *Science of the Total Environment*, *181*(2), 93–100.
- Oken, E., & Bellinger, D. C. (2008). Fish consumption, methylmercury and child neurodevelopment. *Current Opinion in Pediatrics*, *20*(2), 178–183.
- Park, J. D., & Zheng, W. (2012). Human exposure and health effects of inorganic and elemental mercury. *Journal of Preventive Medicine and Public Health*, *45*(6), 344–352.
- Parker, S. K., Schwartz, B., Todd, J., & Pickering, L. K. (2004). Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics*, *114*(3), 793–804.
- Price, C. S., Thompson, W. W., Goodson, B., Weintraub, E. S., Croen, L. A., Hinrichsen, V. L., et al. (2010). Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. *Pediatrics*, *126*(4), 656–664.
- Prüss-Üstün, A., Campbell-Lendrum, D., Corvalan, C., & Woodward, A. (2004). Lead exposure. In Ezzati (Ed.), *Comparative quantification of health risks*. Geneva: World Health Organization.
- Rai, A., Maurya, S. K., Khare, P., Srivastava, A., & Bandyopadhyay, S. (2010). Characterization of developmental neurotoxicity of As, Cd, and Pb mixture: synergistic action of metal mixture in glial and neuronal functions. *Toxicological Sciences*, *118*(2), 586–601.
- Reddy, G. R., & Zawia, N. H. (2000). Lead exposure alters Egr-1 DNA-binding in the neonatal rat brain. *International Journal of Developmental Neuroscience*, *18*(8), 791–795.
- Ris, M. D., Dietrich, K. N., Succop, P. A., Berger, O. G., & Bomschein, R. L. (2004). Early exposure to lead and neuropsychological outcome in adolescence. *Journal of the International Neuropsychological Society*, *10*(2), 261–270.
- Roberts, A. L., Lyall, K., Hart, J. E., Laden, F., Just, A. C., Bobb, J. F., et al. (2013). Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' health study II participants. *Environmental Health Perspectives*, *121*(8), 978–984.
- Rocha-Amador, D., Navarro, M. E., Carrizales, L., Morales, R., & Calderón, J. (2007). Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. *Cadernos de Saúde Pública*, *23*(S4), 579–587.

- Rodier, P. M. (1995). Developing brain as a target of toxicity. *Environmental Health Perspectives*, 103(S6), 73–76.
- Rodríguez-Barranco, M., Lacasaña, M., Aguilar-Garduño, C., Alguacil, J., Gil, F., González-Alzaga, B., et al. (2013). Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. *Science of the Total Environment*, 454–455, 562–577.
- Rossignol, D. A., & Bradstreet, J. J. (2008). Evidence of mitochondrial dysfunction in autism and implications for treatment. *American Journal of Biochemistry and Biotechnology*, 4(2), 208–217.
- Rossignol, D. A., Genuis, S. J., & Frye, R. E. (2014). Environmental toxicants and autism spectrum disorders: a systematic review. *Translational Psychiatry*. doi:10.1038/tp.2014.4.
- Roy, A., Kordas, K., Lopez, P., Rosado, J. L., Cebrian, M. E., Vargas, G. G., et al. (2011). Association between arsenic exposure and behavior among first-graders from Torreón, Mexico. *Environmental Research*, 111(5), 670–676.
- Sagiv, S. K., Thurston, S. W., Bellinger, D. C., Amarasiwardena, C., & Korrick, S. A. (2012). Prenatal exposure to mercury and fish consumption during pregnancy and attention-deficit/hyperactivity disorder-related behavior in children. *Archives of Pediatrics & Adolescent Medicine*, 166(12), 1123–1131.
- Salgueiro, M. J., Zubillaga, M. B., Lysonek, A. E., Caro, R. A., Weill, R., & Boccio, J. R. (2002). The role of zinc in the growth and development of children. *Nutrition*, 18(6), 510–519.
- Sánchez-Martín, F. J., Fan, Y., Lindquist, D. M., Xia, Y., & Puga, A. (2013). Lead induces similar gene expression changes in brains of gestationally exposed adult mice and in neurons differentiated from mouse embryonic stem cells. *PLoS ONE*. doi:10.1371/journal.pone.0080558.
- Schnur, J., & John, R. M. (2014). Childhood lead poisoning and the new centers for disease control and prevention guidelines for lead exposure. *Journal of the American Association of Nurse Practitioners*, 26(5), 238–247.
- Schultz, S. T. (2010). Does thimerosal or other mercury exposure increase the risk for autism? A review of current literature. *Acta Neurobiologiae Experimentalis (Warsaw)*, 70(2), 187–195.
- Scortegagna, M., & Hanbauer, I. (1997). The effect of lead exposure and serum deprivation on mesencephalic primary cultures. *Neurotoxicology*, 18(2), 331–339.
- Shanker, G., & Aschner, M. (2003). Methylmercury-induced reactive oxygen species formation in neonatal cerebral astrocytic cultures is attenuated by antioxidants. *Brain Research. Molecular Brain Research*, 110(1), 85–91.
- Shanker, G., Allen, J. W., Mutkus, L. A., & Aschner, M. (2001). Methylmercury inhibits cysteine uptake in cultured primary astrocytes, but not in neurons. *Brain Research*, 914(1–2), 159–165.
- Shanker, G., Syversen, T., Aschner, J. L., & Aschner, M. (2005). Modulatory effect of glutathione status and antioxidants on methylmercury-induced free radical formation in primary cultures of cerebral astrocytes. *Molecular Brain Research*, 137(1–2), 11–22.
- Shearer, T. R., Larson, K., Neuschwander, J., & Gedney, B. (1982). Minerals in the hair and nutrient intake of autistic children. *Journal of Autism and Developmental Disorders*, 12(1), 25–34.
- Shenker, B. J., Guo, T. L. O. I., & Shapiro, I. M. (1999). Induction of apoptosis in human T-cells by methyl mercury: temporal relationship between mitochondrial dysfunction and loss of reductive reserve. *Toxicology and Applied Pharmacology*, 157(1), 23–35.
- Singh, V. K., Singh, E. A., & Warren, R. P. (1997). Hyperserotoninemia and serotonin receptor antibodies in children with autism but not mental retardation. *Biological Psychiatry*, 41(6), 753–755.
- Singh, R. P., Sharada, S., & Kapur, S. (2004). Free radicals and oxidative stress in neurodegenerative diseases: relevance of dietary antioxidants. *Journal of Indian Academy of Clinical Medicine*, 5, 218–225.
- Singh, A. P., Goel, R. K., & Kaur, T. (2011). Mechanisms pertaining to arsenic toxicity. *Toxicology International*, 18(2), 87–93.
- Singhal, R. L., Merali, Z., & Hrdina, P. D. (1976). Aspects of the biochemical toxicology of cadmium. *Federation Proceedings*, 35(1), 75–80.
- Smedley, P. L., & Kinniburgh, D. G. (2002). A review of the source, behaviour and distribution of arsenic in natural waters. *Applied Geochemistry*, 17(5), 512–568.
- Stone, J. M., Morrison, P. D., & Pilowsky, L. S. (2007). Glutamate and dopamine dysregulation in schizophrenia—a synthesis and selective review. *Journal of Psychopharmacology*, 21(4), 440–452.
- Stowe, H., Wilson, M., & Goyer, R. A. (1972). Clinical and morphologic effects of oral cadmium toxicity in rabbits. *Archives of Pathology*, 94(5), 389–405.
- Suzuki, K., Nakai, K., Sugawara, T., Nakamura, T., Ohba, T., Shimada, M., et al. (2010). Neurobehavioral effects of prenatal exposure to methylmercury and PCBs, and seafood intake: neonatal behavioral assessment scale results of Tohoku study of child development. *Environmental Research*, 110(7), 699–704.
- Svoboda, P., & Flehr, M. (2010). The role of miRNAs and endogenous siRNAs in maternal-to-zygotic reprogramming and the establishment of pluripotency. *EMBO Reports*, 11(8), 590–597.
- Szewczyk, B. (2013). Zinc homeostasis and neurodegenerative disorders. *Frontiers in Aging Neuroscience*. doi:10.3389/fnagi.2013.00033.
- Thatcher, R. W., Lester, M. L., McAlaster, R., & Horst, R. (1982). Effects of low levels of cadmium and lead on cognitive functioning in children. *Archives of Environmental Health*, 37(3), 159–166.
- Tian, L. L., Zhao, Y. C., Wang, X. C., Gu, J. L., Sun, Z. J., Zhang, Y. L., et al. (2009). Effects of gestational cadmium exposure on pregnancy outcome and development in the offspring at age 4.5 years. *Biological Trace Element Research*, 132(1–3), 51–59.
- Tong, S. L., Baghurst, P. A., McMichael, A. L., Sawyer, M. G., & Mudge, J. (1996). Lifetime exposure to environmental lead and children's intelligence at 11–13 years: the port Pirie cohort study. *British Medical Journal*, 312(7046), 1569–1575.
- Tsubaki, T., & Irukayama, K. (1977). *Minamata disease, methylmercury poisoning in Minamata and Niigata, Japan*. Amsterdam: Elsevier.
- U. S. Environmental Protection Agency. (1997). *Integrated risk information system (IRIS) for cadmium*. Washington: Office of Health and Environmental Assessment.
- U. S. Environmental Protection Agency. (2007). *Air Trends Report*. http://www.epa.gov/airtrends/lead.html. Accessed 11 June 2007.
- Ueha-Ishibashi, T., Oyama, Y., Nakao, H., Umabayashi, C., Nishizaki, Y., Tatsuishi, T., et al. (2004). Effect of thimerosal, a preservative in vaccines, on intracellular Ca²⁺ concentration of rat cerebellar neurons. *Toxicology*, 195(1), 77–84.
- Višnjevec, A. M., Kocman, D., & Horvat, M. (2013). Human mercury exposure and effects in Europe. *Environmental Toxicology and Chemistry*. doi:10.1002/etc.2482.
- Warniment, C., Tsang, K., & Galazka, S. S. (2010). Lead poisoning in children. *American Family Physician*, 81(6), 751–757.
- Wasserman, G. A., Liu, X., Parvez, F., Factor-Litvak, P., Ahsan, H., Levy, D., et al. (2011). Arsenic and manganese exposure and children's intellectual function. *Neurotoxicology*, 32(4), 450–457.
- Wecker, L., Miller, S. B., Cochran, S. R., Dugger, D. L., & Johnson, W. D. (1985). Trace element concentrations in hair from autistic children. *Journal of Mental Deficiency Research*, 29(Pt 1), 15–22.
- Weissman, J. R., Kelley, R. I., Bauman, M. L., Cohen, B. H., Murray, K. F., Mitchell, R. L., et al. (2008). Mitochondrial disease in autism spectrum disorder patients: a cohort analysis. *PLoS ONE*. doi:10.1371/journal.pone.0003815.
- Winneke, G. (2011). Developmental aspects of environmental neurotoxicology: lessons from lead and polychlorinated biphenyls. *Journal of Neurological Sciences*, 308(1–2), 9–15.

- World Health Organization. (2007). *Exposure to mercury: a major public health concern*. Geneva: WHO.
- World Health Organization. (2008). Lead. In: *Children's Health and Environment*. Geneva: WHO.
- World Health Organization. (2010). *Exposure to lead: a major public health concern*. Geneva: WHO.
- Wright, R. O., Amarasiriwardena, C., Woolf, A. D., Jim, R., & Bellinger, D. (2006). Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. *Neurotoxicology*, 27(2), 210–216.
- Yang, P. M., Chiu, S. J., Lin, K. A., & Lin, L. Y. (2004). Effect of cadmium on cell cycle progression in Chinese hamster ovary cells. *Chemico-Biological Interactions*, 149(2–3), 125–136.
- Yasuda, H., & Tsutsui, T. (2013). Assessment of infantile mineral imbalances in autism spectrum disorders (ASDs). *International Journal of Environmental Research and Public Health*, 10(11), 6027–6043.
- Yasuda, H., Yoshida, K., Yasuda, Y., & Tsutsui, T. (2012). Two age-related accumulation profiles of toxic metals. *Current Aging Science*, 5(2), 105–111.
- Yasuda, H., Yasuda, Y., & Tsutsui, T. (2013). Estimation of autistic children by metallomics analysis. *Scientific Reports*. doi:10.1038/srep01199.
- Yin, Z., Milatovic, D., Aschner, J. L., Syversen, T., Rocha, J. B., Souza, D. O., et al. (2007). Methylmercury induces oxidative injury, alterations in permeability and glutamine transport in cultured astrocytes. *Brain Research*, 1131(1), 1–10.
- Yorbik, Ö., Kurt, İ., Haşimi, A., & Özlem, Ö. (2010). Chromium, cadmium, and lead levels in urine of children with autism and typically developing controls. *Biological Trace Element Research*, 135(1–3), 10–15.
- Yorifuji, T., Debes, F., Weihe, P., & Grandjean, P. (2011). Prenatal exposure to lead and cognitive deficit in 7- and 14-year-old children in the presence of concomitant exposure to similar molar concentration of methylmercury. *Neurotoxicology and Teratology*, 33(2), 205–211.
- Young, H. A., Geier, D. A., & Geier, M. R. (2008). Thimerosal exposure in infants and neurodevelopmental disorders: as assessment of computerized medical records in the Vaccines Safety Datalink. *Journal of the Neurological Sciences*, 271(1–2), 110–118.
- Yousef, S., Adem, A., Zoubeidi, T., Kosanovic, M., Mabrouk, A. A., & Eapen, V. (2011). Attention deficit hyperactivity disorder and environmental toxic metal exposure in the United Arab Emirates. *Journal of Tropical Pediatrics*, 57(6), 457–460.
- Zahir, F., Rizwi, S. J., Haq, S. K., & Lom, S. (2010). Low dose mercury toxicity and human health. *Environmental Toxicology and Pharmacology*, 20(2), 351–360.