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Neurodevelopmental Effects of Mercury

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Abstract

The toxicology of mercury (Hg) is of concern since this metal is ubiquitously distributed in the environment, and living organisms are routinely exposed to Hg at low to high levels. The toxic effects of Hg are well studied and it is known that they may differ depending on the Hg chemical species. In this chapter, we emphasize the neurotoxic effects of Hg during brain development. The immature brain is more susceptible to Hg exposure, since all the Hg chemical forms, not only the organic ones, can harm it. The possible consequences of Hg exposure during the early stages of development, the additive effects with other co-occurring neurotoxicants, and the known mechanisms of action and targets will be addressed in this chapter.

Keywords

Mercury; brain; thimerosal; LMM-SH; HMM-SH

Introduction:

Mercury is a metal with a unique chemical characteristic, namely, it is silvery liquid at room temperature. Its physical properties, including low viscosity, high density, excellent electrical conductance, and reflective surface characteristics, drew the attention of researchers and industries to the application of Hg (Clarkson and Magos 2006). In this context, there are records of Hg usage as early as ancient China, where cinnabar (HgS) was used to make a red dye. On the American continent, Hg was brought by the Spanish Galleons to be employed in the process of gold and silver extraction (Clarkson and Magos 2006; Oliveira et al. 2017a). Nowadays, Hg is used as part of some medical devices, as a preservative of vaccines, and as a catalyst in caustic soda and chloride factories. In many parts of the world, Hg is still a constituent of dental amalgams (Horowitz et al. 2014). Of particular environmental concern, in countries, such as Brazil, Venezuela, Ecuador, Indonesia, Tanzania, and Ghana, Hg is still used in artisanal small-scale gold mining (ASGM) (Kristensen et al. 2014), and this activity has apparently increased in the last year (Branco et al. 2017). The environmental levels of Hg increased considerably with anthropogenic intervention (Figure 1). In fact, it is estimated that the atmospheric burden of Hg nowadays is 300–500% higher than that in the precolonial period (AMAP/UNEP 2013; De Simone et al. 2016).

In this context, the toxicology of Hg has been extensively studied, and it has been established that Hg does not have biochemical and/or physiologic functions in living organisms (WHO 2007). In fact, exposure to even low levels of Hg can be toxic, causing molecular, cellular, developmental and behavioral alterations in different organisms (Chang et al. 2017; Chauhan et al. 2017; Fujimura and Usuki 2017; Mora-Zamorano et al. 2017), including humans (Choi et al. 2017; Junior et al. 2017). The toxic effects are directly influenced by the chemical form of Hg: inorganic elemental Hg (Hg^0), ionic inorganic mercury (Hg^{2+}) and organic mercury (Hg atom bound to one carbon atom, for example, CH_3Hg^+ and $\text{C}_2\text{H}_5\text{Hg}^+$) (Figure 2).

Although immediately after intoxication, Hg chemical species accumulate in different target organs, multiple studies have demonstrated that they can reach the brain causing the accumulation of Hg^{2+} (Figure 2). The neurotoxic effects of Hg are usually much more pronounced in the immature nervous system. This review will briefly discuss the neurodevelopmental toxic effects caused by mercury exposure.

1. Inorganic Elemental Mercury

Inorganic elemental Hg (Hg^0) is found as a liquid at room temperature, but due to its low vapor pressure (0.2613 Pa at 25 °C), it volatilizes slowly and increasingly with rise in temperature (Risher et al. 2003; Lee et al. 2009; Huber et al. 2006; Gonzalez-Raymat et al. 2017). As a vapor, it can be inhaled and the first target is the respiratory tract (Oz et al. 2012) followed by the nervous and renal systems (Reinhardt 1992; Oliveira et al. 2017a). Hg^0 can easily cross plasma membranes, reaching the intracellular milieu due to its high diffusibility and lipid solubility (Clarkson 1972). In the blood, Hg^0 can be oxidized to Hg^{2+} in erythrocytes by the enzyme catalase (Halbach and Clarkson 1978). The remaining Hg^0 can reach the brain and once inside the brain cells, it can be oxidized to Hg^{2+} (Eide and

Syversen 1983). The oxidized form (Hg^{2+}) has a great affinity for protein thiol ($-\text{SH}$) and selenol ($-\text{SeH}$) groups, causing several alterations that will be further discussed in Section 5 of this chapter.

Hg^0 is found in medical devices such as thermometers, barometers, sphygmomanometers (Risher et al. 2003), and in dental amalgams (Reinhardt 1992); it is also commonly used in fluorescent lamps (Hu and Cheng 2012). The main anthropogenic source of Hg^0 is ASGM, and data from UNEP (United Nations Environment Programme) estimate that 727 tons of mercury were released by gold extraction in 2010 (AMAP/UNEP 2013). Occupational exposure to elemental Hg is common among workers that inappropriately handled the elemental mercury. Contaminated individuals presented symptoms such as skin rash, pruritus, myalgia, sleep disturbance fatigue, insomnia, nightmares, anxiety disorder and elevated hair, urine and blood Hg levels (Schuurs 1999; Mostafazadeh et al. 2013; Noble et al. 2016; Do et al. 2017). In addition, there are cases of accidental or even intentional contamination with Hg^0 (Florentine and Sanfilippo 1991; Gul Oz et al. 2012; Gao et al. 2017).

Intrauterine exposure to Hg^0 has been reported to cause Hg accumulation and neurobehavioral changes in metallothionein-null mice (Yoshida et al. 2002, 2005) and in rats (Danielsson et al. 1993; Morgan et al. 2002). Vimy et al (1990), used pregnant sheep as the experimental model and demonstrated that the Hg^0 released from dental amalgam fillings crossed the placental barrier and accumulated in the fetus' organs. Despite these experimental findings, Watson and co-workers (2012, 2013) did not find a correlation between mothers' dental amalgam and the development of their children at ages 9 and 30 months and 5 years in the Seychelles cohort.

2. Ionic Inorganic Mercury

The ionic inorganic form of Hg, Hg^{2+} , can be formed from the oxidation of elemental mercury or by the cleavage of the carbon-mercury bound in the organic mercury molecules. The process of carbon-mercury bond cleavage is very slow for MeHg^+ , but it is much faster for EtHg^+ (Burbacher et al. 2005; Dórea et al. 2013). These chemical conversions occur in both the environment and in the body (Oliveira et al. 2017a).

Presently, populations are exposed to Hg^{2+} mainly through the ingestion of contaminated water and food (Park and Zheng 2012). Another reported means of Hg^{2+} exposure is the addition of Hg^{2+} to cosmetic creams for skin lightening and acne treatments (Chan 2011; Copan et al. 2015). Although it is known that Hg^{2+} is poorly absorbed by the intestine and skin cells, the toxic effects of the exposure to inorganic Hg^{2+} cannot be neglected.

The primary target of Hg^{2+} is the kidney (Zalups 2000). Some studies have demonstrated that a few hours after intravenous Hg^{2+} injection, approximately 50% of the injected dose is found in the kidneys (Zalups 1993; Zalups and Barfuss 1995; Oliveira et al. 2017b). Hg cations are not found free in the bloodstream; rather, they are bound to thiol ($-\text{SH}$)-containing molecules such as albumin, cysteine, and glutathione (GSH) (Bridges and Zalups 2017; section 5). The high affinity of $-\text{SH}$ -containing molecules for Hg^{2+} (Fuhr and Rabenstein 1973; Rabenstein and Isab 1982), particularly for cysteine, which is abundant in

the blood, will direct Hg-cysteine complexes to the kidneys (section 5). Interestingly, the fate of Hg^{2+} in the soil is also dictated by the thiol present in the dissolved organic matter (Skylberg 2008; Leterme et al. 2014). Hg bound to two cysteines (Cys-Hg-Cys) gets entry into the kidney's proximal tubular cells as a mimic of the amino acid cystine by System b⁰, OAT1 and OAT3 transporters (Bridges et al. 2004; Zalups and Ahmad 2004; Bridges and Zalups 2017). Due to its electrical polarity, Hg^{2+} poorly crosses the plasma membrane or the blood-brain and placental barriers. However, some studies with experimental animals demonstrated that some of Hg^{2+} crosses the placental barrier and accumulates in the fetus's organs, which can be harmful to the animal's development (Danielsson et al. 1984; Bernard et al. 1992; Oliveira et al. 2012, 2015). Moreover, several studies have demonstrated the neurotoxic effects of inorganic mercury in developing mammalian brains (Peixoto et al. 2007; Franciscato et al. 2009; Moraes-Silva et al. 2014; Sahin et al. 2017). Although there are studies showing that in small quantities Hg^{2+} crosses the placental and blood-brain barriers (Alves et al. 2017), the mechanism by which it crosses these barriers is not well understood. Amino acid transporters, similar to those that transport Cys-Hg-Cys complexes in the kidneys, are probably involved.

Of toxicological significance, the access of Hg^{2+} into the immature mammalian brain is higher to that observed in the adult brain. In early life, the blood-brain barrier (BBB) is not completely developed and is leakier to charged toxic metals (Johansson 1990). Rat pups exposed subcutaneously to Hg^{2+} (HgCl_2) during the second week of post-natal life showed behavioral alterations such as loss of motor coordination and delay in the development of the geotaxis reflex (Peixoto et al. 2007; Moraes-Silva et al. 2014). These alterations were observed even after the cessation of HgCl_2 exposure (Franciscato et al. 2009). Huang and colleagues (2014) demonstrated that mice pups exposed to Hg^{2+} accumulate this metal in the cerebral neuron bodies.

Cases of human Hg^{2+} direct contamination causing neurotoxic effects do not exist. However, there is evidence that other chemical species of mercury (organic and elemental) are converted to Hg^{2+} and trapped within the brain (Yamamoto et al. 1986; Burbacher et al. 2005; Ishitobi et al. 2010). Based on a systematic review, Rooney (2014) concluded that the half-life of Hg^{2+} in the brain varies from years to decades. Of particular neurotoxicological significance, data have been published linking Hg accumulation in the brain with neurodegenerative diseases, namely, Alzheimer's disease (Mutter et al. 2004; Walach et al. 2014; Chakraborty 2017), amyotrophic lateral sclerosis (Johnson and Atchison 2009; Pamphlett and Jew 2013, 2014) and Autism Spectrum Disorders (Björklund et al. 2017a,b), as will be discussed in section 4.

3. Organic Mercury

The organic mercury form is represented by a Hg atom bound to a C atom. The major concern of the human population on the subject of the organic mercury species exposure is related to methylmercury (CH_3Hg^+ ; MeHg^+) and ethylmercury ($\text{C}_2\text{H}_5\text{Hg}^+$; EtHg^+). MeHg^+ and EtHg^+ are potent neurotoxic agents. These organic mercury molecules form complexes with low molecular mass thiols (LMM-SH, e.g., cysteine and reduced glutathione, see

section 5 for more details) that can easily cross the plasma membrane and the blood-brain barrier as well as the placental barrier (Farina et al. 2011a,b; Dórea et al. 2013).

Exposure to MeHg^+ is related to eating habits, *i.e.* populations consuming a diet based on seafood/fish from contaminated sites are more likely to be exposed to MeHg (Burger et al. 2005; Gochfeld and Burger 2005; Schmidt et al. 2013; Montero-Alvez et al. 2014; Bosch et al. 2016). Another source of dietary MeHg is rice from contaminated areas (Li R. et al. 2016; Brombach et al. 2017; Cui et al. 2017; Wu et al. 2018). Regarding EtHg^+ , the main source of exposure is Thimerosal, a preservative in vaccines. After the immunization with thimerosal-containing vaccines (TCV), this molecule is metabolized, releasing EtHg^+ (Dórea et al. 2013; Dórea 2017a,b). There are several controversies about the use of thimerosal to preserve vaccines. On the one hand, there are scientists from the pharmaceutical industry supporting the use of thimerosal, claiming that the levels used are within safe limits. On the other hand, there are concerns that the cumulative number of shots during the critical periods of brain development may cause moderate to high dose exposure, and indeed these concerns have led rich countries to ban its use for young children. Independently, , studies have questioned the double standard of using Thimerosal in pediatric vaccines for children in less developed countries (Dórea 2017a,b). From a toxicological point of view, the intentional exposure of humans or animals to any form of mercury is illogical.

The neurotoxic effects of the organic forms of mercury became evident after two outbreaks of human contamination. The first case is known as Minamata disease, which took place in Minamata Bay, Japan. For approximately 20 years (mid 1950s to mid 1970s) a factory released large amounts of Hg^{2+} into Minamata Bay (Kudo and Turner 1999; Harada 1995; Hachiya 2012). Hg^{2+} was used as the catalyst in the synthesis of acetaldehyde, but a small amount of MeHg^+ (about 1%) was formed as byproduct, which may have increased the extent of human and environmental contamination (Kudo and Turner 1999). Once in the aquatic environment, Hg is methylated by bacteria and incorporated in the food chain, leading to the biomagnification and bioaccumulation processes, *i.e.*, predatory old fish accumulated more MeHg^+ than herbivorous or predatory juvenile fish (Oliveira et al. 2017a). As the main source of protein for the Minamata population was fish, they were consequently exposed to high levels of MeHg^+ . Although the adults showed low to moderate neurologic symptoms, the infants, who were exposed indirectly to MeHg^+ (in utero or via breast milk), presented severe learning and locomotor deficits (Harada 1995; Ekino et al. 2007).

The second major case of organic Hg contamination happened in Iraq (1971–1972), where farmers and their families, inadvertently prepared and ate homemade bread made with seeds that had been treated with a fungicide containing organic Hg (MeHg^+ and EtHg^+). Approximately 6,500 people were poisoned and had severe neurological symptoms, and about 500 died. As in Minamata, infants were much more incapacitated neurologically than adults (Bakir et al. 1973; Shikara and Al Dabbagh 1973).

However, human contamination with EtHg^+ (in TCVs) is silent, when compared with the poisonous outbreaks of organic Hg. As mentioned before, infants and children in less

developed countries are constantly exposed to EtHg⁺ after immunization with TCVs during vulnerable periods of brain development (Dórea 2017a,b). Based on this, several epidemiological studies have indicated adverse effects of TCVs in the normal development of children (Geier and Geier 2006; Mrozek-Budzyn et al. 2012; Marques et al. 2014, 2016a).

4. Neurodevelopmental toxicity: Hg versus Autism Spectrum Disorder

The brain is a complex organ that presents non-uniform development, *i.e.*, it occurs in multiple stages. The cortex, hippocampus, and cerebellum are examples of brain structures that show late development (Andersen 2003). Consequently, the vulnerability of different brain areas to neurotoxic insults will be different depending on the developmental period of exposure. In addition, symptoms/effects that are not present during the exposure period may appear later in life. For example, epidemiological evidence has been accumulated supporting the proposal that environmental insults in utero and/or in early postnatal life in association with a genetic predisposition may facilitate the development of neurodegenerative diseases in adult life (Grandjean and Landrigan 2006; Modgil 2014).

Among the environmental insults, metals such as cadmium, lead, manganese, aluminum, and mercury are known to be important neurotoxicants. Neurodevelopmental exposure to mercury, *in utero* and/or in breast milk or even in vaccines, has been associated with learning/locomotor deficits, low IQ, attention deficit disorder, mental retardation and Autism Spectrum Disorder (Johansson et al. 2007; Drum 2009; Debes et al. 2016; Jeong et al. 2017; Geier et al. 2018a).

Autism Spectrum Disorder (ASD) is a group of heterogeneous dysfunctions in social interaction and communication that lead to the appearance of unusual and repetitive patterns of behavior (American Psychiatric Association 2013). The causes of ASD are usually attributed to complex genetic modifications, but the exact genes involved in ASD development are not fully known. A recent review from Fakhoury (2018) highlighted that mutations in genes involved in the pre- and post-synaptic binding proteins, neuronal cell adhesion, and GABA A receptor, among others, may be involved in the development of ASD. However, to quote Dr. Fakhoury, “the characterization of the neurobiological mechanisms by which common genetic risk variants might operate to give rise to ASD symptomatology has proven to be far more difficult than expected.”

As mentioned above, Hg has emerged as a putative environmental associated factor for ASD development. In fact, several studies have demonstrated that ASD patients presented elevated levels of Hg in blood and hair when compared to the same age control subjects (see Table 1 and the elegant review by Kern et al. 2016). The difference in the mercury values in the studies mentioned in Table 1 can probably be explained by different protocols used to quantify mercury, dietary habits of the subjects, and the occurrence of environmental mercury, among others. If on the one hand there are a great number of studies correlating Hg exposure to ASD development, on the other hand, studies carried out by the pharmaceutical industry or entities with an apparent conflict of interest have most often shown no clear evidence (see the critical review of Kern et al. 2017).

Hg is a neurotoxic agent, and an immature organism can be exposed in utero and/or via breast milk (if the mother is/was exposed to metal) or via TCVs, food (fish and rice), and from environmental contamination (for example, children that live close to ASGM areas (Ruggieri et al. 2017). Once Hg reaches the brain, it causes several alterations, including oxidative stress, enzyme inhibition, depletion of thiol molecules, DNA and gene expression alteration, excitotoxicity, and cell apoptosis. These alteration can permanently change the normal brain connectivity either by changing the migration/connection between cells or by decreasing the number of cells (Ceccatelli et al 2010; Farina et al. 2011a,b; Garrecht and Austin 2011; Oliveira et al. 2017a). Hg exposure can also activate the immune system (Hultman et al. 1998; Brenden et al. 2001), and several papers have indicated that the maternal and/or fetal activation of the brain immune system can be interconnected with the neurodevelopmental deficit observed in ASD (Estes and McAllister 2016; Fernández de Cossío et al. 2017; Meltzer and Van De Water 2017; Bilbo et al. 2018).

Further support for the potential role Hg in the etiology of ADS is the fact that males are more affected than females (Loomes et al. 2017; Palmer et al. 2017). Several studies have demonstrated that males are more sensitive than females to mercury exposure (McKeown-Eyssen et al. 1983; Rossi et al. 1997; Gimenez-Llort et al. 2001; Malagutti et al. 2009; Ekstrand et al. 2010; Marques et al. 2015), which corroborates the hypothesis that Hg may be involved in ASD etiology. The differential susceptibility of males to toxic agents, when compared to females, is elegantly discussed by McCarthy and Wright (2017). They hypothesized that during the process of brain masculinization (exposure to high levels of testosterone) the brain is more susceptible to immune activation and/or neurotoxins.

5. Potential molecular target of Hg and mechanism of neurotoxicity

5.1. Thiol (–SH) and Selenol (–SeH) groups—The electrophilic forms of mercury (E^+Hg , i.e., Hg^{2+} , $MeHg^+$ and $EtHg^+$) can interact with different ligands (functional groups) found in the cell milieu and in the natural organic matter found in the environment (Table 2). However, the affinity of E^+Hg for soft nucleophiles (SNu^-) is orders of magnitude higher than that for hard nucleophiles (HNu^-) (Table 3). Thus, the fate of Hg^0 and E^+Hg forms in the environment and inside living cells is greatly influenced by the interaction of Hg^0 or E^+Hg with thiol/thiolate groups (–SH/ S^-) ubiquitously found in complex biological systems (Loux 1998; Skyllberg et al. 2006; Farina et al. 2011a,b, 2017; Gu et al. 2011; LoPachin et al. 2012). Another important functional group that can bind E^+Hg with high affinity is the selenol/selenolate (–SeH/– Se^-) groups found in a small number of selenoproteins (Labunskyy et al. 2014). Although selenol/selenolate groups have a stronger affinity for E^+Hg than their sulfur-containing analogs (Farina et al. 2011a,b; Bjørklund et al. 2017c), the number of studies analyzing the constant of formation are limited (Table 2). Despite this limitation, the affinity of –SeH/– Se^- for E^+Hg is possibly 1 to 4 orders of magnitude higher than that of –SH/– S^- analogs (Sugiura et al. 1976; Rabenstein et al. 1986; Khan and Wang 2009; Farina et al. 2011a,b).

Exposure to $MeHg^+$ occurs via fish consumption, whereas $EtHg^+$ is intramuscularly injected in the chemical form of thimerosal in vaccines. Exposure to Hg^{2+} can occur after the absorption of Hg^0 or occasionally via ingestion of contaminated food and water. For

instance, about 2–10% of the total Hg found in fish meat can be present as inorganic Hg (Montero-Alvarez et al. 2014).

The strong affinity of E^+Hg for $-SH$ and $-SeH$ groups implies that nearly all the E^+Hg will be bound to one of these groups. Since $-SH$ is much more abundant than $-SeH$ (Rocha et al. 2017), the majority of E^+Hg forms will be complexed with $-SH$ groups. In fact, $MeHg^+$ can bind to low molecular mass thiol molecules (LMM-SH, e.g., cysteine, glutathione (GSH)) or to cysteinyl residues in proteins or high molecular mass thiol molecules (HMM-SH). Some important complexes of E^+Hg forms with abundant LMM-SH molecules found in the cellular environment are shown in Figure 3.

Exposure to $MeHg^+$ usually occurs via fish consumption (Burger et al. 2005; Gochfeld and Burger 2005; Schmidt et al. 2013; Montero-Alvarez et al. 2014; Bosch et al. 2016), where the majority of $MeHg^+$ is in the complexed form with cysteine ($MeHg^+-S-Cys$) (Kuwabara et al. 2007). After the digestion of fish proteins containing the $MeHg^+-S-Cys$ complex, the mercurial part can be absorbed by distinct mechanisms that are not yet well characterized. The interaction of E^+Hg with LMM-SH is critical for its distribution in the body of vertebrates and determined by exchange reactions of the type:

Where, R_1-SH and R_2-SH can be hypothetically either LMM-SH or HMM-SH (for a detailed discussion see Rabenstein and Fairhurst 1975; Rabenstein 1978; Rabenstein et al. 1982; Rabenstein and Reid 1984; Farina et al. 2011a,b; 2017). A schematic representation of the fate of dietary $MeHg^+$ or intramuscularly administered $EtHg^+$ is depicted in Figure 4. Hg^{2+} 's fate will also depend on the binding to LMM-SH groups, and here the chemistry is a little more complicated because the exchange reactions can involve one or two thiol groups. The binding of Hg^{2+} to two cysteine molecules is critical for its movement in the body and, particularly, for its renal toxicity (Zalups 2000; Bridges and Zalups 2005, 2010, 2017; Figure 5).

More recently, $MeHg^+$ and other E^+Hg forms have been described in rice (Li R. et al. 2016; Brombach et al. 2017; Cui et al. 2017; Wu et al. 2018), and the exposure to E^+Hg forms via rice ingestion can cause neurodevelopmental toxicity in humans (Rothenberg et al. 2016). Little is known about the speciation of E^+Hg forms in rice (Wu et al. 2018), but in view of their high affinity for $-SH$ groups, we can presume that they will be found forming stable complexes with both LMM-SH and HMM-SH molecules. Accordingly, the metalloproteomic analysis of rice experimentally exposed to E^+Hg forms has indicated that E^+Hg can bind to HMM-SH molecules (Li Y. et al. 2016).

Thimerosal is a complex $EtHg^+$ with 2-mercaptobenzoic acid or thiosalicylic acid (Figure 6) and is usually administered intramuscularly (as part of the TCV). The exposure to free Hg^{2+} is rare, but the presence of Hg^{2+} in contaminated food and whitening or bleaching skin creams has been reported frequently (Agrawal and Sharma 2017; Sun et al. 2017). In food, low and intermediate levels of Hg^{2+} (from picomolar to low micromolar concentrations) will be complexed with low molecular mass containing thiol molecules (LMM-SH, e.g. cysteine

and reduced glutathione-GSH as complexes of the type LMM-S-Hg-S-LMM; Figure 3). In the case of contamination via skin creams, absorption will involve binding to either LMM-SH or to thiol-containing proteins (HMM-SH). Hg^0 is normally absorbed by the lungs, and in the tissues and in the blood it can be oxidized to Hg^{2+} . The free Hg^{2+} formed will rapidly react with free thiol groups of LMM-SH and/or HMM-SH molecules found in the blood or tissues (Figure 3).

As described in Figure 4 for organic mercury forms, the basic molecular events involved in the absorption, transport, distribution and toxicity of Hg^{2+} are determined by exchange reactions of the original complex with one or two free cysteines ($\text{Cys}_2\text{-SH}$) to form a new complex ($\text{Cys}_1\text{-S-Hg-S-Cys}_2$ or $\text{Cys}_2\text{-S-Hg-S-Cys}_2$; for more details, see the caption of Figure 3). The exchange reactions can occur with any free $-\text{SH}$ group, and they are depicted in the scheme by the high molecular mass thiol- or selenol-containing proteins (HMM-SH or HMM-SeH) molecules or by LMM-SH molecules (Cys-SH or $\text{G}_2\text{-SH}$). The reaction of Cys-Hg complexes with other thiol-containing molecules can generate a diverse number of R-S-Hg-S-R complexes either with different LMM-SH free thiols (Cys-SH or GSH) or HMM-SH/HMM-SeH molecules (Prt-SH or PrtSeH), which can be both target or non-target molecules of E^+Hg forms.

In view of the strong affinity of thiol/thiolate and selenol/selenolate groups for electrophilic forms of mercury (E^+Hg), the interaction of E^+Hg forms with $-\text{SH}$ or $-\text{SeH}$ groups will be critical for initiating their toxicity. Nevertheless, our knowledge about the preferential targets of E^+Hg is still incomplete and here we will discuss some of the caveats when deciphering the primary targets of E^+Hg . The first seems to be related to the absorption of E^+Hg forms, which will depend greatly on the type and level of exposure. Here we will not discuss the exposure to high levels of E^+Hg forms, but only to environmentally or occupationally relevant levels. As a rule, exposure to low (pico- or nanomolar) or moderate levels (low micromolar concentrations) of E^+Hg forms does not saturate the E^+Hg binding sites (i.e. the thiol groups of non-target and target proteins) because the concentration of $-\text{SH}$ groups is in the millimolar range in vertebrate fluids and tissues.

The question of potential saturation of $-\text{SeH}$ groups found in a few selenoproteins, which are present at a much lower concentration than the thiol groups, is rather complex because we have practically no information about the distribution and concentration of selenoproteins in different cells and subcellular compartments. Indeed, our knowledge about the physiological function of the roughly two dozen selenoproteins found in vertebrates is incomplete, and only about one-half of them have a defined biochemical role in living cells (Fomenko et al. 2008; Labunskyy et al. 2014). Despite the limited number of studies on the interaction of MeHg^+ with selenoproteins, data in the literature have indicated that important selenoenzymes might be targets for both *in vitro* and *in vivo* MeHg^+ exposures (Wagner et al. 2010; Branco et al. 2011, 2012, 2014, 2017; Dalla Corte et al. 2013; Carvalho et al. 2008, 2011). Studies on the effects of EtHg^+ on selenoenzymes are scarce, but analogous to Hg^{2+} and MeHg^+ , EtHg^+ is also a potent inhibitor of TrxR (Carvalho et al. 2008, 2011; Rodrigues et al. 2015).

There is an large number of studies corroborating the inhibitory effect of E^+Hg in thiol-containing proteins (Farina et al. 2017; some examples are listed in Table 3). Among them, are neurotransmitter receptors, various enzymes and cation channels (Farina et al. 2017). However, the question of concentration, distribution and reactivity of cysteinyl residues in thiol-containing proteins is also a critical point and serious limitation in understanding the neurotoxicity of E^+Hg forms. As in the case of selenoproteins, we have only limited knowledge on the concentration, reactivity, and distribution of the majority of the thousands of proteins containing $-SH$ groups (Weerapana et al. 2010; Ferrer-Sueta et al. 2011; Reisz et al. 2013; Dröse et al. 2014; Rudyk and Eaton 2014; Pereira et al. 2015; Riemer et al. 2015; Short et al. 2016; Wible and Sutter 2017; Heppner et al. 2018).

As mentioned above, any thiol group found in a protein is a potential target for E^+Hg . The total number of cysteinyl residues codified in the human genome is about 550,000, found in about 72,000 proteins recovered from the UniProt database (www.uniprot.org). Considering only the proteins with experimental evidence of expression, which means about 19,000 proteins, one calculates the existence of 260,000 cysteinyl residues.

The human cysteinyl proteome has been estimated to be around 214,000 (Jones and Go 2011; Go et al. 2015), corroborating the number we have calculated above for proteins with experimental evidence. The thiol-containing proteins can have from one to several cysteinyl residues. Cysteine is one of the less abundant amino acids in proteins (Miseta and Csutora 2000; Poole 2015; Wible and Sutter 2017), representing only about 2–3% of amino acids comprising the human proteome. This is possibly due to the reactivity and nucleophilic softness of the cysteinyl group (Fomenko et al. 2008; LoPachin et al. 2012). Indeed, the $-SH$ group is the second most powerful soft nucleophile group found in biomolecules, and the first is the $-SeH$ group (Rocha et al. 2017). Their high reactivity likely restrained their abundance.

In contrast to the thiol groups, which are found in thousands of proteins (Jones and Go 2011; Go et al. 2015), the human genome codifies only about 25 selenoproteins (proteins containing the selenol group found in the selenocysteinyl, U or Sec residues) (Labunsky et al. 2014), and normally they have 1 to a maximum of about 10 Sec residues in selenoprotein P (Table 4), which is a protein involved in the transport of Se to different tissues in mammals (Labunsky et al. 2014; Oliveira et al. 2017a). In fact, the majority of selenoproteins have only one Sec residue and, in some cases, it participates in the analog motif of thiol oxidoreductase $-C-X-X-C-$, i.e., $-C-X-X-U-$ or $-U-X-X-C-$ (Table 4).

In short, there are thousands of targets for $EtHg^+$ forms in the case of HMM-SH molecules, and only a few for HMM-SeH molecules. One important aspect that determines the toxicity of E^+Hg forms is the accessibility and the intrinsic reactivity of the functional or catalytic role of a given cysteinyl or selenocysteinyl residue found in HMM-SH or HMM-SeH molecules. In the case of thiol groups, the cysteinyl residues in several HMM-SH molecules have no significant functional or catalytic role. Consequently, the binding of E^+Hg to their $-SH$ groups will not modify the protein activity. For instance, keratin has several cysteinyl residues that will form disulfide bonds in the secreted protein found in nails and hair. Keratinocytes can accumulate mercury in hair keratin either by incorporating cysteine- E^+Hg

complexes in the place of cysteine (Cernichiari et al. 2007), or E^+Hg forms can binding to cysteinyl thiol groups in keratin before the formation of the disulfide bonds in the pre-keratin (Sippel 1973). Here we have an example where the binding of mercury to a protein will not significantly change the biological function of the protein (Figure 7). Of possible toxicological significance, the high quantity of mercury incorporated in secreted keratin found in hair and nails can be considered as a route of diversion of E^+Hg forms from their target to non-target HMM-SH containing molecules.

The cysteinyl residues (Cys) in HMM-SH molecules can play either a direct or an indirect catalytic role in different classes of oxidoreductases, but an essential role in the catalysis or function of other types of proteins (Miseta and Csutora 2000; Fomenko et al. 2008; Poole 2015). Thiol-groups can also participate in the catalysis of non-redox reactions or have a critical structural role in proteins (Fomenko et al. 2008). Here, the binding of E^+Hg forms to those cysteinyl residues can inactivate the physiological role of the protein, which can have an important toxicological impact on the exposed organism (Table 3). Some hypothetical types of interaction of E^+Hg forms with HMM-SH molecules and the biological consequences of these interactions are depicted in Figure 8.

Some important motifs containing cysteinyl and/or selenocysteinyl residues are $-C-X-X-C-$ or $-C-X-X-U-$, which are found in several oxidoreductases (Fomenko et al. 2008). The number of times that the motif $-C-X-X-C-$ appears in human genes are near 19,000 in about 6,000 proteins (www.uniprot.org), but note that not all of these motifs will appear in native proteins, and not all proteins having the motif $-C-X-X-C-$ will be an oxidoreductase (Table 5). For instance, the motif $-C-X-X-C-$ can also be found in metal-coordinating proteins (Miseta and Csutora 2000; Fomenko et al. 2008), such as in delta-aminolevulinate dehydratase (porphobilinogen synthase; δ -AlaD) (Rocha et al. 2012). This enzyme is an *in vitro* and *in vivo* target for E^+Hg (Rocha et al. 2012); however, a causal link between the enzyme inhibition and the triggering of toxic effects is difficult to establish. Broadly speaking, this is a critical caveat in the neurotoxicology of E^+Hg forms, i.e. the observation that E^+Hg forms can inhibit or disrupt a target protein does not establish a causal relationship between the phenomenon and the toxicological outcomes. Some examples of proteins that have been reported to be inhibited after either *in vitro* or *in vivo* exposure to $MeHg^+$ are depicted in Table 3 (note that the proteins present in Table 3 are from the human genome, and the experimental studies were usually done in rodents or *in vitro*). The number of codified cysteinyl residues in these proteins varied from 1 to 27, and some of them have at least one of the motifs $-C-X-X-C-$, $-C-X-C-$ or $-C-C-$. Others have only different numbers of “independent” $-C-$ residues (Table 3 and 5).

An examination of Table 3 provides some examples of the bottlenecks found in the search for targets of E^+Hg . $MeHg^+$ can either inhibit or stimulate HMM-SH molecules (see for instance, glutathione-S-transferase and phospholipase A2, Table 3). One additional problem that can be inferred from Table 3 is the fact that the inhibition of E^+Hg can be indirect. For instance, acetylcholinesterase has been reported to be inhibited after exposure to $MeHg^+$ or Hg^{2+} ; however, the inhibition cannot be mediated by modifications of its thiol groups because none of them are reactive. In fact, the majority of them participate in $-S-S-$ bridge formation.

Another important factor that we have commented on above is the reactivity of thiol groups. The presence of vicinal thiol groups can increase the potential reactivity of these groups (as found in –C-X-X-C– motifs), but some proteins have “independent”, but highly reactive –C– residues, for instance, in human muscle and mitochondrial creatine kinase (CK). CK and mitochondrial CK have one cysteinyl residue with a very low pKa (Wang et al. 2001; Naor and Jensen 2004), which explains their strong reactivity with electrophiles (Stachowiak et al. 1998; Alvarez and Radi 2003; Glaser et al. 2010a, 2014). Thus, it is imperative to develop new *in silico* tools in the area of predictive toxicology to envisage the structure and the reactivity of thiol groups using the primary structure of a given protein. Another aspect that has to be investigated is the interaction of E⁺Hg forms with nascent proteins, i.e. prior to post-translational processing (this may be the case of pre-keratin, where E⁺Hg forms are incorporated in the protein structure before the assembly of –S–S– bonds).

The physiological role of thiol-containing protein can be modulated by transitory S-glutathionylation, nitrosylation or reversible oxidation of cysteinyl residues (Dröse et al. 2014; Pereira et al. 2015; Poole 2015; Comini 2016). The binding of E⁺Hg to this class of cysteinyl residues can drastically modify the normal dynamics of activating-deactivating redox-regulated thiol-containing proteins. As noted above, the stable binding of E⁺Hg to cysteinyl residues can permanently inactivate the HMM-SH molecules involved in the regulation of cell physiology via thiol switches. Of particular toxicological significance, those proteins that are modulated by thiolation or nitrosylation can be preferential targets of E⁺Hg forms, because their cysteinyl residues involved in these reactions are normally highly accessible and reactive towards strong and soft electrophiles, such as E⁺Hg. However, there are no systematic studies about the interaction of E⁺Hg with these types of proteins. Thus, it is imperative to determine the effects of E⁺Hg in proteins regulated by thiolation and other similar mechanisms. Here we posit that E⁺Hg forms will disrupt the cell metabolism via blockage of cysteinyl residues involved in protein regulation via glutathionylation or nitrosylation. One example of such proteins is complex I in respiratory the chain (Dröse et al. 2014), and data from the literature have indicated that Complex I is inhibited by MeHg⁺ treatment (Table 3; Glaser et al. 2010a, 2013). The detailed *in silico* and *in vitro* systematic studies about the interaction of E⁺Hg with thiol groups in such proteins can help in the construction of virtual and molecular predictive tools to facilitate the difficult task of determining the primary molecular targets of E⁺Hg.

In contrast to thiol groups, the selenol group found in selenoproteins is normally involved in the oxidoreductase catalytic activity of selenoenzymes (Fomenko et al. 2007) and possibly in the physiological role of all the selenoproteins. Thus, the binding of E⁺Hg to the selenocysteinyl residues in selenoproteins is expected to inactivate them. Most characterized selenoproteins are oxidoreductases and catalyze important redox reactions, such as the degradation of peroxides (glutathione peroxidase or GPx isoforms) and the reduction of thioredoxin (thioredoxin reductase or TrxR isoforms). Thus, the inhibition of these antioxidant enzymes is believed to play a role in causing oxidative stress in MeHg⁺ poisoning (Farina et al. 2011a,b).

In addition, the binding mode of E^+Hg species in the respective protein target, depends on the ligand (Cys, GSH or H_2O) bound to the Hg atom; *i.e.*, the molecular structure of the Hg molecule will determine which is its target.

For example, the molecular docking simulations demonstrated that $MeHg^+$ and $EtHg^+$ species (H_2O -HgMe, Cys-HgMe, GSH-HgMe, H_2O -HgEt, Cys-HgEt, GSH-HgEt) (Figure 9) and Hg^{2+} forms (H_2O -Hg-OH, Cys-Hg- H_2O , GSH-Hg- H_2O , Cys-Hg-Cys, Cys-Hg-GSH, GSH-Hg-GSH) (Figure 10) can access the active site of the δ -AlaD enzyme. These E^+Hg species can establish H-bonds, π - π and cation- π interactions, and the $Zn \cdots O$ and $Hg \cdots S$ coordination that helps to stabilize the Hg species in the active site of δ -AlaD. Specifically, the $Hg \cdots S$ coordination from the C124 and/or C132 residues can lead to the formation of an adduct between the enzyme and the Hg species, inhibiting the enzyme due to the denaturation of the active site, as depicted in Figure 11.

On the other hand, the docking simulation between the E^+Hg species and the CK enzyme showed that only the small molecules (E^+Hg species that do not present GSH bound to the Hg atom) can interact in the active site of the enzyme. The C283 residue could be a target for the organic mercury molecules H_2O -HgMe, H_2O -HgEt (Figure 12A), Cys-HgMe and Cys-HgEt (Figure 12B). In addition, the Hg^{2+} molecule, Cys-Hg- H_2O , also showed interactions with C283 (Figure 12C). However, the species H_2O -Hg-OH showed $S \cdots Hg$ interactions with the C146 residue (Figure 12C), indicating that this residue could be a target as well. Due to the proximity of the C283 residue to the active site of CK, the conjugation between C283 and MeHg (Figure 12D) can lead to the enzyme inhibition. The simulations with the Hg conjugated with GSH do not present $S \cdots Hg$ interactions, due to the large distance between the molecule and the cysteinyl residue from the protein (C283(S) $\cdots$ Hg distance $> 7 \text{ \AA}$) (data not shown).

As discussed above, the fate of E^+Hg species in the body will depend greatly on the exchange reactions of the type:

Taking into consideration the results of the docking presented in Figures A-D, we can deduce that the neurotoxicity of E^+Hg -S- complexes will vary depending on the size of the complexes and the reactivity/accessibility of the cysteinyl or selenocysteinyl residues involved in the reaction. Consequently, the targets of different types of $LMM-S-HgE^+$ complexes must be identified for a better understanding of Hg neurotoxicity.

Another crucial aspect that has yet to be studied in detail in animal models is the simultaneous exposure to E^+Hg forms and other potential neurotoxicants (e.g. Pb^{2+} , Al^{3+} , Sn^{2+} , PCBs, etc). This type of study is needed, because humans and animals are normally exposed to a variety of chemical agents (Grandjean and Landrigan 2006). Of particular toxicological significance, synergistic, additive or antagonistic interactions among the toxicants can occur after the simultaneous exposure to E^+Hg forms and one or more neurotoxicants. The determination of specific metabolic pathways and/or molecular targets disrupted after the simultaneous exposure to different neurotoxicants is also required,

particularly on how the binary, tertiary, quaternary, etc. combinations of toxicants can have additive or synergistic neurotoxic effects. In the next section, some examples of the interaction between mercury and other neurotoxicants in developing humans are exemplified.

4.2 Hg and other neurotoxicants: additive effect?—As reviewed in Palumbo et al (2000), hair Hg in pregnancy has been associated with mild neurological effects from 5 to 10 ppm (based on data from the Iraq MeHg⁺ poisoning), while studies of hair Hg derived from fish-eating (in New Zealand and Canada) have indicated an exposure range between 10 and 20 ppm may provoke adverse effects on the central nervous system (Palumbo et al. 2000).

Nevertheless, important longitudinal studies linking Hg-associated neurological deficits have shown inconsistent outcomes; while adverse associations were shown for Faroese children, no adverse effects have been reported for Seychelles children (Palumbo et al. 2000). Among differences between studies related to neurobehavioral-testing methods, source of exposure (whale meat and fish) and concomitant exposure to neurotoxicants may explain inconsistency between the two cohorts (Palumbo et al. 2000).

Often children-based studies examined neurobehavioral effects of one neurotoxicant at the time, when in real-life scenarios low-dose exposure to Hg occurs simultaneously with multiple co-occurring neurotoxic substances. Association between exposure to mercury and neurobehavioral outcomes requires consideration of co-exposure (to other neurotoxicants) and accompanying confounding factors. Indeed there is a body of literature that addressed combined low-level Hg (MeHg⁺ and EtHg⁺) exposures for additive and/or interactions with other environmental toxicants that can contribute to deficits in neurobehavioral test scores. Some of those studies are summarized in Tables 6 and 7.

The effects of multiple exposures during pre- and postnatal life are linked to children's neuropsychological development, but the weight of Hg as the neurotoxic causative factors will depend on the tested parameter. The results revealed a great variability in Hg exposure related to time (prenatal and postnatal) and route of exposure (injected and breastfeeding), marker of exposure (blood, hair, vaccination records), and co-occurring neurotoxicants (Al, Pb, PCBs, and unidentified sources of pollutants related to mining and smoking). In most of the studies, prenatal Hg exposure did not show a predominant neurodevelopment outcome in the first months of postnatal age.

Infants (less than six months) have the highest combined exposures of neurotoxicants. Most of the exposures originate during pregnancy and likely continue during breastfeeding. The potential for the highest body burden at this early stage is further increased by the EtHg-Al exposure after a full schedule of thimerosal-containing vaccines. Nevertheless, the measured outcomes seem to be limited (Table 6). On the basis of prenatal exposure to neurotoxicants, the additional burden of EtHg-Al (in thimerosal-containing vaccines) is a main cause of concern; the risk of insults that may change neurodevelopmental outcomes has been shown in some studies (Table 6).

Table 7 summarizes the outcomes of neurobehavioral tests in preschoolers and schoolchildren. In preschoolers, most studies did not show significant associations of Hg and deficits in test outcomes; coincidentally, the few studies showing statistically significant Hg interactions were in children living in mining environments (Marques et al. 2012; Dórea et al. 2014), or exposed to a larger suite of neurotoxic metals (Boucher et al. 2014; Freire et al. 2018). It is worth mentioning that in 30 month-old children, internalizing behavior was affected by prenatal levels of PCBs but not by Hg (Tatsuta et al. 2012); neurodevelopment measured at 42 months by the Kaufman Assessment Battery for Children showed similar results (Tatsuta et al. 2014).

Studies in schoolchildren (Table 7) and prenatal Hg exposure used different neurobehavioral tests (assessing sensory processing, speech, hearing, and socialization). Sensitivities of tests regarding motor, cognitive, and mental performance are not discussed here. However, the diversity of constitutional and environmental factors coupled to the different combinations of neurotoxicants makes it challenging to extricate the weight of the Hg toxicity. Nevertheless, the outcomes highlight the importance of the statistical models chosen. Neurophysiological outcomes related to response inhibition deficits were differently affected by cord-blood PCBs and Pb but not by Hg (Boucher et al. 2012a).

Significant association of neurodevelopmental delays with cord-blood-Hg was seen in few studies (Yorifuji et al. 2011; Boucher et al. 2012a, 2016; Tratnik et al. 2017). Prenatal exposure showed distinct domain-specific adverse effects for PCBs (impaired visual recognition memory), Hg (work memory), and Pb (slower speed of information processing) measured by the Fagan Test of Infant Intelligence and the A-not-B tests (Boucher et al. 2014). Altered fine-motor function in school children that were prenatally exposed to these neurotoxicants in traditional diets showed distinct neurological outcomes: higher current PCB levels were associated with poor Santa Ana Form Board and Finger Tapping performances; higher current Hg levels were independently associated with poor Finger Tapping (Boucher et al. 2016). Recently, Kalia et al (2017) reported a beneficial effect on Gesell Development Scores in Chinese children by reducing Polycyclic Aromatic Hydrocarbon exposure but no significant association with Hg. Indeed, several studies showed neurotoxic effects of Hg in parallel with other pollutants: Boucher et al (2012b) reported no MeHg effect *per se*, but significant interactions with lead and PCB. White et al (2011) showed that interaction of MeHg and PCB displays more Functional Magnetic Resonance Imaging in wide areas of the brain.

Children on a traditional diet that were prenatally exposed to MeHg, PCBs, and Pb showed significant associations between Attention Deficit Hyperactivity Disorder and neurotoxicants from children's own dietary sources at the time of tests (Boucher et al. 2012b). Gump et al (2017) showed distinct domain influences of low-level exposures Pb (children with higher Pb levels "exhibit higher levels of hostile distrust and oppositional defiant behaviors, were more dissatisfied and uncertain about their emotions, and had difficulties with communication") and Hg (positively associated with autism spectrum behaviors). Wang et al (2014) studied low-level MeHg exposure in school children already exposed to Pb and reported no adverse effects on several neurodevelopment tests (Rapid Sequential Movements from the Neurological Examination for Subtle Signs; Full-Scale IQ,

Broad Reading, List A Memory and Learning Slope, Attention/Executive Functions from the Neuropsychological Assessment, Adaptive Skills, and Hit Reaction Time).

In order to evaluate cognitive and psychomotor functions in older children, the results of Table 7 are organized as preschool (1–5 years) and school children (> 5 years). In preschoolers, performance tests were assessed by cognitive and psychomotor scales (Gesell Development Scores; Bayley Scales of Infant Development; Comprehensive Developmental Inventory for Infants and Toddlers; McCarthy Scales of Children's abilities; Fagan Test of Infant Intelligence; Kaufman Assessment Battery for Children), visual function (visual evoked potentials; A-not-B). Personality tests were assessed as behavioral outcomes (Child Behavior Checklist; Toddler Temperament Scale). During this intermediary stage, the weight of mercury was not outstanding; most outcomes with a significant weight of mercury happened with an unmeasured mining pollution (Table 7).

As the child develops and matures other tests measure behavioral problems (Differential Reinforcement of Low Rates; Attention-deficit hyperactivity disorder; Teacher Report Form; Disruptive Behavior Disorders Rating Scale; Neurological Examination for Subtle Signs), learning ability (Wide Range Assessment of Memory and Learning), motor performance (Santa Ana Form Board; Finger Tapping Test) and intelligence (Intelligence Quotient; Wechsler Intelligence Scale for Children-Revised) in school children. Because of the variety and specificity of tests, it is challenging to draw an outcome profile for the exposure combinations. However, it is possible to conclude that unaccounted variables can interfere positively/negatively with neurodevelopment.

Gascon et al (2017) summarized the prenatal and postnatal exposures to neurotoxicants and neuroprotective components co-occurring during childhood; they showed that depending on the study characteristic, for the individual role of Hg there was no effect or a negative effect. In their Spanish cohort, neurodevelopment was seen to be positively impacted by breastfeeding, fish consumption, and nutritional profiles. This overall positive effect of prenatal fish consumption and breastfeeding were also observed in association with students' achievement scores (Schmiedel et al. 2017).

The variation of a specific time window for exposure and comparable age of testing, along with a defined combination of neurotoxicants, makes neurobehavioral outcomes challenging to interpret. Due to environmental and constitutional confounding factors, the children's neurologic outcomes related to low-level exposures to either fish-MeHg or EtHg *per se* remain unpredicted. In most cases of multiple low-level Hg exposures with other neurotoxicants, deficits are in the normal range and are not prodromes of neurological diseases. However, the clinically unperceived or "subtle" individual neurodevelopmental deficit has societal costs that are reflected in public spending on special education resources and/or in diminished social achievements or work productivity. Economic models to estimate these costs were made for exposures to MeHg (Gaskin et al. 2015; Bellinger et al. 2016; Trasande et al. 2016) and EtHg (Geier et al. 2016, 2018b)

Concluding Remarks

Mercury is one of the most neurotoxic elements found in the environment, and exposure to E⁺Hg forms can have long-lasting behavioral consequences. Consequently, the banning of intentional exposure to E⁺Hg forms (e.g. thimerosal) should be extended to all young children (not just in rich countries). In addition, unintentional exposure to MeHg should be avoided by adopting preventive attitudes; for instance, by decreasing or eliminating the consumption of piscivorous or predatory fish during gestation and lactation. A link between exposure to low levels of mercury during human brain development and permanent behavioral disabilities remains debatable. However, a massive set of experimental data supports the deleterious neurobehavioral and neurochemical effects of low levels of exposure to Hg, strongly suggesting that E⁺Hg forms are contributing factors in neurodevelopmental diseases. Indeed, the neurochemical indications that E⁺Hg forms disrupt normal brain functioning at different subcellular and molecular levels are conclusive. For instance, E⁺Hg forms have been shown to impair the synaptic biochemistry and physiology at multiple points, which can have a causal role in neurodegenerative diseases (Poirel et al. 2018). Nevertheless, although many targets for E⁺Hg forms have been described, we know little about their primary molecular targets. As discussed above, co-exposure to mercurial and other neurotoxicants can exacerbate the neurodevelopmental effects of Hg in developing humans, but our knowledge about the molecular events that synergistically or additively exacerbate the neurotoxicity of E⁺Hg forms is still elusive. Thus, in addition to taking preventative measures to avoid Hg exposure, the development of new experimental and virtual approaches to study the molecular targets of E⁺Hg forms and other neurotoxicants will be crucial to better understand how neurotoxicants inflict permanent neurodevelopmental disabilities on humans.

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Figure 1: Natural and anthropogenic sources of Hg emission in the environment. The volcanic and erosion processes are natural sources of Hg. The process of gold extraction, the uncontrolled release of waste from industry and medical devices increase the emission/levels of Hg in the environment almost exponentially. The red dotted line represents the emission of Hg.

Figure 3 -

Low Molecular Mass (LMM-SH) complexes of cysteine and/or glutathione with electrophile forms of mercury (E^+Hg , i.e., $MeHg^+$; $EtHg^+$ or Hg^{2+}). The formation of the LMM-S- E^+Hg complexes depicted here is of crucial importance for the preferential distribution of E^+Hg forms to their target organs (Zalups 2000; Bridges and Zalups 2005, 2010, 2017; Farina et al. 2011a,b). The distribution of $EtHg^+$ -S-complexes has been rarely studied in the literature (Dórea et al. 2013).

Figure 4 –.

The fate of methylmercury (MeHg^+) from the diet and ethylmercury (thimerosal) intramuscularly injected. The methylmercury-cysteine complex is represented by $\text{Cys}_1\text{-SHgCH}_3$ and thimerosal (ethylmercury) is represented by $\text{HOOC-Ph-S-Hg-CH}_2\text{-CH}_3$. In the figure, the first complex of MeHg^+ ($\text{Cys}_1\text{-SHgCH}_3$) will enter the body and be exchanged with a second cysteine ($\text{Cys}_2\text{-SH}$) to form a new complex ($\text{Cys}_2\text{-S-Hg-R}$). Thimerosal ($\text{HOOC-Ph-S-Hg-CH}_2\text{CH}_3$, which is the complex of Ethylmercury (EtHg^+) with thiobenzoic acid (HOOC-Ph-SH)) will exchange with a free cysteine or $\text{Cys}_1\text{-SH}$ to release the free thiobenzoic acid (HOOC-Ph-SH) and the complex of ethylmercury with the $\text{Cys}_1\text{-SH}$ ($\text{Cys}_1\text{-S-Hg-CH}_2\text{CH}_3$). To simplify, both the complexes of ethyl- and methyl-mercury are represented as R-Hg-Cys in the second set of reactions (inside the $\{\}$). The reaction of either MeHg-Cys_1 or EtHg-Cys_1 complexes with different free thiols in LMM-SH ($\text{Cys}_2\text{-SH}$ or G_2SH) or HMM-SH molecules (Prt-SH or PrtSeH) will form new complexes of E^+Hg with target and non-target molecules. The symbol “ $\leftrightarrow$ ” indicates that the exchange reactions and the reactions can occur in both directions. Here it is important to emphasize that although the constant of formation of Hg-S bond is extremely high and, consequently, thermodynamically favorable, the Hg-S can rapidly exchange with another similar thiolate group (R-S^-).

Figure 5–.

The fate of Hg^{2+} from the diet, bleaching skin creams and those oxidized from Hg^0 absorbed in the lungs. After entering the body, any free Hg^{2+} will rapidly react with free thiol groups. Here the low molecular mass thiol-containing molecules (LMM-SH molecules) are represented by cysteine ($\text{Cys}_1\text{-SH}$, $\text{Cys}_2\text{-SH}$ or complexed with Hg^{2+} and other organic groups represented by $\text{G}_2\text{S-}$, Prt-S- or Prt-Se-). The complex $\text{Cys}_1\text{-S-Hg-S-Cys}_1$ can be absorbed from the intestinal tract and transported in the blood to the main target tissue (i.e., the kidney). (The molecular basis of why the kidney is the target organ of Hg^{2+} is elegantly reviewed in Zalups 2000). The reactions represented here can involve only one new thiol group (for instance, only one $\text{Cys}_2\text{-SH}$ can react with the complex $\text{Cys}_1\text{-S-Hg-S-Cys}_1$ forming $\text{Cys}_2\text{-S-Hg-S-Cys}_1$ and $\text{Cys}_1\text{-SH}$ as products and this applies to all the other thiols and complexes depicted in Figure 3.

((2-carboxyphenyl)thio)(ethyl)mercury

2-mercaptobenzoic acid

sodium ((2-carboxylatophenyl)thio)(ethyl)mercury

sodium 2-mercaptobenzoate

Figure 6 -

Thimerosal is a complex of Mercaptobenzoate with ethylmercury (Et-Hg^+) – The structures of thimerosal (either as an acid or a sodium salt) and mercaptobenzoic or salicylic acid are depicted in the figure.

Figure 7 –.

Schematic representation of accumulation of E^+Hg forms in the keratin in hair or nails. The $MeHg^+$ and $EtHg^+$ coordinate with one $-S^-$ group, whereas Hg^{2+} coordinates with two $-S^-$ groups. The deposition of mercury in hair or nails usually does not change the biological function of the altered protein, and the quantification of Hg in hair is largely used to evaluate the exposure to Hg (Marques et al. 2009; 2011, 2012; Kusanagi et al. 2018)

Figure 8 –.

MeHg⁺ or EtHg⁺ can interact with thiol-containing proteins (HMM-SH molecules) and inactivate permanently (top) or transiently (middle) the protein function. In the third type of interaction, the binding of E⁺Hg to the HMM-SH did not modify the protein function (this is somewhat similar to that represented in Figure 7, except that here the E⁺Hg will only transiently interact with the HMM-SH molecule).

Figure 9.

Interactions between the MeHg^+ and EtHg^+ species with $\delta\text{-AlaD}$. H-bonds are shown in green dotted lines, $\text{Zn}\cdots\text{O}$ and $\text{Hg}\cdots\text{S}$ interactions are in red dotted lines, and the cation- π interactions are in orange lines. Only the main residues involved in the interactions are shown. The distances are in Å and the molecular docking simulations were carried out with the Auto Dock Vina 1.1.1 program (Trott and Olson 2010) using the docking configuration according to Nogara and Rocha 2017.

Figure 10.

Interactions between the Hg^{2+} species with δ -AlaD. H-bonds are shown in green dotted lines, $\text{Zn}\cdots\text{O}$ and $\text{Hg}\cdots\text{S}$ interactions are in red dotted lines, and the cation- π interactions are in orange lines. Only the main residues involved in the interactions are shown. The distances are in Å and the molecular docking simulations were carried out with the Auto Dock Vina 1.1.1 program (Trott and Olson 2010) using the docking configuration according to Nogara and Rocha 2017.

Figure 11.

Simulation of the δ -AlaD denaturation caused by MeHg^+ (A) and Hg^{2+} (B-C). H-bonds are showed in green dotted lines and the cation- π interactions are in orange lines. Only the main residues involved in the interactions are shown. The simulation of the enzyme denaturation was done manually in the software Avogadro 1.1.1 (Hanwell et al. 2012) using the amino acid residues at 5Å of the ligands (with the C α frozen) and geometrically optimized with the universal force field (UFF) (5000 steps).

Figure 12.

Interactions between the Hg species with CK. (A) MeHg-H₂O and EtHg-H₂O interactions. (B) Cys-HgMe and Cys-HgEt interactions. (C) Cys-Hg-H₂O and [H₂O-Hg-OH]⁺ interactions. (D) Simulation of the Se-Hg bond formation. H-bonds are shown in green dotted lines, Zn²⁺⋯O and Hg⋯S interactions are in red dotted lines, and the cation-π interactions are in orange lines. Only the main residues involved in the interactions are shown. The distances are in Å. The molecular blind docking simulations were carried out with the Auto Dock Vina 1.1.1 program (Trott and Olson 2010) using the human brain-type Creatine Kinase (PDB: 3DRB) (Bong et al. 2008), with the coordinates x= -58.518, y=1.229, z=5.558, and the grid box size of 64×68×50Å, and an exhaustiveness = 100. The simulation of the enzyme S-Hg conjugation was done manually in the software Avogadro 1.1.1 (Hanwell et al 2012) using the amino acid residues at 5Å of the ligands (with the Cα frozen) and geometrically optimized with the universal force field (UFF) (5000 steps).

Table 1:

Levels of Hg in ASD patients: examples of case-control studies.

Hg levels	Sample	Country	Reference
Control: 0.30 µg/g Autism: 4.50 µg/g	Hair	Kuwait	Fido and Al-Saad 2005
Control: 0.37 µg/g Autism: 1.61 µg/g	Hair	India	Priya and Geetha 2011
Control: 2.87 µg/g Autism: 4.02 µg/g	Nail	India	Priya and Geetha 2011
Control: 0.07 µg/g Autism: 0.15 µg/g	Baby teeth	United States	Adams et al. 2007
Control: 0.25 µg/g Autism: 0.39 µg/g	Hair	Egypt	Mohamed et al. 2015
Control: 0.12 µg/g Autism: 0.79 µg/g	Hair	Egypt	El-baz et al. 2010
Control: 2.71 µg/g Autism: 3.66 µg/g	Red Blood Cells	Saudi Arabia	El-Ansary et al. 2017
Control: 13.47 µg/L Autism: 55.59 µg/L	Blood	China	Li et al. 2018
Control: 12.08 µg/L Autism: 32.90 µg/L	Blood	Egypt	Khaled et al. 2016
Control: 0.60 µg/g Autism: 7.00 µg/g	Hair	Oman	Hodgson et al. 2014

Table 2.

Formation constants of MeHg^+ or Hg^{2+} with nucleophilic centers found in biomacromolecules. The nucleophilic centers can be categorized in hard (HNu^-) or soft (SNu^-) centers. $-\text{SeH}$ is the softest of the SNu^- centers found in living cells, followed by $-\text{SH}$. The $-\text{NH}$ and $-\text{COOH}$ -containing molecules are HNu^- and the centers containing O are harder than those containing N (Hancock and Martel 1996; Martin 2002).

Functional group	MeHg^+	Hg^{2+}
R-COOH	$\approx 2.5\text{--}3.0$	$\approx 4\text{--}7$
R-(COOH)₂	---	$\approx 5\text{--}9$
R-(COOH)₃ (citrate)	---	≈ 11
R-NH₂	$\approx 7\text{--}8$	$\approx 4\text{--}5$
R-(NH₂)₂	---	≈ 11
R₂-NH	≈ 6.7	$\approx 4\text{--}5$
R-S-R	$\approx 7\text{--}8$	$\approx 6\text{--}12$
R-SH	$\approx 15\text{--}26$	$\approx 40\text{--}50$
R-SeH	$\approx 16\text{--}18$	$\approx 50\text{--}60$

The values represent the log of the constant and a high value indicates that a given complex has high thermodynamic stability. The values were obtained from Stricks and Kolthoff 1953; Rabenstein et al. 1974; Rabenstein and Fairhurst 1975; Rabenstein 1978; Jawaaid and Ingman 1981; Arnold and Canty 1983; Arnold et al. 1986; Berthon 1995; Seby et al. 2001; Anderegg et al. 2003; Mousavi 2011; Liem-Nguyem et al. 2017.

Table 3:

Examples of human thiol-containing proteins involved in the regulation of brain physiology that are targets of E⁺Hg forms. The Hg effects were based on animal models or in vitro studies. The proteins affected in rodents or in cultured cells were selected, and then the human protein information was obtained at www.uniprot.org.

Part A: ENZYMES											
Protein	Gene	N° CXXC	N° CXC	N° CC	N° C	N° aa	Function	Localization	Hg effects	Reference	
5'-nucleotidase	NT5E	1	0	0	10	574	Nucleotide-binding	Plasma membrane	Inhibition	Sood et al. 1995	
Acetylcholinesterase	ACHE	0	0	0	8	614	Neurotransmitter degradation	Plasma membrane	Inhibition	Franciscato et al. 2009; Moraes-Silva et al. 2014	
Caspase-8	CASP8	1	0	1	13	479	Apoptosis	Cytoplasm	Activation	Shenker et al. 2002	
Complex I (NADH-ubiquinone oxidoreductase 75 kDa subunit)	NDUFS1	3	0	0	18	727	Electron transport	Mitochondrion	Inhibition	Glaser et al. 2010a	
Complex II (Succinate dehydrogenase flavoprotein subunit)	SDHA	0	0	2	18	664	Electron transport	Mitochondrion	Inhibition	Glaser et al. 2010a	
Complex III (Cytochrome b-c1 complex subunit 1)	UQCRC1	0	0	0	12	480	Electron transport	Mitochondrion	Inhibition	Glaser et al. 2010a	
Complex IV (Cytochrome C oxidase subunit 1)	MT-CO1	0	0	0	1	513	Electron transport	Mitochondrion	Inhibition	Glaser et al. 2010a	
Cytochrome C	CYCS	1	0	0	2	105	Apoptosis	Mitochondrion	Release	Shenker et al. 1999; 2002	
Creatine kinase B-type	CKB	0	0	0	5	381	Transferase	Cytoplasm	Inhibition	Glaser et al. 2010b	
Creatine kinase S-type	CKMT2	0	0	0	9	419	Transferase	Mitochondrion	Inhibition	Glaser et al. 2010a	
Cystathionine gamma-lyase	CTH	2	0	0	10	405	Cysteine synthesis	Cytoplasm	Inhibition	Bridges et al. 2012	
Glutamate-cysteine ligase catalytic subunit	GCLC	0	1	1	14	637	Glutathione synthesis	Cytoplasm	Induction	Thompson et al. 1999	
Glutamine synthetase	GLUL	0	0	0	11	373	Glutamine and GABA synthesis	Mitochondrion	Inhibition	Known and Park 2003	
Glutathione reductase	GSR	0	0	0	10	522	Glutathione reduction	Mitochondrion	Activation	Stringari et al. 2008; Glaser et al. 2010a; Zemolin et al. 2012	
Glutathione S-transferase	GSTA1	0	0	0	1	222	Conjugation of reduced glutathione	Cytoplasm	Activation	Zemolin et al. 2012	

Phospholipase A2, membrane associated
PLA2G2A 0 2 2 14 144 Lipid degradation Plasma membrane Activation Mazerik et al. 2007; Verity et al. 1994;

Part B: RECEPTORS

Protein	Gene	N° CXXC	N° CXC	N° CC	N° C	N° aa	Function	Localization	Hg effects	Reference
D(1A) dopamine receptor	DRD1	0	0	1	16	446	G-protein coupled receptor	Plasma membrane, Endoplasmic reticulum membrane	Dysfunction	Daré et al. 2003
D(2) dopamine receptor	DRD2	0	1	0	12	443	G-protein coupled receptor	Plasma membrane	Dysfunction	Daré et al. 2003
D(3) dopamine receptor	DRD3	1	0	1	16	400	G-protein coupled receptor	Plasma membrane	Dysfunction	Daré et al. 2003
Gamma-aminobutyric acid receptor subunit alpha-1	GABRA1	0	0	0	5	456	Ion channel, receptor	Plasma membrane	Inhibition	Bondy and Agrawal 1980
Gamma-aminobutyric acid receptor subunit beta-1	GABRB1	0	0	1	5	474	Ion channel, receptor	Plasma membrane	Inhibition	Bondy and Agrawal 1980
Muscarinic acetylcholine receptor M3	CHRM3	1	1	0	12	590	Inhibition of adenylate cyclase	Plasma membrane	Inhibition	Abd-Elfattah and Shamoo 1981; Abdallah and Shamoo 1984
Muscarinic acetylcholine receptor M5	CHRM5	2	0	0	17	532	Inhibition of adenylate cyclase	Plasma membrane	Inhibition	Abd-Elfattah and Shamoo 1981; Abdallah and Shamoo 1984

Part C: TRANSPORTERS

Protein	Gene	N° CXXC	N° CXC	N° CC	N° C	N° aa	Function	Localization	Hg Effect	Reference
Calcium-transporting ATPase 1	ATP2B1	0	0	0	17	1,258	Calcium transport	Plasma Membrane	Inhibition	Berg and Miles 1979
Cysteine/glutamate transporter	SLC7A11	0	0	0	7	501	Amino-acid transport	Plasma Membrane	Inhibition	Allen et al. 2001; Fonfria et al. 2005

Part D: OTHER

Protein	Gene	N° CXXC	N° CXC	N° CC	N° C	N° aa	Function	Localization	Hg Effect	Reference
Kelch-like ECH-associated protein 1	KEAP1	0	1	1	27	624	Transcription regulation	Nucleus, Cytoplasm	Modulation	Yoshida et al. 2014

Nuclear factor erythroid 2-related factor 2	NFE2L2	0	0	0	6	605	DNA-binding	Nucleus, Cytoplasm	Up-regulation	Ni et al. 2010
Tubulin beta chain	TUBB	0	1	0	8	444	Nucleotide-binding, microtubule	Cytoskeleton	Oxidation	Kromidas et al. 1990

Table 4:

Examples of human selenoproteins involved in the regulation of brain physiology that can be inhibited by E⁺Hg. The Hg effects were based on animal or in vitro models. The proteins that affected rodents or in cultured cells were selected and then the human protein information was obtained at www.uniprot.org.

Protein	Gene	CXXC	CXC	CC	C	CXXU	CXU	CU	U	aa	Function	Localization	Hg effects	Reference
Glutathione peroxidase 1	GPX1	0	0	0	5	0	0	0	1	203	Oxidoreductase	Cytoplasm	Inhibition	Franco et al. 2009
Glutathione peroxidase 4	GPX4	0	0	0	9	0	0	0	1	197	Peroxidase	Mitochondrion	Inhibition	Zemolin et al. 2012
Iodothyronine deiodinase Type I	DIO1	0	0	0	4	0	1	0	1	249	Thyroid hormone synthesis	Endoplasmic reticulum	Inhibition	Pantaleão et al. 2017
Iodothyronine deiodinase Type II	DIO2	0	0	0	6	0	0	0	2	273	Thyroid hormone biosynthesis,	Plasma Membrane	Inhibition	Mori et al. 2006
Selenoprotein P	SELENOP	1	1	1	17	1	4	1	10	381	Transport of selenium	Extracellular region	Inhibition	Sasakura et al. 1998
Selenoprotein W	SELENOW	0	0	0	2	1	0	0	1	87	Antioxidant, redox-related process	Cytoplasm	Down-regulation	Kim et al. 2005
Thioredoxin reductase 1	TXNRD1	1	0	0	17	0	0	1	1	649	Oxidoreductase	Cytoplasm	Inhibition	Carvalho et al. 2008

Table 5.

Thiol groups residues found in the proteome of two mammals, human and mouse. We separated the proteins into two main types: 'sp' for UniProtKB/Swiss-Prot and 'tr' for UniProtKB/TrEMBL. This is the regular classification used in the UniProt Database.

Organism	Total Protein	Protein Type	Thiol groups			
			CXC	CXXC	CC	C
<i>Homo sapiens</i>	71,444	sp	8,573	19,038	8,486	259,182
		tr	9,574	17,146	9,036	278,316
<i>Mus musculus</i>	51,949	sp	7,290	12,629	6,277	212,172
		tr	9,407	21,372	10,107	290,020

Table 6.

Summary of studies addressing co-occurring exposures to neurotoxicants and their effects on neurobehavioral tests in infants (adapted and expanded from Dórea 2017a,b).

Neurotoxic Agents	Aim of study:	Neuro-behavioral Tests (age): Outcomes	Reference (Country)
MeHg; EtHg	To compare the effect of time Hepatitis-B shots (<24h or >24hs after birth) on neurodevelopment.	<i>Gesell Developmental Schedules (6 months)</i> : Infants immunized 2–4 days after delivery showed no significant difference in neurodevelopment compared to the group immunized within 24 h.	Marques et al. 2007 (Brazil)
MeHg; EtHg	To use Principal Component Analysis as a screening of variables linked to pre- and post-natal Hg exposure.	<i>Gesell Developmental Schedules (6 months)</i> : Principal Component Analysis discriminated variability of neurodevelopment outcomes associated with variables that included pre- and post-natal Hg exposure.	Marques et al. 2008 (Brazil)
Hg ²⁺ ; MeHg; EtHg	To evaluate the association between infant Hg and Gesell Developmental Schedules.	<i>Gesell Developmental Schedules (6, 36, 60 months)</i> : Length of lactation was positively correlated with GDS scores and hair-Hg concentrations were negatively correlated with Gesell Developmental Schedules scores.	Marques et al. 2009 (Brazil)
MeHg; EtHg	To study the neurodevelopment of infants exposed to thimerosal in tetanus-diphtheria vaccines during pregnancy.	<i>Gesell Developmental Schedules (6 months)</i> : No difference was observed.	Marques et al. 2010 (Brazil)
PCB; MeHg	To study a birth cohort to clarify the effects of PCB and MeHg on infants' neurodevelopment.	<i>Neonatal Behavioral Assessment Scale (3days)</i> : MeHg adversely affects neurobehavioral function.	Suzuki et al. 2010 (Japan)
MeHg; EtHg	To compare Hg effects on neurodevelopment of infants from one urban center and two rural villages.	<i>Gesell Developmental Schedules (6 months)</i> : A higher score of neuro-development was negatively associated with exposure to additional TCV-EtHg in urban infants.	Dórea et al. 2012 (Brazil)
PCB; MeHg; Pb	To examine the effects of prenatal exposure to PCBs, MeHg, and Pb on cognitive development infants.	<i>Fagan Test of Infant Intelligence; A-not-B test; Bayley Scales of Infant Development–2nd Edition (6.5 and 11 months)</i> : Outcomes of impairment in specific domains were different for the tested neurotoxicants; Hg was associated with poorer performance on A-not-B test.	Boucher et al. 2014 (Canada)
MeHg; EtHg; Pb; Al	To study the neurodevelopment of children living in the vicinity of tin-ore kilns and smelters and of children living in a fishing village.	<i>Bayley Scales of Infant Development–2nd Edition (6 and 24 months)</i> : Mental Development Index and Psychomotor Development Index were lower at 24 months of age for children living in the vicinity of tin-ore kilns and smelters.	Marques et al. 2014 (Brazil)
MeHg; EtHg	To study Hg exposure and neurodevelopment in children from a tin-ore open-pit mine.	<i>Bayley Scales of Infant Development–2nd Edition (6 and 24 months)</i> : There was a significant sex difference with boys showing more sensitivity related to Bayley Scales of Infant Development–2nd Edition delays and Thimerosal-containing vaccines.	Marques et al. 2015 (Brazil)
MeHg; EtHg	To study neurodevelopment of children in relation to prolonged breastfeeding and Hg exposure.	<i>Bayley Scales of Infant Development–2nd Edition (6 and 24 months)</i> : MeHg and EtHg exposure did not show a significant dose effect (related to the length of breastfeeding) on neurodevelopment among groups.	Marques et al. 2016b (Brazil)
MeHg; EtHg	To study neurodevelopment of children exposed to MeHg and EtHg.	<i>Bayley Scales of Infant Development–2nd Edition (6 and 24 months)</i> : There was a significant delay in Bayley Scales of Infant Development related to the combined exposure to Hg.	Marques et al. 2016a (Brazil)

EtHg: ethylmercury; MeHg: methylmercury; PCBs: polychlorinated biphenyls; TCV: Thimerosal-containing vaccines

Table 7.

Summary of studies addressing co-occurring exposures of neurotoxicants and their effects on neurobehavioral tests in preschooler and school-aged children. (adapted and expanded from Dórea 2017a,b).

Neurotoxic Agents	Aim of study:	Neuro-behavior Tests (age): Outcomes	Reference (Country)
PRESCHOOLERS			
PCB; MeHg	To verify the possible additive and/or interactive effects between PCB and MeHg.	<i>McCarthy Scales of Children's Abilities (38, 54 months)</i> : A significant interaction between cord blood PCBs and maternal hair Hg was found.	Stewart et al. 2003 (United States)
PCB; MeHg; Pb	To evaluate the impact of chronic exposure to PCBs and MeHg on visual brain processing.	<i>Visual Evoked Potentials (5–6 years)</i> : Exposure to MeHg and PCBs was associated with alterations of visual evoked potential responses, especially for the latency of the N75 and of the P100 components.	Saint-Amour et al. 2006 (Canada)
MeHg; EtHg	To assess the dependence on fish consumption of families and its impact on nutritional status and neurodevelopment of pre-school children.	<i>Gesell Developmental Schedules (1–59 months)</i> : Fish consumption (as hair Hg) had no impact on Gesell Developmental Schedules.	Marques et al. 2011 (Brazil)
PCB; MeHg; Pb	To assess whether PCB, MeHg, and Pb influence infants' maladaptive behavior problems.	<i>Child Behavior Checklist (30 months)</i> : Internalizing behavior was affected by prenatal exposure to low levels of PCBs. No statistically significant association with Hg or Pb.	Tatsuta et al. 2012 (Japan)
EtHg; Pb	To examine the relationship between neonatal exposure to Thimerosal-containing vaccines and child development.	<i>Bayley Scales of Infant Development–2nd Edition (12, 24 months)</i> : The overall deficit in the psychomotor development index was significantly higher in TCV group.	Mrozek-Budzyn et al. 2012 (Poland)
MeHg; EtHg; Al	To assess the effects of fish consumption and undernutrition on neurodevelopment of pre-school children.	<i>Gesell Developmental Schedules (1–59 months)</i> : Among others, hair Hg was associated with a delay in language and personal-social development.	Marques et al. 2012 (Brazil)
Hg, Mn; As; Pb	To explore the relationship between in utero exposure to environmental neurotoxic metals and neurodevelopment.	<i>Comprehensive Developmental Inventory for Infants and Toddlers (24 months)</i> : Significant adverse association with neurodevelopment only for manganese and lead.	Lin et al. 2013 (Taiwan)
MeHg; EtHg	To assess milestone achievements and neurodevelopment in toddlers associated with MeHg and EtHg exposure.	<i>Gesell Developmental Schedules (12, 59 months)</i> : Milestone achievement was delayed in toddlers from tin-ore mining communities.	Dórea et al. 2014 (Brazil)
PCB; MeHg; Pb	To study the relationships between PCB, MeHg and Pb and IQ scores.	<i>Kaufman Assessment Battery for Children (42 months)</i> : Scores were negatively affected by prenatal exposure to PCBs. No statistically significant association with Hg or Pb.	Tatsuta et al. 2014 (Japan)
PCB; Hg; Pb; Cd	To assess the neurocognitive development of children exposed in utero to environmental neurotoxicants.	<i>Bayley Scales of Infant Development–2nd Edition (24 months)</i> : Only PCB118 had a negative impact on neurocognitive development.	Brucker-Davis et al. 2015 (France)
Hg; Pb	To study the associations between prenatal and early life exposure to Hg and Pb with toddler temperament.	<i>Toddler Temperament Scale (24 months)</i> : No significant association between Pb and Hg exposure was observed in the temperament classification.	Stroustrup et al. 2016 (Mexico)
Bisphenol A; PCB; Phthalate; Mn; Hg; Pb	To evaluate the association of prenatal exposure to neurotoxicants and neurodevelopment.	<i>Bayley Scales of Infant Development–2nd Edition (12, 24 months)</i> : Maternal exposure to several xenobiotics was associated with adverse neurodevelopmental performances among the children.	Kim et al. 2017 (South Korea)
Hg, Pb; Cd	To investigate cognitive development during the first five years of life in relation to heavy metal exposure.	<i>Bayley Scales of Infant Development–2nd Edition and Wechsler Preschool and Primary Scale of Intelligence (6 to 60 m)</i> : The stability of cognitive development was unrelated to the umbilical cord level of heavy metals.	Lee et al. 2017 (South Korea)
As; Cd; Hg; Mn; Pb	To investigate the effects of prenatal co-exposure to As, Cd, Hg, Mn, and Pb on infants' cognitive and motor function.	<i>McCarthy Scales of Children's Abilities (4–5 years)</i> : Hg was associated in a dose-response manner with lower scores on the verbal function, and non-linearly related to poorer motor function and gross motor skills.	Freire et al. 2018 (Spain)

Neurotoxic Agents	Aim of study:	Neuro-behavior Tests (age): Outcomes	Reference (Country)
SCHOOL-AGED CHILDREN			
PCB; MeHg; Pb	To study performance in delayed reinforcement schedules in children exposed to environmental mixtures of PCBs, MeHg, and Pb.	<i>Differential reinforcement of low rates (9.5 years):</i> Children exposed to PCB, MeHg, and Pb demonstrated an impaired performance.	Stewart et al. 2006 (United States)
Hg; Pb; Al	Possible contribution of environmental neurotoxicants on attention-deficit hyperactivity disorder.	<i>Test battery for attention performance of children (8–12 years):</i> Evidence confirms that elements of attention-deficit hyperactivity disorder are adversely affected by low levels of Pb, but not by other neurotoxic trace metals.	Nicolescu et al. 2010 (Romania)
MeHg; Pb	To evaluate the effects of MeHg and Pb exposure on infants' neurodevelopment.	<i>Bayley Scales of Infant Development–2nd Edition (2, 5, 7 years):</i> Tested postnatal MeHg exposure levels had no adverse effects on children's IQ.	Cao et al. 2010 (United States)
MeHg; Pb	To assess the effects of prenatal Pb and MeHg exposure on cognitive deficits.	<i>Wechsler Intelligence Scale for Children (7, 14 years):</i> Some interaction terms between lead and methylmercury suggested that the combined effect of the exposures was less than additive.	Yorifuji et al. 2011 (Faroe Islands)
PCB; MeHg	To determine brain function alterations related to neurobehavior in subjects with high prenatal exposure to MeHg and PCBs.	<i>Functional Magnetic Resonance Imaging (15 years):</i> Subjects with high mixed exposure to MeHg and PCBs showed activation in more areas of the brain and different and wider patterns of activation than the low mixed exposure group.	White et al. 2011 (Faroe Islands)
PCB; MeHg; Pb	To examine the neurophysiological correlations of response inhibition deficits in children exposed to PCB, MeHg, and Pb.	<i>Go/No-go Performance (11.3 years):</i> Hg concentrations were not related to any outcome on this task but showed significant interactions with other contaminants on certain outcomes.	Boucher et al. 2012a (Canada)
PCB; MeHg; Pb	To examine the relationship of developmental exposure to MeHg, PCBs, and Pb to behavioral problems at school age.	<i>Disruptive Behavior Disorders Rating Scale (11.3 years):</i> Hg was not related to impairment in response inhibition but showed significant interactions with Pb and PCB.	Boucher et al. 2012b (Canada)
PCB; Hg; Pb	To assess the impact of exposure to contaminants on visual brain development in school-age children.	<i>Visual Evoked Potentials (10.9 years):</i> Cord blood Hg was associated with a reduction of the N75 amplitude at the highest contrast level and with a delay of the N75 latency at the 12% contrast level.	Ethier et al. 2012 (Canada)
Cigarette smoke; Hg; Pb	To assess the interactions of prenatal smoking with Pb and Hg.	<i>Teacher Report Form and the Disruptive Behavior Disorders Rating Scale (11.3 years):</i> Co-exposure to Pb and Hg do not appear to exacerbate tobacco effects.	Desrosiers et al. 2013 (Canada)
MeHg; Pb	To study the effects of low-level postnatal MeHg and Pb exposure.	<i>Rapid Sequential Movements from the Neurological Examination for Subtle Signs, Full-Scale IQ, Broad Reading, Memory and Learning Slope, Attention/Executive Functions from the Neuropsychological Assessment, Adaptive Skills, and Hit Reaction Time (7 years):</i> No detectable adverse effect on neuropsychological development due to the relatively low MeHg exposure.	Wang et al. 2014 (United States)
PCB; Hg; Organochlorine	To evaluate the effects of prenatal neurotoxicant exposures on memory and learning.	<i>Wide Range Assessment of Memory and Learning (8 years):</i> Hg was associated with decrements of Visual Memory, Learning, and Verbal Memory.	Orenstein et al. 2014 (United States)
PCB; MeHg; Pb	To verify the association of prenatal exposure to neurotoxicants and fine motor function.	<i>Santa Ana Form Board, Finger Tapping Test (11.3 years):</i> High Hg levels were independently associated with poorer Finger Tapping performance.	Boucher et al. 2016 (Canada)