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Review

The relationship between mercury and autism: A comprehensive review and discussion

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ABSTRACT

The brain pathology in autism spectrum disorders (ASD) indicates marked and ongoing inflammatory reactivity with concomitant neuronal damage. These findings are suggestive of neuronal insult as a result of external factors, rather than some type of developmental mishap. Various xenobiotics have been suggested as possible causes of this pathology. In a recent review, the top ten environmental compounds suspected of causing autism and learning disabilities were listed and they included: lead, methylmercury, polychorinated biphenyls, organophosphate pesticides, organochlorine pesticides, endocrine disruptors, automotive exhaust, polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers, and perfluorinated compounds. This current review, however, will focus specifically on mercury exposure and ASD by conducting a comprehensive literature search of original studies in humans that examine the potential relationship between mercury and ASD, categorizing, summarizing, and discussing the published research that addresses this topic. This review found 91 studies that examine the potential relationship between mercury and ASD from 1999 to February 2016. Of these studies, the vast majority (74%) suggest that mercury is a risk factor for ASD, revealing both direct and indirect effects. The preponderance of the evidence indicates that mercury exposure is causal and/or contributory in ASD.

Contents

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1. Introduction

Autism spectrum disorders (ASD) is defined by persistent deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities [1]. Although an ASD diagnosis is defined behaviorally by the American Psychiatric Association, other features, more physical or health related, are associated with an ASD diagnosis.

ASD is considered to be heritable with complex inheritance and genetic heterogeneity [2]; however, a consensus is emerging that the total fraction of ASD attributable to genetic inheritance may only be 30–40% [3]. Chromosomal microarray testing reveals that approximately 80% of children with ASD have a normal genome [4]. Of the remaining 20%, approximately half of those have various polymorphisms of unknown significance and the other half of those have de novo mutations with little or no commonality. These findings suggest that non-genetic factors have a significant role in the etiology of ASD.

In addition, many brain pathology studies indicate marked and ongoing neuroinflammation in ASD [5–14]. This type of reactive pathology is suggestive of insult and with concomitant neuronal damage [15] rather than some type of developmental mishap as has been suggested [16,17]. A developmental mishap does not explain the evidence of neuroinflammatory reactivity and neuronal damage within the brain in ASD which includes: (1) activated microglia (immune macrophages within the brain); (2) activated astrocytes (a broad class of cells that support neurons within the brain); (3) elevated levels of glial fibrillary acidic protein (GFAP; an intermediate filament protein that is expressed by astrocytes possibly to maintain structural integrity, known to be upregulated in response to injury); (4) increased oxidative stress (e.g., elevated neurotrophin-3, elevated 3-nitrotyrosine, and oxidized glutathione levels, etc.); (5) elevated levels of 8-oxo-guanosine (a product of oxidative damage to DNA); (6) elevated proinflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin 6, and granulocyte-macrophage colony-stimulating factor); (7) aberrant expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB, a protein complex that regulates transcription and reflects the cellular response to stress); and (8) neuronal cell loss [8,15,18–21]. Nor does it explain the classic regression found in autism that occurs around 15–22 months of age where these children lose previously acquired neurological function, such as language and other interactive skills and abilities [22].

Various xenobiotics have been suggested as causal agents in the pathology of ASD. In a highly-cited review, Grandjean and Landrigan [23] identified five industrial chemicals as developmental neurotoxicants based on epidemiological evidence: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. In an Environmental Health Perspectives editorial, Landrigan et al. [3] note that neurodevelopmental disabilities affect over 10% of children born in the US each year and listed the top ten environmental compounds suspected of causing autism and learning disabilities: lead, methylmercury, polychorinated biphenyls, organophosphate pesticides, organochlorine pesticides, endocrine disruptors such as phthalates, automotive exhaust, polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers (brominated flame retardants), and perfluorinated compounds. Both teams specify "methylmercury" rather than the broader class "mercury", possibly because more studies exist on the methylmercury form (found in fish), and possibly because ethylmercury (found in Thimerosal-containing vaccines) and mercury vapor (released from dental amalgams) are unpopular targets.

Of the numerous studies that have been conducted over the last three decades that examine the relationship between mercury exposure and ASD, the majority of the studies found that mercury is a risk factor for ASD. However, there are also several studies that suggest mercury is *not* a risk factor for ASD, therefore evaluating the totality of the evidence is not easy.

This review will focus on mercury exposure and ASD by conducting a comprehensive literature search of original studies in humans that examine the potential relationship between mercury and ASD from 1999 to February 2016, including studies of human tissue levels of mercury, studies of biomarkers for mercury exposure, and epidemiological studies. The literature search includes published original research studies on mercury and ASD, from PubMed and Google Scholar; however, references cited in identified publications were also searched to locate additional studies. Search words included: autism, autism spectrum disorders, ASD, pervasive developmental disorders, PDD, mercury, Hg, Thimerosal, metals, methyl-mercury, ethyl-mercury, inorganic-Hg, mercury chloride.

This review will categorize, summarize, and discuss the published research that addresses this topic. Each section of this paper will present an area of scientific inquiry on the issue and the studies which have been published on it. An associated table(s) in each section will briefly describe the pertinent studies and their findings. This review will begin with studies that examine brain biomarkers and mercury levels in children with ASD.

2. Brain biomarkers and mercury levels in children with ASD

Many studies show production of numerous auto-antibodies which react with specific brain proteins and brain tissues in children with ASD. These auto-antibodies can also act to alter the function of the respective brain tissue [24]. In addition, studies show that anti-brain antibodies are associated with more severe cognitive and behavioral profiles in children with ASD [25]. Moreover, recent studies (see Table 1) have found that certain brain auto-antibodies correlate with mercury levels in children with ASD [26,27].

This finding is biologically plausible since studies show that mercury exposure, especially to the mercury-based compound Thimerosal, can cause autoimmune dysfunction. For example, Voldani et al. [28] conducted a study that demonstrated certain dietary peptides, bacterial toxins, and xenobiotics, such as Thimerosal, can bind to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism. Havarinasab et al. [29] also found that Thimerosal can induce (in genetically susceptible mice) a systemic autoimmune syndrome.

Table 1
Studies that show brain biomarkers correlate with mercury levels in children with ASD.

Biomarker	Authors and Journal	N Age	Purpose of Study	Findings
Brain Tissue Autoantibodies (antineuronal antibodies)	Mostafa and Al-Ayadhi [26] Egypt. J. Pediatr. Allergy Immunol.	ASD 40 Controls 40 3–8 y	Serum antineuronal antibodies and blood mercury levels were estimated between autism and controls	Higher seropositivity for antineuronal antibodies and higher blood mercury in autism vs. controls. Seropositivity of antineuronal antibodies had positive association with elevated blood mercury (found in 70% of autistic children). Both markers positively associated with behavioral abnormalities, autistic regression, EEG abnormalities
Brain Tissue Autoantibodies (anti-MBP auto-antibodies)	Mostafa and Refai [27] Clin. Cell. Immunol.	ASD 50 Controls 30 5–12 y	Blood mercury levels and seropositivity of anti-MBP autoantibodies in autistic children	Serum levels of blood mercury were significantly higher in autistic children than healthy controls; increased levels of blood mercury were found in 48% of autistic patients, and 72% of autistic children had anti-MBP auto-antibodies. There was a significant positive association between the elevated levels of blood mercury and anti-MBP auto-antibodies in autistic children.
Brain Neuropeptides in Serum	Mostafa et al. [30] Metab. Brain Dis.	ASD 84 Controls 84 3–10 y	Examined pro-inflammatory neuropeptides and mercury in serum	significant and positive linear relationship between levels of serum neurokinin A and blood mercury in moderate and severe ASD, but not controls
Brain Oxidative Stress – 3-NT	Sajdel-Sulkowska et al. [31] Am. J. Biochem. Biotechnol.	ASD 9 Controls 10 5–37 y	Oxidative stress marker 3-NT, mercury, and the antioxidant selenium in autism and controls	Significant increases in the mean cerebellar levels of 3-NT and in the ratio of mercury/selenium in the brains of subjects diagnosed with autism when compared to controls; there was a significant dose-dependent positive correlation between oxidative stress markers and total mercury levels

ASD = autism spectrum disorders; anti-MBP = anti myelin basic protein; 3-NT = 3-nitrotyrosine; EEG = electroencephalogram; y = years of age.

In a recent study, Mostafa et al. [30] found a significant and positive linear relationship between levels of serum neurokinin A (a pro-inflammatory neuropeptide) and blood mercury levels in children with moderate and severe ASD, but not in healthy control children. They found that 78.3 % of the children with ASD with increased serum levels of neurokinin A had elevated blood mercury levels.

In addition, Sajdel-Sulkowska et al. [31] reported that mercury levels in the cerebellar areas of the brain correlate with the oxidative marker neurotrophin-3 (NT-3) in the brains of those with a diagnosis of ASD. In contrast, Khan et al. [32] measured brain levels of mercury and the oxidative stress marker, 3-nitrotyrosine (3-NT) in both male and female control and ASD cases, age 4–16 years. The researchers found that although 3-NT was increased in overall ASD, mercury levels measured only in the extracortical regions (brain stem and cerebellum) were not different between cases and controls (see Table 2). This finding may suggest that the same levels of mercury may promote oxidative stress only in susceptible individuals.

Pamphlett and Kum Jew [33] examined the human locus ceruleus, a region of the brain that has been implicated in ASD. They found that controls were significantly more likely to have mercury in their locus ceruleus than the individuals with ASD. It is difficult to interpret the meaning of that finding, so that study was categorized as not showing a relationship between mercury and ASD and placed in Table 2.

3. Human tissue mercury levels and ASD symptom severity

This section looks specifically at human tissue studies which examine the relationship between mercury and symptom severity in ASD. In the studies that examine blood (whole blood and red blood cells) and nails, results show that the higher the mercury levels, the worse the autism symptoms. However, hair levels are not simple to interpret. The first study showing a relationship between autism severity and hair mercury levels was published by Holmes et al. [34]. They originally hypothesized that the higher the mercury levels in the hair, the greater the autism severity (due to greater exposure). However, they found that the more severely affected the child was, the lower the hair mercury levels. When the researchers found that hair mercury levels in the children with autism were lower than controls (to be discussed more in the following section), they proposed the “poor excretor theory” suggesting that children with autism have more difficulty excreting mercury than typically developing children and are more prone to accumulate the mercury. Other studies, however, have found that the higher the hair mercury concentrations, the worse the autism symptoms [35]. In addition, evidence suggests that the time of hair growth analysis is likely important because younger children with ASD show lower

Table 2
Studies that did *not* show brain mercury levels were different in children with ASD vs. controls.

Biomarker	Authors and Journal	N Age	Purpose of Study	Findings
Brain	Khan et al. [32] J. Physiol. Pharmacol.	ASD 10 Controls 11 4–16 y	Brain mercury levels measured in extracortical regions autism vs. controls	Brain mercury levels measured in extracortical regions in children with autism vs. controls were not different
Brain- Locus ceruleus	Pamphlett and Kum Jew [33]	ASD 6 Controls 11 16–48 y	Levels on mercury in the locus ceruleus	Higher levels of mercury were found in the controls

ASD = autism spectrum disorders; y = years of age.

Table 3
Studies that show that human tissue mercury levels are associated with ASD symptom severity.

Body Tissue	Authors and Journal	N Age	Purpose of Study	Findings
Hair	Holmes et al. [34] Int J Toxicol	ASD 94 Controls 45 1–2 y	Relationship between autism and hair mercury levels	Mercury levels *inversely correlated* with symptom severity
Hair and nails	Lakshmi Priya and Geetha [35] Biol. Trace Elem. Res.	ASD 45 Controls 50 4–12 y	Lead and mercury in hair and nails autism vs. controls	The elevation was much pronounced in LFA group subjects when compared among autistic groups MFA and HFA
Hair	Elsheshtawy et al. [37] Middle East Curr. Psychiatry	ASD 32 Controls 32 Children	Investigated the relationship between autism and mercury, lead, copper, zinc	Positive correlation of CARS scores with mercury from hair samples
Hair	Geier et al. [38] Int. J. Environ. Res. Public Health	ASD 18 1–6 y	Hair toxic metal concentrations and ASD severity	Increasing hair mercury concentrations significantly correlated with increased ASD severity
Whole blood and RBC	Adams et al. [39] Biol. Trace Elem. Res.	ASD 51 Controls 40 3–15 y	Investigated toxic metals in autism and autism severity in whole blood, RBCs, and urine	Found a strong association in the degree of severity of autism for all the severity scales with mercury (whole blood and RBC)
Red Blood Cells (RBC)	Alabdali et al. [40] Behav. Brain Funct.	ASD 30 Controls 30 3–12 y	Concentration of lead and mercury were measured in red blood cells, plus GST and vitamin E	Levels of mercury GST, and vitamin E were correlated with severity of social and cognitive impairment measures

GST = glutathione-*s*-transferase; CARS = Childhood Autism Rating Scale; ASD = autism spectrum disorders; ATEC = Autism Treatment Evaluation Checklist; LFA = low functioning autism; MFA = mid functioning autism; HFA = high functioning autism; RBC = red blood cells; y = years of age.

levels of hair mercury, while older children with ASD show higher levels than their respective controls [36]. These findings suggest two competing variables: (1) susceptibility (poor excretors) and (2) exposure (higher exposure). Furthermore, these two variables may change over time, as detoxification pathways become blocked or cleared, and as exposures change, such that an absence of clear associations between tissues levels and symptoms would be unsurprising. Nonetheless, based on the studies reviewed, some trends can be observed. Table 3 lists human tissue (hair, nails, blood) studies that show a correlation between tissue mercury levels and ASD symptom severity [34,35,37–40].

No studies were found during our literature search that examined tissue mercury levels and autism severity that did not find a correlation. Thus, none are presented.

4. Body tissues studies that examine mercury levels in ASD vs. controls

This section differs from the previous section because it does not address symptom severity, but rather whether children with ASD have different levels of mercury in tissues than do control children. The majority of studies find differences in mercury levels between children with ASD and healthy controls [34–37,40–52]. These studies are presented in Table 4. However, many do not find differences [56–63]. These studies are presented in Table 5 .

Worth noting is that the studies in Table 6 which compare the mercury levels of children with ASD versus children with other neurodevelopmental disorders show no differences in mercury levels [64–66]. In many instances neurodevelopmental disorders are difficult to clearly separate, because of frequent overlap in core and associated features. This finding suggests that it is difficult to separate these children based on biomarkers and/or xenobiotic levels as well.

5. Porphyrin biomarkers of mercury body burden and ASD severity

Studies have shown that urinary porphyrins (heme precursors formed in the heme synthesis pathway) can afford a measure of xenobiotic exposure and of tissue toxic metal body-burden, particularly with respect to mercury [67–69]. Mercury toxicity has been demonstrated to be associated with elevations in urinary coproporhyrin (cP), pentacoproporphyrin (5cxP), and an atypical porphyrin, called precoprpophyrin (prcP) which is not found in the urine of unexposed controls. As such, prcP is considered to be a specific porphyrin marker for mercury exposure [67–69], and elevated urinary prcP is suggestive of mercury body burden [70]. The higher the urinary prcp levels, the higher the mercury body burden.

Six of the seven studies in this section found a relationship between the porphyrin biomarkers of mercury body burden and ASD severity (Table 7) [63,61–76]. However, one did not find a dif-

Table 4
Human Tissue Studies that Show Significantly Different Mercury Levels in ASD vs. Healthy Controls.

Body Tissue	Authors and Journal	N Age	Purpose of Study	Findings
Hair	Holmes et al. [34] Int. J. Toxicol.	ASD 94 Controls 45 1–2 y	Relationship between autism and first baby hair mercury levels	The level of mercury was significantly lower in cases 0.47 ppm versus 3.63 ppm in controls
Hair and nails	Lakshmi Priya and Geetha [35] Biol. Trace Elem. Res.	ASD 45 Controls 50 4–12 y	Lead and mercury in hair and nails autism vs. controls	Significant elevation in the levels of mercury in both hair and nail samples in autism vs. controls
Hair	Majewska et al. [36] Acta Neurobiol Exp	ASD 91 Controls 75 3–9 y	Levels of hair mercury in autism vs. controls	Autistic children significantly differed from healthy peers in the concentrations of mercury in hair
Hair	Elsheshtawy et al. [37] Middle East Curr. Psychiatry	ASD 32 Controls 32 3–4 y	Investigated the relationship between autism and mercury, lead, copper, zinc	The level of mercury was significantly lower in cases (0.55 ± 0.06 μg/mg) than in controls (3.2 ± 0.2 μg/mg)
Hair	Mohamed et al. [41] Behav. Neurol.	ASD 100 Controls 100 2–15 y	Assess the levels and possible environmental risk factors from metals	Hair mercury levels were higher in children with ASD than controls
Hair	Tabatadze et al. [42] Georgia Med. News	ASD 30 Controls 30 4–5 y	Evaluation levels of essential trace elements and heavy metals in ASD vs. controls	High contamination to mercury in ASD children compared to controls
Hair	Adams et al. [43] Toxicol. Environ. Chem.	ASD 78 Controls 31 Born between 1988 and 99	First baby haircuts evaluated for mercury and ASD	Children with lower levels of mercury in hair were 2.5 times more likely to have ASD
Hair	DeSoto and Hitlan [44] J. Child Neurol.	ASD 82 Controls 55 ASD mean 7.2 y Controls mean 7.8 y	Examine mercury levels in hair and blood	Significant relation does exist between the blood levels of mercury and ASD with ASD having higher blood mercury levels
Hair	Blaurock-Busch et al., [45] Maedica (Buchar)	ASD 44 3–9 y	Assessed the levels of ten toxic metals and essential elements in hair samples of children with autism	Elevated hair concentrations were noted for mercury in autism vs. controls
Hair	Hodgson et al. [46] Exp. Biol. Med. (Maywood)	ASD 27 Controls 27 ASD mean 5.3 y Controls mean 5.5 y	Investigated hair mercury levels in autism and controls	Mercury levels were markedly elevated in the hair of autistic subjects vs. control subjects
Hair	Obrenovich et al. [47] Biol. Trace Elem. Res.	ASD 22 Controls 39 <6 y	Hair toxic metals in autism vs. controls	Significant alteration in deposition of several heavy metal species, including mercury in hair samples between the groups
Hair	Al-Ayadhi 2005 [48] Neurosciences (Riyadh)	ASD 77 Controls 77 <14 y	Hair metals in autism vs. controls	Higher levels of mercury in ASD vs. controls
Hair	Fido and Al-Saad [49] Autism	ASD 40 Controls 40 4–8 y	Toxic metals in the hair of children with autism vs. controls	Children with autism had significantly ($p < 0.001$) higher in-hair concentration levels of lead, mercury and uranium.
Blood and hair	Yassa [50] Environ. Toxicol. Pharmacol.	ASD 45 Controls 45 2–10 y	Blood and hair samples from 45 children from Upper Egypt with autism vs. controls	High level of mercury and lead among those kids with autism, with significant decline in the blood level of lead and mercury with the use of DMSA as a chelating agent
Red Blood Cells (RBC)	Alabdali et al. [40] Behav. Brain. Funct.	ASD 20 Controls 20 3–15 y	Concentration of lead and mercury were measured in red blood cells, plus GST and vitamin E	ASD had significantly higher lead and mercury levels and lower GST activity and vitamin E concentrations compared to controls
RBC	Geier et al. [51] Acta Neurobiol. Exp. (Wars)	ASD 83 Controls 89 ASD mean 7.3 y Controls mean 11.4 y	Mercury levels in children with ASD vs. controls	Mean mercury levels were 1.9-fold significantly increased in ASD (21.4 microg/L) vs. controls (11.4 microg/L).
Blood (plasma)	El-Ansary [52] Data in Brief	ASD 20 Controls 20 3–15 y	Mercury levels	Blood mercury levels were higher in ASD
Urine	Bradstreet et al. [53] J. Am. Phys. Surg.	ASD 221 Controls 18 3–16	Children with ASD and controls treated with multiple doses of DMSA	Children with ASD excreted six-fold greater mercury than controls in their urine
Urine	Blaurock-Busch et al. [54] Maedica (Buchar)	ASD 44 Controls 146 3–9 y	Exposure to mercury and other heavy metals in children with autism spectrum disorders versus controls	Statistically significant differences in the mean urine levels of mercury
Baby Teeth	Adams et al. J. Toxicol. Environ. Health A [55]	ASD 15 Controls 11 4–9 y	Level of mercury, lead, and zinc in baby teeth in autism vs. controls	Children with autism had significantly (2.1-fold) higher levels of mercury

RBC+ red blood cells; GST = glutathione-s-transferase; DMSA = 2, 3-dimercaptosuccinic acid; y = years of age.

Table 5
Body tissue studies that did *not* find significantly different mercury levels in ASD vs. healthy controls.

Type of Study	Authors and Journal	N Age	Purpose of Study	Findings
Hair	De Palma et al. [56] J. Aut. Dev. Disord.	ASD 44 Controls 61 Children	Hair toxic metals in autism vs. controls	Found no association between autism and hair mercury
Hair and blood	Ip et al. [57] J. Child. Neurol.	ASD 82 Controls 55 ASD mean 7.2 y Controls mean 7.8 y	Hair and blood mercury levels and autism	No difference in the mean mercury levels
Blood	Hertz-Picciotto et al. [58] Environ. Health Perspect.	ASD 452 2–5 y	Blood mercury levels in autism vs. controls	After accounting for dietary and other differences in mercury exposures, total mercury in blood not statistically different
Blood	Yau et al. [59] Environ. Res.	ASD 84 Controls 159 <1 y	Prenatal and early-life exposures to mercury	Total mercury in serum collected from mothers during mid-pregnancy and newborn bloodspots were not significantly associated with ASD
Blood	Rahbar et al. [60] Neurotox. Res.	ASD 109 Controls 109 2–8 y	Investigate the association between blood mercury concentrations in control children and ASDs	Did not find a significant difference (P = 0.61) between blood mercury concentrations and ASDs
Blood/toxicokinetic model	McKean et al. [61] Environ. Health	ASD 164 DD 35 Controls 58 Mother infant pairs 274 <1 y	Using methyl-mercury concentration estimates from toxicokinetic model, methyl-mercury exposure estimated in autism, DD, and controls	Cumulative methyl-mercury exposure does not appear to detectably elevate the risk of autism or developmental delay
Urine	Soden et al. [62] Clin. Toxicol. (Phila)	ASD 15 Controls 4 3–7 y	24-h provoked urine excretion test for heavy metals in children with autism	Excess chelatable body burden of As, Cd, Pb, or mercury is zero
Urine	Woods et al. [63] Environ. Health Perspect.	ASD 64 PDD 19 Controls 114 2–12 y	Mean mercury levels were evaluated between autism, PDD, and NT	No differences were found between NT and autism in urinary mercury levels or in past mercury exposure

DD = developmental delay; NT = neurotypical; PDD = pervasive developmental disorder; As = arsenic; Cd = cadmium; Pb = lead; y = years of age.

Table 6
Body Tissue Studies that did *not* Find Significantly Different Mercury Levels in ASD vs. Children with Neurological Disorders, Neuropsychiatric Disorders, or Learning Disabilities.

Type of Study	Authors and Journal	N Age	Purpose of Study	Findings
Blood	Macedoni-Lukšič et al. [64] Biol. Trace Elem. Res.	ASD 52 Other neurologic disorders 22 1–16 y	Levels of metals in blood aluminum, lead, mercury in ASD compared to children with neurological disorders	No significant difference in blood levels of metals between the groups was found
Blood, urine and hair	Albizzati et al. [65] Przegl. Epidemiol.	ASD 17 Neuropsychiatric disorders 17 6–16 y	Metals in blood, urine and hair samples from children with autism and children with neuropsychiatric disorders, unspecified	No difference was found between children with autism and children with neuropsychiatric disorders, unspecified
Urine	Wright et al. [66] PloS One	ASD 56 Siblings 42 Controls 121 Delayed 34 5–16 y	Urinary mercury levels between children with ASD and controls- normal and with learning disabilities	No statistically significant differences were found between children with ASD and controls

ASD = autism spectrum disorders; y = years of age.

ference between the ASD cases and controls or a relationship with ASD severity (see Table 8) [77].

6. Human tissue studies that show an increased susceptibility to mercury (or "pro-oxidant environmental toxins") in ASD

Earlier in Section 2, the issue of susceptibility to mercury in ASD was mentioned. Many studies suggest that children with ASD represent a population vulnerable to the adverse effects of mercury [78]. This section covers studies which examine susceptibility to mercury in ASD, listed in Table 9 . These studies use a variety of tissues, including brain tissue, lymphoblastoid cell lines (LCLs), and blood samples [52,79–92]. A major focus is the transmethylation/transsulfuration concentrations, which are consistently found to be abnormal in ASD [52,78,81–88,90]. Several of these studies suggest that children with ASD have limited thiol availability and decreased glutathione (GSH) reserve capacity, resulting in a compromised detoxification capacity and increased oxidative stress [52,78,81–88,90].

Table 7
Studies that Show that Mercury Body Burden Biomarkers Correlate with ASD Severity.

Biomarker	Authors and Journal	N Age	Purpose of Study	Findings
Heme Synthesis Pathway Metabolite (precoproporphyrin)	Nataf et al. [71] Toxicol. Appl. Pharmacol.	ASD 106 Controls 163 2–15 y	Examined urinary porphyrin levels in children with neurodevelopmental disorders	The atypical molecule precoproporphyrin, a specific indicator of heavy metal toxicity, was also elevated in autistic disorder but not significantly in Asperger's
Heme Synthesis Pathway Metabolite (coproporphyrins)	Geier and Geier [72] Neurotox. Res.	ASD 37 7–22 y	Examined urinary porphyrin pattern indicative of mercury toxicity	An apparent dose-response effect was observed between autism severity and increased urinary coproporphyrins
Heme Synthesis Pathway Metabolites (pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin)	Geier et al. [73] J. Neurol. Sci.	ASD 26 2–13 y	Urinary porphyrins and transsulfuration metabolites in ASD were examined	Mercury intoxication-associated urinary porphyrins were significantly correlated with increasing CARS scores and GSSG levels.
Heme Synthesis Pathway Metabolites (coproporphyrins)	Geier et al. [74] J. Toxicol. Environ. Health A	ASD 71 Controls 14 ASD 3–22 y Controls 3–59 y	Evaluated relationship between ASD severity and urinary porphyrins	Participants with severe ASD had significantly increased cP I, cP III, and total cP levels in comparison to participants with mild ASD. A significant correlation was observed between increasing cP levels and CARS scores.
Heme Synthesis Pathway Metabolites (pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin)	Kern et al. [75] Biometals	ASD 24 2–13 y	Urinary porphyrins and specific domains of the ATEC	The results of the study indicated that the overalll ATEC scores and each of the ATEC subscales (Speech/Language, Sociability, Sensory/Cognitive Awareness, Health/Physical/Behavior) were linearly related to urinary porphyrins associated with mercury toxicity.
Heme Synthesis Pathway Metabolite (pentacarboxyl (penta) and coproporphyrins)	Heyer et al. [76] Autism Res.	ASD 30 PDD 14 Controls 32 2–12 y	Evaluated penta and coproporphyrins as biological indicators of ASD, PDD-NOS, neurotypical (NT) controls	ASD and PDD childrenhad higher mean urinary penta and copro-porphyrin concentrations compared with same-aged NT children. Combined Z-score measure had 33% and 21% sensitivity for autism and PDD-NOS, respectively, with 100% specificity.
Heme Synthesis Pathway Metabolite pentacarboxyl-, precopro- and copro-porphyrins	Woods et al. [63] Environ. Health Perspect.	ASD 100 PDD 27 Controls 117 2–12 y	Mean porphyrin and mercury levels were evaluated between autism, PDD and NT	Elevated copro-, hexacarboxyl- and pentacarboxyl- porphyrin concentrations were associated with autism but not PDD-NOS.

cP = coproporphyrin; cP I = coproporphyrin I; cP III = coproporphyrin III; penta = pentacarboxyl ASD = autism spectrum disorders; ATEC = Autism Treatment Evaluation Checklist; GSSG = oxidized glutathione; NT = neurotypical; PDD-NOS = pervasive developmental disorder −not otherwise specified; y = years of age.

Table 8
Studies that did *not* Show that Mercury Body Burden Biomarkers Correlate with ASD Severity.

Biomarker	Authors and Journal	N Age	Purpose of Study	Findings
Heme Synthesis Pathway Metabolite	Shandley et al. [77] Autism Res.	ASD 70 Siblings 36 Controls 54 2–6 y	Investigated whether porphyrin profiles can reliably be used to (a) differentiate ASD cases from healthy controls; and (b) predict ASD severity	Analyses did *not* to find support for the hypotheses that porphyrin levels could be used as a valid tool to detect ASD cases or predict severity

ASD = autism spectrum disorders; y = years of age.

Four of these studies are on brain tissue, showing increased susceptibility to toxic substances in the brains of subjects with ASD. Most of these studies show susceptibility to mercury because they show a suboptimal detoxification capacity, however, some of the studies show direct evidence of increased mercury damage in individuals with autism as compared to controls [79–81,89].

7. Epidemiological studies that examine Thimerosal in vaccines as a risk factor for ASD

One of the most controversial areas of study is the epidemiological investigation of mercury in Thimerosal – containing vaccines (TCVs) as a risk factor for ASD. The controversial nature of these studies is reflected by the fact that most of the studies that are conducted *without* public health and/or industry support arrive

Table 9
Tissue Studies that Examine Susceptibility to Mercury (or "pro-oxidant environmental toxins") in ASD.

Body Tissue/Substance	Authors and Journal	N Age	Purpose of Study	Findings
LCLs	Rose et al. [79] J. Toxicol.	ASD 16 Controls 16 ASD 5–13 y Controls 5–37 y	Human LCL in autism vs. controls exposed to TM	Autism LCLs exhibited greater reduction in ATP-linked respiration, maximal respiratory capacity, and reserve capacity, compared to control LCLs exposed to TM
LCLs	Rose et al. [80] Transl. Psychiatry	ASD 22 Controls 14 ASD mean 7.8 y Controls mean 27.7 y	Human LCL in autism and mitochondrial reserve capacity	Depletion of reserve capacity making them more vulnerable to pro-oxidant environmental toxins
LCLs	James et al. [81] FASEB J.	ASD 10 Controls 10 ASD mean 7.8 y Controls mean 27.7 y	LCLs derived from autistic children and controls, effects of TM on and GSH levels	TM resulted in greater decrease in GSH/GSSG ratio and increase in free radical generation in autism vs. control cells
Brain	Rose et al. [82] Transl. Psychiatry	ASD 15 Controls 15 ASD 4–39 y Controls 4–36 y	Examined cerebellum and temporal cortex (Brodmann area 22 (BA22))	GSH was significantly decreased in both the cerebellum and BA22 in autism vs. controls; decreased GSH/GSSG redox/antioxidant capacity and increased oxidative stress in the autism brain
Cerebellum and temporal cortex	Chauhan et al. [83] Neurochem. Res.	ASD 10 Controls 10 4–39 y	Compared GSH redox status in postmortem brain samples from cerebellum and frontal, temporal, parietal and occipital cortex of subjects with ASD vs. controls	Levels of reduced GSH were significantly decreased in autism compared to controls: redox ratio of GSH to GSSG was also significantly decreased
Cerebellum	Gu et al. [84] Free Radic. Biol. Med.	ASD 10 Controls 10 ASD mean 11.1 y Controls mean 11.3 y	Activities of GSH-related enzymes in the cerebellum tissues from autism and controls	GPx, GST, GR, and GCL activity were significantly decreased in autism compared to that of the control group.
Plasma	Frye et al. [85] Transl. Psychiatry	ASD 18 Controls 18 ASD mean 8.5 y Controls mean 8.8 y	Plasma markers of oxidative stress and measures of cognitive and language development and ASD behavior	ASD groups demonstrated lower fGSH and fGSH/GSSG
Plasma	Geier et al. [86] J. Neurol. Sci.	ASD 28 2–16 y	Examined plasma transsulfuration metabolites	Decreased plasma levels of reduced glutathione (GSH), cysteine, and sulfate were observed among study participants relative to controls
Plasma	James et al. [87] Am. J. Clin. Nutr.	ASD 40 Controls 42 2–7 y	Plasma concentrations of transmethylation/transsulfuration metabolites and glutathione redox status in autistic children	Transmethylation/transsulfuration pathway concentrations in autistic children were significantly different from values in the control; and decreased glutathione redox status in autism vs. controls
Plasma	James et al. [88] Am. J. Med. Genet. B Neuropsychiatr. Genet.	ASD 80 Controls 73 3–14 y	Plasma concentrations of transmethylation/transsulfuration metabolites and glutathione redox status in autistic children	Plasma levels of cysteine, glutathione, and the ratio of reduced to oxidized glutathione, an indication of antioxidant capacity and redox homeostasis, were significantly decreased
B-lymphocytes	Sharpe et al. [89] J. Toxicol.	ASD 4 Controls 4 5–13 y	TM exposure in B-lymphocytes taken from individuals with autism, their nonautistic twins, and their nontwin siblings	Exposure to TM resulted in four of the families showed thimerosal hypersensitivity, whereas none of the control individuals displayed this response
Peripheral blood mononuclear cells	Rose et al. [90] Autism Res. Treat.	ASD 43 Controls 41 3–10 y	Quantified the intracellular glutathione redox couple (GSH/GSSG) in resting peripheral blood mononuclear cells	Both glutathione and cysteine redox ratios were decreased in autistic compared to control children
Human serum albumin	Vojdani et al. [91] Int. J. Immunopathol. Pharmacol.	ASD 50 Controls 50 3–14 y	Measured IgG, IgM and IgA antibodies against CD26, CD69, streptokinase, gliadin and casein peptides and against ethyl mercury bound to human serum albumin in autism	TM binds to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism
Blood RNA, Gene Expression	Stamova et al. [92] Neurotox. Res.	ASD 33 Controls 51 2–5 y	Correlations between gene expression and mercury levels in blood of boys with and without autism	Findings suggest different genetic transcriptional programs associated with mercury levels in autism compared to controls
Blood (plasma)	El-Ansary [52] Data in Brief	ASD 20 Controls 20 3–15 y	Levels of GSH/GSSG	Blood GSH levels were lower in ASD

LCL = lymphoblastoid cell lines; TM = Thimerosal; GSH = reduced glutathione; fGSH = reduced free glutathione; GSSG = oxidized glutathione; GPx = glutathione peroxidase; GST = glutathione-S-transferase; GR = glutathione reductase; GCL = glutamate cysteine ligase; y = years of age.

Table 10
Epidemiological studies that show thimerosal in vaccines is a risk factor for ASD.

Type of Study/Source of Exposure	Authors and Journal	Database Age or Time Frame	Purpose of Study	Findings
Epidemiology TCVs	Gallagher and Goodman [93] J. Toxicol. Environ. Health A	NHIS database 3–17 y	Examine NHIS 1997–2002, boys 3–17 years old, born before 1999 and exposure to TM	U.S. male neonates vaccinated with the hepatitis B vaccine prior to 1999 (from vaccination record) had a threefold higher risk for parental report of autism diagnosis compared to boys not vaccinated as neonates during that same time period
Epidemiology TCVs	Gallagher and Goodman [94] Toxicol. Environ. Chem.	NHANES database 1–9 y	Examine National Health and Nutrition Examination Survey 1999–2000, children aged 1–9 years	Boys given Thimerosal (Hep B) more susceptible to developmental disability than unvaccinated boys
Epidemiology TCVs	Young et al. [95] J. Neurosci.	VSD database Birth to 13 months	Ecological study of TM containing vaccines and risk of NDs	Increased risk of an ASD diagnosis with TCVs
Epidemiology TCVs	Geier and Geier [96] J. Toxicol. Environ. Health A	VAERS database 1994–1998	Dose (50 vs. 25 micrograms) of mercury from TM in VAERS	Increased odds ratios for autism with higher doses of TM
Epidemiology TCVs	Geier and Geier [97] Med. Sci. Monit.	VAERS database 1997–2001 VSD database 1992–1997	Association between TCVs DTaP comparison to TM-free DTaP and autism in VAERS and VSD	Exposure to mercury from TCVs administered in the US was a consistent significant risk factor for autism
Epidemiology TCVs	Geier and Geier [98] Pediatr. Rehabil.	VAERS database USDE 2001	Dose of TCVs and autism in VAERS and USDE data	Dose-response curves showed increases in odds ratios of NDs (autism) from both VAERS and USDE closely linearly correlated with increasing doses of TM-containing childhood vaccines
Epidemiology TCVs	Geier and Geier [99] Exp. Biol. Med.	VAERS database 1992–2000	TM-DTaP and NDs in VAERS	An association was found between TM-DTaP and autism
Epidemiology TCVs	Geier and Geier [100] Med. Sci. Monitor.	BSS-CDC database USDE CDC yearly live birth estimates	Mercury doses from TCVs on population prevalence of autism	Evidence showing a direct relationship between increasing doses of mercury from TCVs and autism
Epidemiology TCVs	Geier et al. [101] Biol. Trace Elem. Res.	VSD database PDD 534 PDD mean 4.1 y	Relationship between Thimerosal-containing Hib and the risk for PDD	Evidence supporting TCVs as a risk factor for PDD
Epidemiology TCVs	Geier et al. [102] IJERPH	VSD database 1991–2000	NDs/PDD and Thimerosal dose	Evidence supporting TCVs as a risk factor for NDs/PDD that is dose dependent
Epidemiology TCVs	Geier et al. [104] Transl. Neurodegener.	VAERS database 1998–2000 VSD database 1991–1999	Risk of ASD following TCVs	Evidence supporting TCVs as a risk factor for ASD
Epidemiology TCVs	Geier et al. [104] J. Biochem. Pharmacol. Res.	VAERS database 1997–1999 2004–2006	Risk of NDs following Thimerosal-preserved DTaP	Evidence supporting TCVs as a risk factor for NDs/PDD

HepB = Hepatitis B vaccine; TCVs = Thimerosal containing vaccines; ASD = autism spectrum disorders; PDD = pervasive developmental disorders; ND = neurodevelopmental disorder; TM = Thimerosal; DTaP = Diphtheria, Tetanus, acellular Pertussis; HepB = Hepatitis B vaccine; Hib = Haemophilus influenzae Type b; RhoGAM = Rho (D) Immune Globulin; VAERS = Vaccine Adverse Events Reporting System; VSD = Vaccine Safety Datalink; USDE = US Department of Education; TCVs = Thimerosal-containing vaccines; EPA = Environmental Protection Agency; RBC = red blood cells; DD = developmental disability; NHANES = National Health and Nutrition Examination; NHIS = National Health Interview Survey; BSS-CDC = Biological Surveillance Summaries of the Centers for Disease Control; y = years of age.

at conclusions that stand in sharp contrast to most of the studies conducted or supported by public health entities and/or industry. Table 10 presents studies which find Thimerosal in vaccines to be a significant risk factor for ASD [93–104]. Table 11 presents studies which find Thimerosal in vaccines is *not* a significant risk factor for ASD [105–112].

It should be mentioned, that Thimerosal was included in this review even though the mercury in Thimerosal is part of a compound: sodium ethyl-mercury thiosalicylate. This is because Thimerosal is 49.55% mercury by weight and rapidly decomposes in aqueous saline solutions into ethyl-mercury hydroxide and ethyl-mercury chloride. Thimerosal is estimated to contribute to about half of the mercury exposure of infants [113]. Thimerosal is still used in many vaccines to date, particularly in developing countries [78].

It should also be mentioned that a review of the potential relationship between Thimerosal and ASD by Schultz [114] did not include studies that used the VAERS database. Schultz stated that the VAERS system is a passive reporting system to which anyone can report and thus is a bias dataset. However, VAERS-based studies were included in this review because the Centers for Disease Control (CDC) states that the reports of possible vaccine-associated events to the VAERS are submitted by informed and conscientious healthcare professionals and that despite the limitations of spontaneous reports, the VAERS database provides vital information of clinical importance. The VAERS Working Group of the CDC and the Food and Drug Administration (FDA) have published epidemiologic studies based upon the VAERS [115].

8. Epidemiological studies that examine mercury in RhoGam as a risk factor for ASD

Rho(D) immune globulin (Trade names include RhoGAM) is given to a woman to prevent the formation of antibodies to Rh

Table 11
Epidemiology Studies that did *not* Find a Relationship between Thimerosal in Vaccines is a Risk Factor for ASD.

Type of Study Source of Exposure	Authors and Journal	Database Age or Time Frame	Purpose of Study	Findings
Epidemiology TCVs	Verstraeten et al. [105] Pediatrics	VSD database 1991–1998	Assessed the possible toxicity of TCVs among infants	No analyses found significant increased risks for autism
Epidemiology TCVs	Madsen et al. [106] Pediatrics	Danish Psychiatric Central Research Register 2–10 y	TCVs in Denmark and incidence of autism	Data do not support a correlation between TCVs and autism
Epidemiology TCVs	Stehr-Green et al. [107] Am. J. Pre. Med.	US – Special Education Services Sweden – National database Denmark- National registry Mid 1980s – mid 1990s	TCVs and autism	No correlation between TCVs and autism
Epidemiology TCVs	Hviid et al. [108] JAMA	Danish National registry 1990–1996	To determine whether vaccination with a TM-containing vaccine is associated with autism	Results do not support a causal relationship between TCVs and ASD
Epidemiology TCVs	Andrews et al. [109] Pediatrics	United Kingdom National registry 1988–1997	Relationship between the amount of TM an infant receives via DTP or DT vaccine and NDs (autism)	No evidence of an association with TM exposure
Epidemiology TCVs	Price et al. [110] Pediatrics	VSD 1994–1999 ASD 256 Controls 752 6–13 y	TCVs and autism	No findings of increased risk for any of the three ASD outcomes
Epidemiology TCVs	Schechter and Grether [111] Arch. Gen. Psychiatry	California Department of Developmental Services 1995–2007	Autism prevalence in California after removal of TM from most childhood vaccines	Data do not support the hypothesis that exposure to TCVs during childhood is a primary cause of autism
Epidemiology TCVs	Mrozek-Budzyn et al. [112] Przegl. Epidemiol.	Medical Records ASD 96 Controls 193 Children	To determine an association of TCVs exposure with the risk of autism	No evidence of an association between TCVs and autism

TCVs = Thimerosal containing vaccines; ASD = autism spectrum disorders; ND = neurodevelopmental disorder; TM = Thimerosal; DTaP = Diphtheria, Tetanus, acellular Pertussis; VSD = Vaccine Safety Datalink; y = years of age.

Table 12
Epidemiological Studies that Show Thimerosal in RhoGam is a Risk Factor for ASD.

Type of Study Source of Exposure	Authors and Journal	N Age or Time Frame	Purpose of Study	Findings
Epidemiology RhoGAM	Geier et al. [116] Neuro Endocrin. Lett.	NDs 298 Controls 124 Controls 2021 1980–2001 Controls 2002+	Maternal Rh-negativity/TM-containing RhoGAM	Increases in maternal Rh-negativity among children with NDs, autism spectrum disorders, and attention-deficit-disorder/attention-deficit-hyperactivity-disorder
Epidemiology RhoGAM	Geier and Geier [117] J. Matern. Fetal. Neonatal. Med.	ASD 53 Controls 926 ASD 1987–2001 Controls 1980–1989	Maternal Rh-negativity/TM-containing RhoGAM	Significant dose-response relationship between the severity of the regressive ASDs and total mercury dose children received from RhoGAM

RhoGAM = Rho (D) Immune Globulin; NDs = neurodevelopmental disorders.

Table 13
Epidemiological Studies that did *not* Show Thimerosal in RhoGam is a Risk Factor for ASD.

Type of Study Source of Exposure	Authors and Journal	N Age or Time Frame	Purpose of Study	Findings
Epidemiology RhoGam	Miles and Takahashi [118] Am. J. Med. Genet. A	ASD 214 Children diagnosed between1995-2005	Association between Rh status, RhoGam use in pregnancy and autism	No association was found between maternal RhoGam use and autism

RhoGAM = Rho (D) Immune Globulin.

positive blood. It is an injection given at around 28 weeks of pregnancy to Rh negative mothers. For many years RhoGam was preserved with Thimerosal. Three epidemiological studies have been conducted to examine the safety of Rhogam preserved with Thimerosal. Two studies (Table 12) conducted by independent investigators, found Thimerosal in RhoGam to be a risk factor for ASD [116,117]. The third study (Table 13), sponsored by the RhoGam manufacturer, Johnson and Johnson, Inc., did *not* find Thimerosal in RhoGam to be a risk factor for ASD [113]. In 2001, Thimerosal was removed from Rh immune globulin [118].

Table 14
Epidemiological Studies that Show Mercury in Air Pollution is a Risk Factor for ASD.

Type of Study Source of Exposure.	Authors and Journal	N Age or Time Frame	Purpose of Study	Findings
Epidemiology Prenatal Mercury Exposure	Zhang and Wong [119] Environ. Int.	Total mercury emission based on the data of 1999 in China	Examined mercury exposure increases in China	Evidence suggests an increase in autism related to increasing mercury exposure
Epidemiology Coal-burning power plants	Palmer et al. [120] Health Place	Texas Education Department 2000–2001 EPA- Toxic Release Inventory 2004 4 million children enrolled in grades K through 12	Mercury release, special education rates, and autism disorder	Association between environmentally released mercury and special education rates were fully mediated by increased autism rates.
Epidemiology Coal-burning power plants	Palmer et al. [121] Health Place	EPA-Toxic Release Inventory 1998	Proximity to mercury release and autism prevalence	Association between proximaty of released mercury and autism
Epidemiology Coal burning power plants	Blanchard et al. [122] Rev. Environ. Health	US EPA National Scale Air Toxins Assessment 2002 Texas Education Association	Occurrence of autism related to distribution of mercury in ambient air	Risk of autism is greater in the geographic areas of higher levels of ambient mercury
Epidemiology Industrial facilities releasing arsenic, lead or mercury into air	Dickerson et al. [123] Sci. Total Environ.	US EPA- Toxics Release Inventory1991-1999 ADDM 2000–2008	ASD prevalence and proximity to industrial facilities releasing arsenic, lead or mercury	Association between urban residential proximity to industrial facilities emitting air pollutants and higher ASD prevalence
Epidemiology Air Pollution	Windham et al. [124] Environ. Health Perspect.	HAP concentrations 1996 ASD 284 Controls 657 Born in 1994	ASD and environmental exposures, ambient air, San Francisco Bay	Increased risk of ASD associations included mercury, cadmium, nickel, trichloroethylene, and vinyl chloride
Epidemiology Air Pollution	Roberts et al. [125] Environ. Health Perspect.	US EPA Nurse's Health Study II ASD 325 Controls 22,101	Associations between U.S. EPA – levels of hazardous air pollutants at time and place of birth and ASD	Overall measure of metals were significantly associated with ASD, with odds ratios ranging from 1.5 (for overall metals measure) to 2.0 (for diesel and mercury)

EPA = Environmental Protection Agency; ASD = autism spectrum disorders; ADDM = Autism and Developmental Disabilities Monitoring; HAP = hazardous air pollutant.

Table 15
Epidemiological studies that did *not* show mercury in air pollution is a risk factor for ASD.

Type of Study Source of Exposure	Authors and Journal	N Age or Time Frame	Purpose of Study	Findings
Epidemiology Coal	Lewandowski et al. [126] J. Toxicol. Environ. Health A	Texas Toxic Release Inventory School District Autism Prevalence 2001–2007	Mercury exposure from coal-fired power plants and autism in Texas	Analysis suggests mercury emissions not consistently associated with autism prevalence in Texas school districts

Table 16
Epidemiological studies that show mercury from other sources is a risk factor for ASD.

Type of Study Source of Exposure	Authors and Journal	N Age or Time Frame	Purpose of Study	Findings
Epidemiology mercury dental amalgams	Geier et al. [128] Acta Neurobiol. Exp. (Wars)	ASD 100 7–13 y	Maternal dental amalgams during pregnancy and risk of autism	Subjects with > or = 6 amalgams were 3.2-fold significantly more likely to be diagnosed with autism (severe) in comparison to ASD (mild) than subjects with < or = 5 amalgams.
Epidemiology General/Pink Disease	Shandley and Austin [129] J. Toxicol. Environ. Health	Australian Pink Disease Support Group 2009	Tested the hypothesis that individuals with a known hypersensitivity to mercury (pink disease survivors) may be more likely to have descendants with an ASD	Prevalence rate of ASD among the grandchildren of pink disease survivors (1 in 22) to be significantly higher than the comparable general population prevalence rate (1 in 160).

ASD = autism spectrum disorders; y = years of age.

9. Epidemiological studies that examine mercury in the air as a risk factor for ASD

Several studies suggest that mercury in air pollution is a risk factor for ASD, as shown in Table 14 [119–125]. The Palmer et al. study [120] which found an association between mercury release and ASD rates was partially replicated by Lewandowski et al. [126]; however, Lewandowski and colleagues concluded that mercury emissions were not consistently associated with autism prevalence in Texas school districts, thus their study was placed in the category of not finding a relationship between mercury and ASD (Table 15). Overall, a 2014 meta-analysis of the evidence of the impact of pre-

natal and early infancy mercury exposures on autism risk found a significant association between increasing environmental mercury exposures and an increasing ASD risk (odds ratio = 1.66, 95% confidence interval = 1.14–2.17) [127]. It was observed that this effect remained similar after excluding studies not adjusted for confounders . Table 16 presents studies that show mercury from other sources is a risk factor for ASD.

10. Epidemiological studies that examine mercury from other sources as a risk factor for ASD

Geier et al. [128] found that maternal mercury fillings during pregnancy were a risk factor for ASD. Austin and Shandley [129] hypothesized and found that descendents of pink disease (mercury poisoning) survivors would have a higher rate of ASD. In contrast, however, van Wijngaarden et al. [130] found no relationship between prenatal methyl-mercury exposure and ASD phenotypic behaviors (Table 17).

11. Discussion

As mentioned in the Introduction, numerous studies have been conducted over the last three decades that examine the relationship between mercury and ASD. This comprehensive search for human studies that examined the potential relationship between mercury and ASD found 91 studies between 1999 to February 2016. The findings from the vast majority (74%) of those studies suggest that mercury is a risk factor for ASD. These studies reveal both direct and indirect effects of mercury exposure. How these effects may interact in ASD is summarized in Fig. 1. Fig. 1 illustrates mercury effects on the brain in ASD as suggested by the research, showing both causal and correlative findings. The figure shows, starting from the top, that mercury causes (purple arrows) autoimmune activation, oxidative stress, neuroinflammation, neuronal damage, and loss of neuronal connectivity. These are direct effects from mercury exposure. In the next line from the top, the figure shows that autoimmune activation, oxidative stress, neuroinflammation can then also cause (purple arrows) neuronal damage and loss of neuronal connectivity. These are indirect effects from mercury exposure. The lower part of the figure shows the relevant correlations (green arrows), such as autism symptom severity correlates with neuronal damage and neuronal loss of connectivity. In addition, autism symptom severity also correlates with mercury levels, which, in turn, correlate with autoimmune activation, oxidative stress levels, and neuroinflammatory biomarkers.

11.1. Mercurial compounds and toxicity

Mercury exists in three forms: elemental mercury (e.g., vapor from dental amalgams), inorganic mercury compounds (e.g., mercuric chloride), and organic mercury compounds (e.g., methyl and ethyl mercury). According to the US Environmental Protection Agency, all forms of mercury are quite toxic [131]. Organic compounds generally exert stronger cytotoxic effects as compared to inorganic mercury [132]. Methyl mercury can be formed by the reaction of metallic mercury with organic molecules. Bacteria can facilitate the formation of methyl mercury. An example of methyl mercury poisoning is the Minamata tragedy where fish were contaminated with methyl mercury from the dumping of mercury-tainted waste into water in Minamata, Japan. Exposed newborns showed delayed neurodevelopmental toxicity [133]. Ethyl mercury, which is used in Thimerosal (ethyl mercury thiosalicylate) and as a fungicide, is man-made. An example of ethyl mercury poisoning is the 1960 Iraq ethyl mercury tragedy where many families suffered illness and death from eating grains treated with ethyl mercury [134].

Exposure to ethyl mercury is said to be safer than exposure to methyl mercury because the blood half-life of intramuscular ethyl mercury from Thimerosal in vaccines in infants has been found to be substantially shorter than that of oral methyl mercury in adults [135]. However, it is important to note that mercury from Thimerosal is found in the brain and kidney and that even when mercury levels are decreased in the blood, the mercury levels have been found to be unchanged in the brain [136]. It is also important to note that once the mercury from Thimerosal enters the brain, some of it remains in the form of ethyl mercury, and some is found as methyl mercury and inorganic mercury. As stated by Rodrigues et al. [137], of the total mercury found in the brain after Thimerosal exposure, 63% is in the form of inorganic mercury, 13.5% is ethyl mercury, and 23.7% is methyl mercury. They further stated that mercury in the tissues and blood following Thimerosal treatment is predominantly found as inorganic mercury, but a considerable amount of ethyl mercury is also found in the liver and brain.

Thimerosal is sometimes referred to as an adjuvant, a substance (as one added to a vaccine) that enhances the immune response to an antigen [138]. More commonly, however, it is considered a preservative, while aluminum salts are considered the most common adjuvant [139]. Both Thimerosal and aluminum are considered xenobiotics and toxic, with Thimerosal being the more toxic of the two [140]. In the US Thimerosal is still in over 50% of the flu vaccines which are recommended for infants, children, and pregnant women. It is also in tetanus and in one version of the multidose meningococcal vaccine in the US. In the developing countries around the world Thimerosal is still present in many of the childhood vaccines [141].

11.2. Other neurotoxicants

Evidence suggests other possible causal or contributory exposures, such as lead [35], organophosphate insecticides [142], phthalates [143], glyphosates [144], and pyrethroids [145]. Exposure to these other suggested xenobiotic exposures may also be causal and/or contributory in ASD; however, some research suggests that their level of exposure and contribution may conceivably be less than mercury [146]. Future studies could include further analysis of the attributable risk from neurotoxins.

11.3. Brain pathology and susceptibility

As mentioned in the Introduction, the brain pathology in ASD indicates marked and ongoing inflammatory reactivity with concomitant neuronal damage. When brain inflammation is sustained, as is seen in ASD, there is loss of neuronal connectivity, which is also seen in ASD. It is conceivable that all of the suggested neurotoxicants are able to bring about loss of connectivity through direct insult as well as by activating a neuroinflammatory process from which collateral damage is likely.

When the brain pathology in ASD is examined, it matches the brain pathology found in mercury intoxication [18]. Kern et al. [18] describe 20 different brain pathologies found in both ASD and mercury intoxication. Lead and organophosphates have also been shown to be capable of producing some of the same pathology [147], although not as similar as that produced by mercury [18]. It is also important to mention that toxicants can work synergistically by depleting the sulfur dependent detoxification system, and glutathione reserves in particular.

Many neurotoxicants, and particularly mercury, are sequestered or detoxified by cellular thiols (organo-sulfur compound that contains a carbon-bonded sulfhydryl (—C—SH or R—SH) group, such as glutathione) and thiol availability is known to be limited in ASD

Table 17
Epidemiological studies that did *not* show mercury from other sources is a risk factor for ASD.

Type of Study Source of Exposure	Authors and Journal	N Age or Time Frame	Purpose of Study	Findings
Epidemiology Maternal	van Wijngaarden et al. [130] Epidemiology	Seychelles Child Development Study 1986–1990	Evaluated the association between prenatal methylmercury exposure and ASD phenotype	Prenatal exposure to methylmercury was not associated with ASD phenotypic behaviors

ASD = autism spectrum disorders.

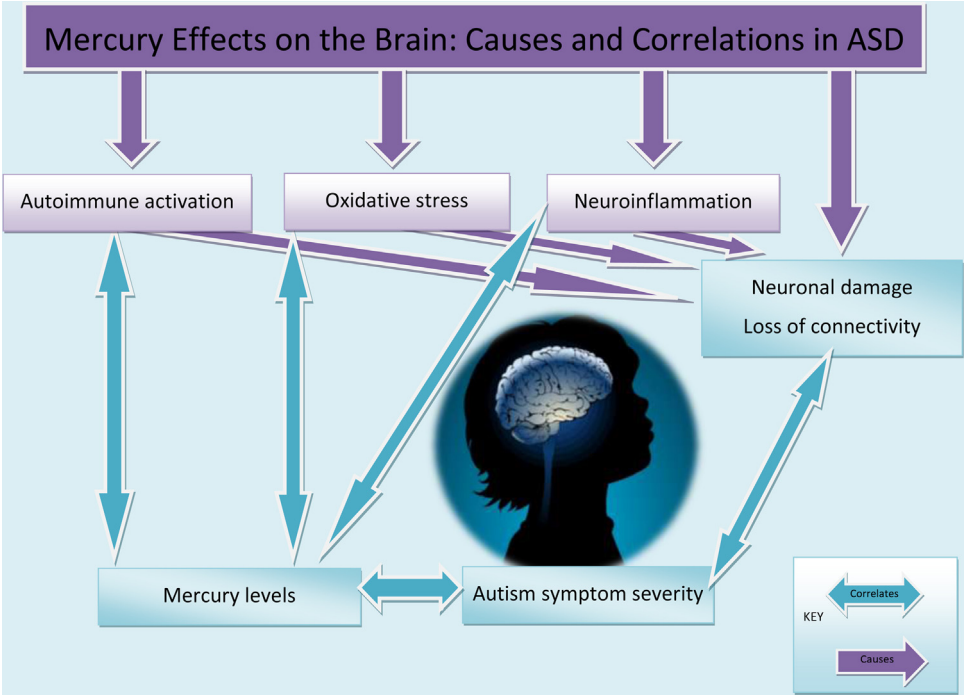

Fig. 1. This figure illustrates mercury effects on the brain in ASD suggested by the research, both causal and correlative findings.

making this population of individuals more susceptible to toxicants. For example, Chauhan et al. [83] reported that in cerebellum and temporal cortex samples from subjects with ASD, glutathione levels were significantly decreased. Several other studies show that children diagnosed with an ASD have abnormal sulfation chemistry, limited thiol availability, and decreased glutathione (GSH) reserve capacity, with a resulting and subsequent compromised oxidation/reduction (redox) and detoxification capacity [81,87,88] and a concomitant vulnerability to brain insult [78].

11.4. Neurodevelopmental disorders in general

The findings from this collection and review of the literature on the relationship between ASD and mercury may have broader implications. ASD has increased over the past three decades, but so have other neurodevelopmental disorders [148–156]. Some examples are as follows: In the 1980s, 1 child in 1000 developed autism, and by 2013, 1 child in 45 developed autism [149–152]. In 1976, 1 child in 30 was learning disabled, while by 2013, 1 child in 6 was learning disabled [148,149]. In 1996, 1 in 18 children developed attention deficit/hyperactivity disorder (ADHD), and by 2012, 1 in 8 children developed ADHD, an increase of about 75 percent [153]. The rate among children three to four years old with an ADHD diagnosis has almost doubled since 1997 [153]. Tic disorder, once considered rare, is now considered to be the most common movement disorder, with 0.2-46.3% of school children experiencing tics during his/her lifetime [154]. Similarly, obsessive compulsive disorder, also once considered rare, now affects at least 1 in 50–100 children depending on the estimates [155]. The needs and numbers of emotionally disturbed youth are also growing such that by 2004, about 1 in 11 children are were diagnosed with emotional disturbances [156]. Overall, as of 2011, 1 in 6 children in the United States had a neurodevelopmental disorder, which also represents a dramatic increase in the last few decades [147,149].

11.5. Governmental policies and neurodevelopmental disorders in general

It appears that lack of governmental intervention and regulation may be a contributing factor to the epidemic of neurodevelopmental disorders. Limited government action has taken place in regard to reducing prenatal and postnatal exposure to mercury and other neurotoxicants resulting in an ever increasingly toxic environment, possibly due to conflict-of-interest issues and conflict between areas of government. For example, the 2008 Obama/Biden Plan for a Healthy America included the reduction of toxicants such as mercury, stating that, "*More than five million women of childbearing age have high levels of toxic mercury in their blood, and approximately 630,000 newborns are born at risk every year*." However, in January 2012 when the US Food and Drug Administration (FDA) drafted a rule prohibiting the use of mercury-based dental fillings in pregnant women, nursing mothers, children aged less than 6 years of age, and other sensitive groups, the United States Department of

Health & Human Services (HHS), under President Obama, failed to release it [157,158]. As a consequence nothing was accomplished.

12. Conclusion

The research that examines the relationship between mercury and ASD is extensive. One of the purposes of this review of the scientific literature was to bring together and organize the plethora of studies to make it easier for researchers to examine and interpret the evidence. It is a compilation of every original study with any investigation of ASD and any potential exposure to mercury from any source, at any time point, in the human population. In order to limit the introduction of any bias, the authors of this review did not analyze each study, evaluate bias or study quality, or discuss similarities and difference between the studies.

From this inventory of the available research, it is clear that the vast majority of the research, conducted by multiple research groups, from many different countries, using many different methodologies, supports a link between mercury exposure and a diagnosis of ASD. In this evaluation, it was found that 74% of studies support a link between mercury exposure and ASD, which corroborates a previous evaluation of the same issue conducted in 2010. In that study, Desoto and Hitlan also found that 74% of studies support a link between mercury exposure and ASD [159]. This agreement in science six years later is compelling and supports the validity of the finding.

The compilation of the evidence indicates that children with ASD are more susceptible to mercury than typically developing children, and that is reflected in significantly different levels of mercury, or biomarkers indicative of mercury, in the brain, blood, urine, baby teeth, hair, and nails. In addition, many of these studies have found that the mercury, or biomarkers indicative of mercury, correlate with symptom severity such that the higher the mercury levels the worse the autism symptom severity. The majority of the epidemiological research also support the hypothesis that mercury is a risk factor for ASD. Based on the preponderance of the evidence, mercury exposure is causal and/or contributory in ASD. With the increase in neurodevelopmental disorders in general, and especially ASD, the evidence suggests that governmental/public policy changes are urgently needed.

Author contributions

Dr. Kern and Mr. Geier conceptualized the design of the study. Dr. Kern wrote the majority of the initial draft of the paper. Mr. Geier, Reverend Sykes, Dr. Haley, and Dr. Geier critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of interest

The authors have been involved in vaccine/biologic litigation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jtemb.2016.06.002.

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