SUPERIOR COURT OF THE STATE OF CALIFORNIA
COUNTY OF LOS ANGELES

NC, a minor

Plaintiff,

v.

Hain Celestial Group, Inc.; Beech-Nut Nutrition Company; Nurture, Inc.; Plum, PBC, d.b.a. Plum Organics; Gerber Products Company; Walmart, Inc.; Sprout Foods, Inc.; Ralphs Grocery Company; and DOES 1 through 100 inclusive

Defendants.

Case No. 21STCV22822
Judge: Hon. Amy D. Hogue

Department: 7

EXPERT REPORT OF DR. MICHAEL ASCHNER, PH.D. IN SUPPORT OF GENERAL CAUSATION

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I. RELEVANT QUALIFICATIONS AND EXPERIENCE

I received my PhD from the Department of Anatomy and Neurobiology at the University of Rochester, School of Medicine and Dentistry, Rochester, NY in 1985. I pursued an academic career, and I presently serve (2013-) as the Harold and Muriel Block Endowed Chair and Professor of Molecular Pharmacology; Professor of Neuroscience, Professor of Pediatrics; Investigator, Rose F. Kennedy Intellectual and Developmental Disabilities Research Center; Member, Nathan Shock Center of Excellence in the Basic Biology of Aging at the Albert Einstein College of Medicine, Bronx, NY.

My Ph.D. focused on potential neurotoxic effects of methylmercury (MeHg). Upon completion of my Ph.D. program, I served as a post-doctoral fellow at the University of Rochester School of Medicine and Dentistry, Rochester, NY (1985-1987).

Following completion of this fellowship, I served as an Assistant Professor in the Department of Pharmacology and Toxicology at the Albany Medical College, Albany NY. During my tenure there (1988-1994), I was promoted to an Associate Professor. I then moved to the Bowman Gray School of Medicine, Wake Forest University school of Medicine, Winston Salem, NC, where I served as an Associate (1994-1999) and Full Professor (1999-2004) with Tenure in the Department of Physiology and Pharmacology.

From 2004-2013, I served as the Gray E. B. Stahlman Endowed Chair in Neuroscience, and Professor, Departments of Pediatrics and Pharmacology, as well as Senior Scientist at the Kennedy Center for Research on Human Development, Member of the Vanderbilt Brain Institute, Vanderbilt University Medical Center, Nashville, TN. From 2005-2013, I served as the Director of Division of Pediatric Toxicology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN.

In addition to my tenured professorship at Albert Einstein College of Medicine (2013-present), as of 2015, I am a Member of the Institute for Exposomic Research at the Icahn School of Medicine at Mount Sinai, New York, NY, and as of 2017, I serve as Adjunct Professor and NIEHS P30 Center Member in the Department of Environmental Medicine & Public Health,

Lautenberg Laboratory for Environmental Health, Icahn School of Medicine at Mount Sinai, New York, NY.

As of 2018, I am a European Registered Toxicologist (ERT). The European Register of Toxicologists constitutes a list of high-profile toxicologists that meet criteria defined at a European level: high standards of education, skills, experience, and professional standing, and comply with the requirements defined by EUROTOX and National Societies of Toxicology.

My research interest is on the interaction between genetics and the environment in triggering brain diseases both during central nervous system development and senescence. As such, in addition to toxicology, I have experience interpreting epidemiological studies during the regular course of my research.

I have extensive experience in both *in vivo* and *in vitro* models of blood-brain barrier and neurotoxicity and mechanisms of neurodegeneration. Experimental work in my laboratory uses a number of animal models (*C. elegans*, tissue culture and rodents), and they are designed to:

- increase the understanding of the genetic influences on health, especially as it relates to neurological diseases;
- increase knowledge of the pathway involved in neurotoxicity as well as the impact of these processes on neurodegeneration;
- develop improved research models for environmental sciences and biology; and
- use environmental toxicants to understand basic mechanisms of neurobiology.

My main research work has been continuously funded by the National Institute of Environmental Health Science (NIEHS), National Institutes of Health (NIH) with one grant (R01) in its 29th consecutive year, and the other in its 20th consecutive year.

I have trained numerous pre- and post-doctoral students, have served on multiple PhD thesis committees, and was the Director of both a NIEHS Center in Molecular Toxicology (P30) and a pre-doctoral and postdoctoral NIEHS Training Grant in Molecular Toxicology (T32) during my tenure at Vanderbilt University Medical Center. I have been recognized for teaching, having received the Vanderbilt University Medical Center Annual Postdoctoral Mentor of the

Year Award in 2008. I have also received in 2012 an honorary Ph.D. from the 4th Military Hospital in Xi'an, China.

I am the past president of the International Neurotoxicology Association (2001), and past president of the International Society for Trace Element Research in Humans (2015). I was honored to receive the Society of Toxicology (SOT) highest possible peer recognition, the Merit Award (2011), as well as the Career Achievement Award from the Metal Specialty Section (2016), and the Distinguished Neurotoxicologist Award from the Neurotoxicology Specialty Section (2020). I have served as the President of the Academy of Toxicological Sciences (2019-2020), and was recently elected as Vice-President-Elect of the Society of Toxicology (2020), an approximately 8,000-member society, a professional and scholarly organization of scientists from academic institutions, government, and industry representing the great variety of scientists who practice toxicology in the US and abroad.

I am also a Fellow of the American Academy for the Advancement of Science (AAAS). AAAS. *Fellows* are a distinguished cadre of *scientists*, engineers and innovators who have been recognized for their achievements across disciplines, from research, teaching, and technology to administration in academia, industry and government, to excellence in communicating and interpreting *science* to the public.

I have served, and in some cases chaired, numerous national and international committees, including with National Institutes of Health (NIH), US Environmental Protection Agency (EPA), Agency for Toxic Substances and Disease Registry (ATSDR) a branch of The Center for Disease Control (CDC), and Department of Defense (DoD), and Health Canada, to name a few, and I presently serve on the European Food Safety Authority (EFSA) panel committee tasked to address the tolerable upper intake level (UL) for manganese (Mn).

I presently chair the External Advisory Board of the National Center for Toxicological Research (NCTR; Jefferson, AR), a US Food and Drug Administration (FDA) Center. I have served on both National Academy of Science (NAS) and the Institute of Medicine (IOM) Committees, evaluating health effects associated with exposures experienced during the Gulf

War, health effects of copper in drinking water, the safety of anthrax vaccine, and submarine evacuation action levels (SEALS), to name a few. As of 2021, I am also a Member of the Board of the Federation of American Societies for Experimental Biology (FASEB), an umbrella organization of 30 scientific member societies, representing more than 130,000 researchers from around the world, with a mission to "advance health and well-being by promoting research and education in biological and biomedical sciences through collaborative advocacy and service to our societies and their members."

I have served on numerous peer-review editorial boards, such as Neurochemistry Research, Food and Chemical Toxicology, Toxicological Sciences, BMC Pharmacology and Toxicology, Toxicology Reports, Toxics, and Frontiers in Toxicogenomics, Neurotoxicology (to name a few), and have reviewed hundreds of manuscripts for a variety of peer-reviewed journals. I am currently also the Co-Editor of Advances in Neurotoxicology.

As a neurotoxicologist, I specialize in the assessment of adverse effects of pharmaceuticals, non-therapeutic chemicals, and other potential toxins on humans, with emphasis on their neurological outcomes. During the course of my career, I have had the unique opportunity to have evaluated, consulted on with physicians, and researched the effects of chemicals on the nervous system.

In addition to teaching, I have been active in the research arena throughout my career, focusing on the adverse effects of, or poisoning by, environmental or other toxins. I have authored 837 peer-reviewed publications (listed in PubMed), approximately 120 book chapters, and hundreds of abstracts, and co-edited several books related to Neurotoxicology. One noteworthy book chapter is in the most authoritative toxicology book, **Casarett and Doull's Toxicology: The Basic Science of Poisons, Eighth Edition**, where I have co-authored the chapter on Neurotoxicology.

Based on Google Scholar (https://scholar.google.com/citations?user=XnUMcGcAAAAJ), I have been cited more than 48,900 times and my h-index is 103 (a metric for evaluating the cumulative impact of an author's scholarly output and performance; a h-index of 103 implies that

103 of my peer-reviewed manuscripts have been cited a minimum of 103 times).

As listed in my *Curriculum vitae* (see attached), I have lectured extensively, both nationally and internationally, on topics in the field of neurotoxicology, including neurodevelopmental toxicology.

A more detailed recitation of my experience and professional qualifications can be found in my *Curriculum vitae* (see attached).

II. PRIOR EXPERT TESTIMONY AND COMPENSATION

In the last four years I have provided expert testimony in the following case: *Hoffmann, et al., v. Syngenta Crop Protection, LLC, et al.* (Circuit Court, Twentieth Judicial Circuit St. Clair County, Illinois, No. 7-L-517). I am being compensated for my time at a rate of $750/hr.

III. CHARGE

I have been asked to provide my opinions regarding whether early life exposure to lead, arsenic, and mercury can cause ASD, and whether early life exposure to lead can cause ADHD. This report contains a summary of my analysis and conclusions. I reserve the right to amend this report and the analysis and/or conclusions herein in light of new information, the opinions of defendants' expert witnesses, or any other reason. I also reserve the right add new opinions regarding the relationship of baby foods that contain lead, arsenic, and mercury and their ability to cause ASD, and baby foods that contain lead and their ability to cause ADHD once this case proceeds to a stage where I will have access to information specific to the foods at issue. Finally, I also reserve the right to use demonstratives and other visual material – including animations – at any evidentiary hearing or trial in support of my opinions and testimony.

IV. SUMMARY OF OPINIONS

I have reviewed and analyzed the toxicological and epidemiological evidence relevant to the question of whether the heavy metals lead, mercury, and arsenic can cause autism spectrum disorder (ASD) and whether lead can cause attention deficit hyperactivity disorder (ADHD).

Following my review and analysis of the data, drawing on my experience and expertise

as a scientist, and applying the principles of toxicology, I have formed the following primary scientific opinions:

1. To a reasonable degree of scientific certainty, arsenic, mercury, and lead are well-established neurotoxins, capable of inflicting permanent brain damage, especially in younger children. There are well-established mechanisms for each of these metals to not only pass through the blood-brain barrier, but to cause significant and permanent disruption to the neuropathways in the human brain. These mechanisms of action are even more acute in the developing brain of a young child.
2. To a reasonable degree of scientific certainty, exposure to arsenic, mercury and lead can cause ASD in children. This conclusion is supported by a wealth epidemiological data and the toxicological profile of these heavy metals.
3. To a reasonable degree of scientific certainty, exposure to lead can cause ADHD in children. This conclusion is supported by a wealth epidemiological data and toxicological profile of this heavy metal.
4. To a reasonable degree of scientific certainty, exposure to arsenic, mercury and lead causes ASD through biologically plausible mechanisms. This conclusion is supported by a wealth epidemiological data and toxicological profile of these heavy metals.
5. To a reasonable degree of scientific certainty, exposure to lead, causes ADHD through biologically plausible mechanisms. This conclusion is supported by a wealth of epidemiological data and toxicological profile of this heavy metal.
6. To a reasonable degree of scientific certainty, exposures to metal mixtures of these metals will lead to the additive and synergistic effects of the metals, given that they share common toxicological modes-of-action. Thus, neurotoxicity of these metals as mixtures will increase the cumulative risk of neurological dysfunction.

V. BACKGROUND ON TOXICOLOGICAL METHODS

As a toxicologist, I periodically must apply basic scientific principles to the assessment of whether a medication or other substance (natural or anthropogenic) is capable of causing a particular adverse health outcome in humans. Before a causal relationship between an exposure and a particular outcome can be inferred, there must first be reliable scientific evidence of an association between exposure at the dose of concern and the particular outcome of interest. In the presence of an established association between a relevant dose and outcome, discussion of a biological mechanism becomes sequitur.

A. THE DOSE MAKES THE POISON

A classic toxicology maxim is embodied in the phrase "the dose makes the poison" credited to Paracelsus (1494-1541), a Swiss physician, alchemist, and philosopher of the German Renaissance. The essence of this principle is the recognition that every chemical substance, including those that are vital to the sustenance of life (even water and oxygen) and those that we come in contact with on a daily basis, can be toxic – "All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison." For every substance, dose differentiates between a benign (or even beneficial) effect and a potentially toxic effect.

What makes any substance toxic, benign, or beneficial is the dose of the substance delivered at the site of action. We cannot assume a linear dose-response relationship: effects seen at high doses often do not occur at lower doses. Indeed, many substances have a threshold dose, below which no harmful effects are seen, but above which a linear dose-response relationship exists.

For example, low to moderate doses of (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid—better known as ibuprofen, or by trade names Advil®, Midol®, or Motrin®—are used to treat moderate pain, fever, inflammation, menstrual cramps, and various types of arthritis, to name a few. However, high doses and/or overuse of ibuprofen can be toxic, potentially damaging the digestive system, interfering with hormone homeostasis, and increase the risk of heart attacks and stroke (Ershad, 2020). At exceedingly high exposure dose, ibuprofen can even lead to death.

Other commonly consumed substances that have starkly different dose responses include Tylenol, aspirin, and cough syrup.

Another example is botulinum toxin, one of the most poisonous biological substances known that is produced by the bacterium *Clostridium botulinum*. The lethal dose for a person by the oral route is estimated at 30 ng, by the inhalational route at 0.80 to 0.90 µg, and by the intravenous route at 0.09 to 0.15 µg. Botulinum interferes with neural transmission by blocking the release of acetylcholine, the principal neurotransmitter at the neuromuscular junction, causing muscle paralysis (Nigam and Nigam, 2010; Tighe and Schiavo, 2013). As such, at low doses it has been highly efficacious in management of a wide variety of medical conditions, especially strabismus and focal dystonias, hemifacial spasm, and various spastic movement disorders, headaches, hypersalivation, hyperhidrosis, and some chronic conditions that respond only partially to medical treatment. It is therefore always necessary to consider the dose in evaluating whether a substance, essential or non-essential for biological functions, is capable of inducing adverse health effects.

In addition to dose, the toxicity of any substance will depend on the particular chemical form of the substance, the route of exposure, and the age/developmental stage of the target organ at the time of the exposure. Critically, a toxicologist must also consider the timing and duration of exposure, as this will impact not just the magnitude of the effect, but also the mechanism. This concept is referred to in toxicology as chronic vs. acute dosing. For example, consuming a liter of vodka over the course of several weeks has a different effect on the human body than consuming a liter of vodka over the course of an hour. Intoxication and other short–term (acute) effects of alcohol are caused largely by temporary, reversible changes in specific receptors and associated molecules. With repeated (chronic) alcohol exposure, long–lasting changes occur in receptors and in the series of chemical interactions they signal. Drinking too much chronically, in turn, can cause chronic physical and mental health issues and contribute to liver damage, cardiovascular disease, and multiple types of cancer (Shield et al., 2013; Seitz, et al., 2018).

I have given careful consideration to these fundamental toxicological principles in

arriving at my conclusions in the case at hand.

B. METHODOLOGY

To evaluate the question on the relationship between exposure to heavy metals, specifically, arsenic, lead and mercury, and brain dysfunction in the form of ASD or ADHD, I reviewed the relevant scientific literature, including animal studies and epidemiological papers. I have searched articles on PubMed with keywords such as: mercury, lead, arsenic, neurodevelopment, brain, and neurotoxicity. The PubMed database as an engine for the search of relevant literature is commonly employed by toxicologists in assessing causality.

For the animal studies, I have carefully evaluated the quality of the studies by addressing statistical methods, appropriateness of dose, soundness of outcome measures, and the use of adequate laboratory practices. With respect to the epidemiological studies, I considered the benefits and limitations of observational epidemiology in general, as well as the strengths and weaknesses of specific epidemiological studies prior to arriving at my conclusions.

As noted in the Reference Manual for Scientific Evidence (3rd Edn), "*both epidemiology and toxicology have much to offer* in elucidating the causal relationship between chemical exposure and disease. These sciences often go hand in hand with assessments of the risks of chemical exposure, without artificial distinctions being drawn between them." Reference Manual at 657-68 (emphasis added). Indeed, as noted below, I have reviewed and considered the epidemiology relevant to my toxicological analysis to ensure coherence in my opinions. As the Reference Manual notes: "the two disciplines complement each other, particularly when the approaches are iterative." Reference Manual at 660. This is routinely done by toxicologists in my field in making causality determinations. However, I am not an epidemiologist, and have not elected to use the Bradford Hill factors to assess causality. My focus, as outlined in this report, is on the "scientific information regarding the increased risk of contracting a disease at any given dose" and whether the toxicological evidence "contributes to the weight of evidence supporting causal inferences by explaining how a [the heavy metal at issue] causes a specific

disease through describing metabolic, cellular, and other physiological effects of exposure." Reference Manual at 637.

In reaching my conclusions, I have relied on the principles I have discussed above, and the expertise I have accumulated in studying the neurotoxicity of heavy metals and other xenobiotics over >35 years of my career, which has involved the interpretation of both toxicological and epidemiological data.

C. CONSIDERATIONS IN ASSESSING EXPERIMENTAL ANIMAL STUDIES

A summary of the neurological effects of arsenic, mercury and lead in experimental animal studies can be found in extensive reviews by the Agency of Toxic Substances and Disease Registry (ATSDR, 1999, ATSDR, 2007, ATSDR 2020). These studies clearly establish that arsenic, mercury and lead do harm the nervous system. Nonetheless, while these *in vivo* studies in animal models are informative, they also have limitations that must be carefully considered before concluding that effects in animal studies can be extrapolated to humans.

Indeed, experimental animal studies have often been poor predictors of human responses to chemicals or drugs (Aschner, 2020). For example, isotretinoin, more commonly known as Accutane, is toxic and causes birth defects in rabbits and monkeys, as well as in humans, but not in mice or rats. Corticosteroids are not teratogenic in humans—namely they do not relate to or cause developmental malformations—but do have that effect in experimental animals. Thalidomide is a teratogen in humans, but not in many experimental animal species. There are many reasons why animal studies can be poor predictors of human outcomes, and why they fail to translate to human responses. To identify a few such examples:

- The studies may be poorly designed (length of experiments, methods of randomization, distinctions in laboratory techniques) and methodologically inadequate;
- The study results may not be consistently and carefully replicated and are rarely subjected to meta analyses;
- The tested species or strains differ from humans in metabolic pathways and metabolism of the substance being studied; and

- Disease manifestation in the animals may be distinct from those encountered in human.
- Disease effects on the nervous system may be secondary to effects of chromium in other organs.
- Untoward effects on the nervous system are frequently not studied, but they may occur secondary to effects on other organs (for example, hypoxic lung injury causes brain damage).

Perhaps most importantly, animal studies often use doses that are far higher than doses humans would plausibly encounter under normal dosage or use condition, as is the case above. For example, lysolecithin is used in rodents to model demyelination, a hallmark of several human diseases including multiple sclerosis (MS), yet lysolecithin is also commonly used in beauty products (Hooijmans et al., 2019). Animal studies examining whether arsenic, mercury, and lead cause neurotoxicity also typically use doses that are greater than human exposure levels, and often a method of exposure (injection) that is not a plausible human exposure pathway. Nonetheless, these studies can provide insightful information on the mechanisms (such as oxidative stress, mitochondrial damage, etc.) of arsenic, mercury, and lead-induced neurotoxicity and transport into the brain, establishing the basic principles that guide their accumulation and adverse effects in the brain.

While extrapolation from animal studies to humans can be inappropriate given the often-used high doses and general lack of information on blood arsenic, mercury, and lead levels, the studies do establish the propensity of these metal ions to readily penetrate and damage the nervous system, as explained further below, and it would be improper to disregard the results of such studies merely because they use higher doses.

In evaluating the associations between arsenic, mercury and lead and ASD and the association between lead and ADHD, I have given careful consideration to any issues surrounding interpretation of the experimental animal literature, and I rely on such data for the understanding of the mechanisms of their neurotoxicity, pointing out some of the most prevalent modes-of-action in these experimental models.

D. CONSIDERATIONS IN ASSESSING *IN VITRO* STUDIES

An *in vitro* study is conducted using components of an organism that have been removed from a living organism and are thus studied in a controlled environment that is isolated from the complex environment of the intact living organism. These experiments may be performed on cells or tissue (for example a brain slice) grown in a petri dish in an artificial culture medium, or on cell or tissue homogenates, i.e., a slurry that is generated by mechanical disruption (e.g., grinding) that destroys cell-tissue membrane structure.

Isolated cells or tissues fail to mimic normal metabolism, which means they may not replicate effects in an intact living organism, let alone intact living organisms of different species. For example, cells in a living animal may be protected from toxic substances by a number of biochemical and physiological defense mechanisms, such as the blood-brain barrier, skin, testicular barrier, gastrointestinal tract, liver, antioxidant and immune defenses, among others. These physical protective barriers along with detoxification processes are an essential part of how our bodies deal with the range of potentially toxic substances to which we are exposed on a daily basis.

Due to the artificiality of the *in vitro* environment, the response of tissues or cells to an exposure in vitro will very often differ from the response in the intact organism. For example, when investigating the potential effect of a substance on brain structure and/or function, it is of limited utility to know that the substance investigated will kill neurons *in vitro* at a particular concentration, unless you know the dose that must be administered to a human before the toxic concentration can be achieved at the neurons in the brain. This is especially significant with regard to the brain, because it is protected from toxic insults by an anatomical barrier called the blood-brain barrier, which prevents or hinders the passage of many substances from the blood into the brain. In addition, most tissue cultures are composed of a single cell type, perhaps with some impurities; hence the reductionist approach of tissue culture negates the cross-talk and homeostatic control that is inherent to living organisms and which is essential for metabolism and protection.

Because *in vitro* models eliminate and do not account for these complex defense systems, cell responses *in vitro* may be markedly exaggerated or may be different altogether than those encountered *in vivo*. Thus, while *in vitro* studies can be informative as to potential mechanisms by which an agent may affect cells or tissues, such studies must be analyzed and interpreted with consideration of the limitations discussed above.

V. THE NON-ESSENTIAL METALS ARSENIC, LEAD, AND MERCURY READILY CROSS THE BLOOD-BRAIN BARRIER AND ACCUMULATE IN THE CENTRAL NERVOUS SYSTEM.

Arsenic, lead and mercury are non-essential metals with no biological function in humans (Tchounwou et al., 2012). Nonetheless, they can be absorbed via various routes, and accumulate in various organs. In order to accumulate in the brain tissue *per se*, metals have to be first absorbed from the gastrointestinal tract (assuming exposure via food consumption) into the systemic circulation. The three metals discussed herein are all readily absorbed from the gastrointestinal tract, albeit their absorption rates differ.

Arsenic is well absorbed across the human gastrointestinal tract, with approximately 95% absorption (ATSDR, 2007).

Mercury absorption is in the range of 5-95%, with the highest absorption for organic species such as methylmercury and lowest absorption for inorganic mercury (ATSDR, 1999).

The rate of gastrointestinal absorption for lead is 20–70%, and in children it is even higher.

Several metals (calcium, copper, magnesium, manganese, iron, zinc, cobalt, and molybdenum) are essential and required for normal and optimal brain function. They play important roles in brain function as catalysts, second messengers, signaling, and gene expression regulators, to name a few. However, non-essential metals, such the three metals discussed herein, namely arsenic, lead and mercury can also readily accumulate in the brain by utilizing transporters localized at the blood-brain barrier. As I noted above, none of these metals is deemed essential for any biological function (Tchounwou et al., 2012)

Transport of metal ions across the blood-brain barrier is the first and a requisite step in regulating their levels and effects in the brain. The blood-brain barrier is composed of layers of endothelial cells that are joined together by tight junctions. The layers separate the circulating blood from the central nervous system. These tight junctions are absent from peripheral blood vessels. The blood-brain barrier is semi-permeable - it allows some materials, but not others to cross. The barrier is supposed to protect the central nervous system from potentially harmful materials while regulating transport of essential molecules and maintaining a stable environment. Under normal conditions, the blood-brain barrier prevents the entry of bacteria, large molecules, and most small molecules into the brain (Sweeny et al., 2019). Entry into the brain requires molecules to be either small in size, without high electrical charge, or lipid soluble (tending to combine with or dissolve in lipids or fats, also called lipophilic).

Metal translocation to the brain is strictly controlled and often prevented by the blood-brain barrier. A series of active or receptor-mediated transport systems inherent to the blood-brain barrier vasculature serve to control the transport of metals into and out of the brain, maintaining their optimal concentrations.

However, as explained below, the most pertinent blood-brain barrier transport systems for arsenic, mercury, and lead, allow these non-essential metals to cross the blood-brain barrier and accumulate in the brain, in many cases, the mechanisms for their excretion are not as efficient as those for uptake, or they bind to macromolecules which prevent them from crossing back from the brain into the systemic circulation (Branco et al., 2017). Furthermore, the relative brain accumulation of these metals in toddlers is likely to be significantly higher than in adults, given the absence of fully developed blood-brain barrier. The consequences of such accumulation are also far more detrimental in toddlers, given that their brains are undergoing a series of dynamic processes related to postnatal brain development, which are absent in the adult brain (see below for additional discussion).

A. ARSENIC

Several studies have shown that arsenic readily crosses the blood-brain barrier and

directly affects the central nervous system. The mammalian glucose transporter GLUT1 has been postulated to be a major pathway uptake for arsenic across this barrier, contributing to arsenic-related neurotoxicity (Liu et al., 2006).

B. MERCURY

As a consequence of its high affinity for –SH groups, most of the mercury in tissues is normally conjugated to water-soluble sulfhydryl-containing molecules, primarily L-cysteine, glutathione (GSH), hemoglobin, albumin and other thiol-containing polypeptides. MeHg-L-cysteine conjugates are structurally analogous to the neutral amino acid L-methionine. L-methionine is an endogenous substrate, which is transported intracellularly on the L-type large neutral amino acid transporter 1 (LAT1). L-methionine has a high-affinity constant for this carrier. LAT1 functions as one of the major nutrient transport systems at the blood-brain barrier, and is highly expressed in brain capillary endothelial cells. Methylmercury-L-cysteine conjugate is a substrate for the neutral amino acid transporter, LAT1, which actively transports MeHg across membranes, resulting in mercury accumulation in the brain (Yin et al., 2008).

C. LEAD

Lead rapidly enters from the blood into the brain and is transported across the blood-brain barrier via an anion exchanger and calcium channels. A mechanism allowing rapid passive transport of Pb at the brain endothelium comprising the blood-brain barrier has been documented, likely in the form of a hydroxyl complex ($PbOH^+$). In addition, lead uptake into brain occurs via active transport by the calcium-ATP-dependent pump (Bradbury and Deane, 1993).

In summary, although non-essential, all three metals, arsenic, lead and mercury utilize transporters inherent to the blood-brain barrier, and therefore readily accumulate and concentrate in the brain. As explained below, given these metals' inherently neurotoxic effects, their accumulation in the brain poses substantial risks of harm to the neurodevelopment of children.

VI. REGULATORY LIMITS AND REFERENCE DOSES FOR HEAVY METALS

The EPA defines an oral reference dose (RfD) as an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. In other words, a reference dose (RfD) is defined as an estimate of a daily exposure to the human population (including sensitive subpopulations) that is likely to be without an appreciable risk of deleterious effects during a lifetime.[1] Therefore, exposure to a compound, heavy metals in this instance, at a level below the RfD is assumed to be safe, while exposure at levels above the RfD is assumed to cause adverse health effects. The RfD describes the exposure conditions that are unlikely to cause health effects, which are typically assumed to have a threshold dose above which deleterious health effects would be expected to occur.

As an example, for inorganic arsenic (IRIS, 2007), the RfD is 0.0003 milligram per kilogram of body weight per day (one microgram is one millionth of a gram). The "safe" dose of arsenic for any given person is the RfD multiplied by the person's body weight in kilograms. For example, a 60-kilogram (132-pound) woman's safe daily dose is (0.0003 milligram of arsenic per kilogram of body weight per day) x (60 kilograms) = 0.018 milligrams of arsenic.

The RfD for methylmercury is 0.0001 mg/kg/day based on developmental neurologic abnormalities in human infants (IRIS, 1997).[2]

For lead toxicity the EPA did not establish a safe exposure limit, and therefore, no RfD exists for this metal.

It is noteworthy that the US Food and Drug Administration (FDA) has set the maximum allowable levels in bottled water at 10 ppb for inorganic arsenic.

Noteworthy is also the fact that for mercury, the US Food and Drug Administration (FDA) has set the maximum allowable levels in bottled water at 2 ppb (ECP, 2021).

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[1] https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/reference-dose.

[2] https://www3.epa.gov/ttn/atw/112nmerc/volume1.pdf

The US Food and Drug Administration (FDA) has set the maximum allowable levels in bottled water at 5 ppb lead.

However, it must be noted that exposure to certain compounds below the RfD or maximum allowable levels does not mean that there is no risk of harm. As explained below, exposure to the metals discussed herein, even at very low levels, has been observed to have an adverse effect on pediatric neurodevelopment because children's developing brains are particularly susceptible to the neurotoxic effects of these metals. That is why many research, professional and governmental bodies have argued that, for children, no "safe" level of exposure to these metals exists. For example, in a lead Poisoning Fact Sheet recently published by the WHO it is stated "[t]here is *no level of exposure* to lead that is known to be without harmful effects."[3] (emphasis added). Similarly, the US EPA and the Centers for Disease Control and Prevention (CDC) "agree that there is *no known safe level* of lead in a child's blood"[4] (emphasis added).

It is further noteworthy that in its list prioritizing substances based on their frequency, toxicity, and potential for human exposure, the US Agency of Toxic Substances and Disease Registry (ATSDR, a division of the CDC) ranks arsenic as number one among environmental substances that pose the most significant potential threat to human health, followed by lead (second) and mercury (third).[5]

The ATSDR 2019 Substance Priority List

2019 Rank	Substance Name
1	ARSENIC
2	LEAD
3	MERCURY

[3] (https://www.who.int/news-room/fact-sheets/detail/lead-poisoning-and-health)
[4] (https://www.epa.gov/ground-water-and-drinking-water/basic-information-about-lead-drinking-water)
[5] www.atsdr.cdc.gov/spl/index.html#2019spl.

VII. OVERVIEW OF AUTISM SPECTRUM DISORDER (ASD) AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by altered communication, emotional status, and social interaction. ASD may include reduced intelligence scores, social interaction, and memory, deficits in reading and language capabilities, along with a myriad of other health issues as summarized by the CDC.[6]

Attention Deficit Hyperactivity Disorder (ADHD) is usually first diagnosed in childhood and often lasts into adulthood. Children with ADHD may have trouble paying attention, controlling impulsive behaviors (may act without thinking about what the result will be), or be overly active.[7]

VIII. NEUROTOXIC EFFECTS OF ARSENIC, MERCURY AND LEAD

The following section provides insight to the sequalae of human exposures to each of the metals (arsenic, mercury and lead) along with a brief description of their neurotoxic mode of action; this is further expanded upon in the "Summary" section.

I have reviewed in excess of 150 papers addressing the issue at hand. Given the toxicological focus of this report and the fact that the majority of the relevant data is in the form of epidemiological studies, many of the epidemiological papers are not explicitly discussed in this report, although cited in my reference materials. While some disagreement exists on the role of the metals discussed here in the etiology of ASD and ADHD, it is noteworthy that of the over 150 manuscripts that I have reviewed ~70-80% attest to an association and/or causation between exposures to these metals and adverse neurological outcomes, including ASD and ADHD. This constitutes a near-consensus within the scientific community. These effects were reported from multiple children cohorts around the world, emphasizing that these outcomes are largely reflected by exposures *per se* to these metals, and likely less so by genetic susceptibility. Furthermore, the mechanism by which these metals are known to cause neurodevelopmental

[6] (https://www.cdc.gov/ncbddd/autism/facts.html).
[7] https://www.cdc.gov/ncbddd/adhd/facts.html).

disorders in children further strengthens our understanding of a causal association observed in the substantial body of epidemiological literature. The data, taken in totality, and considered in light of our understanding of how these neurotoxic chemicals interact with the human brain (modes-of-action) clearly support a causal association between exposure to arsenic, lead and mercury and ASD, and exposure to lead and ADHD.

A. ARSENIC

Mechanistically, arsenic causes dysfunctional cognitive behaviors, primarily impacting synaptic plasticity of neurons in the hippocampus. Arsenic also increases β-amyloid protein, which induces the hyperphosphorylation of tau protein resulting in neurodegeneration
It can also alter the metabolism of assorted neurotransmitters such as monoamines, acetylcholine, gamma amino butyric acid (GABA), and glutamate. Its toxic effects are also attributable to oxidative stress and reduction in glutathione, glutathione peroxide (GPx) and glutathione synthase (GS) activity and elevate the lipid peroxidation, which have been associated with the development of ASD. Furthermore, arsenic activates p38 mitogen-activated protein kinase (P38 MAPK) and c-Jun N-terminal kinase 3 (JNK3), leading to neuronal cell death (Karri et al., 2016).

Many epidemiological studies and case reports have established that exposure to inorganic arsenic causes brain injury. For example, in adults, acute, high-dose exposures (2 mg arsenic/kg/day or above) lead to encephalopathy, characterized by symptoms such as headache, lethargy, mental confusion, hallucination, seizures, and coma (summarized in ATSDR, 2007), which commonly commences with numbness in the hands and feet, and often encompasses sensory and motor nerves, causing muscle weakness.

Tolins et al. (2014) reviewed the published epidemiological and toxicological literature on the developmental neurotoxicity of arsenic, asserting that arsenic is able enter and accumulate the developing brain, with ensuing neurotoxic effects. They further note that prenatal and early postnatal exposure to arsenic in animals cause reduction in brain weight, reductions in numbers of glia and neurons, and alterations in neurotransmitter systems, with the generation of reactive

oxygen species (ROS) as a triggering mechanism for such effects, recognized precursors to ASD. They further reviewed 15 epidemiological studies (through 2014), corroborating that in humans, early life exposure to this toxic metal results in deficits in intelligence and memory, effects that may occur at levels of exposure below current safety guidelines. Furthermore, they advance the hypothesis (which I will discuss below) that neurocognitive sequalae of arsenic exposure may be unmasked later in life and note that concomitant exposures (such as other metals; see below), and the timing of exposure may exacerbate developmental neurotoxic outcomes of early life exposure to arsenic. They also note that 4 epidemiological studies have failed to show behavioral outcomes of arsenic exposure.

Exposure to arsenic in children has been shown to cause intellectual deficits. For example, in a cross-sectional evaluation of intellectual function in 201 children 10 years of age whose parents were part of a larger cohort in Bangladesh, Wasserman et al. (2004) showed that water arsenic levels were significantly and negatively associated with both Performance and Processing speed (measures of neurobehavioral function).

In another study of 351 children aged 5–15 years from West Bengal, India, von Ehrenstein et al. (2007) found significant associations between urinary arsenic concentrations and reductions in scores of tests of vocabulary, object assembly, and picture completion. Ecological studies in children in Taiwan (Tsai et al. 2003) showed that adolescents exposed to low levels of inorganic arsenic (0.0017–0.0018 mg arsenic/kg/day; n=20) in their drinking water displayed decreased performance in the switching attention task; children exposed to high inorganic levels in their drinking water (0.0034–0.0042 mg arsenic/kg/day; n=29) displayed decreased performance in both the switching attention task and in tests aimed to detect deficits in memory, when compared to unexposed control children (n=60).

Similarly, ecological studies in China (Wang et al. 2007) in children (age 8– 12 years) found that children whose mean arsenic concentration in the drinking water was 0.190 mg/L had a mean IQ score of 95 compared with 101 for children (n=253) with 0.142 mg/L arsenic in the water and 105 for control children (n=196) with 0.002 mg/L arsenic in the drinking water,

establishing statistically significant differences in IQ scores between the two exposure groups and the control group. Taken together, studies have consistently shown that arsenic exposure significantly and negatively effects neurodevelopment in children, as by a highly pronounced decrease in Full Scale IQ (FSIQ), specifically, in verbal and performance domains, as well as memory. As noted in the ECP (2021), astonishingly, for every 50% increase in arsenic levels, there is an approximate 0.4 decline in a child's IQ.

A.1 Arsenic and ASD

The epidemiological data concerning arsenic and the development of ASD and ASD-associated behaviors is strong. And, importantly, it is consistent with the toxicological profile of arsenic and its effects on the human brain, especially in younger children.

Wang et al. (2019) carried out a systematic review and combined the data into a meta-analysis to evaluate the available human evidence on the relationships between arsenic and ASD. The authors identified 14 studies on arsenic exposure and their respective associations with ASD, with 8 (53.3%) reporting a positive association, and none reporting an inverse association. In a follow-up meta-analysis, the authors reported statistically significant higher arsenic concentrations in hair and blood of children diagnosed with ASD compared with controls. The authors state: "we concluded that there is consistent evidence supporting a positive association between early life arsenic exposure and diagnosis of ASD."

Long et al. (2019) measured amniotic fluid (AF) levels of endocrine disrupting compounds (EDCs) and metals to investigate the possible link between prenatal exposure to these compounds and risk for ASD risk. Arsenic was detected in up to 22.7% of the AF samples, and the study indicated that prenatal arsenic exposure contributed to the development of childhood ASD.

In a recent study, Fiore et al. (2020) examined children with ASD in Catania, Italy. A significant and positive correlation was found between hair metal burden (as well as lead, aluminum and arsenic levels) and severity of ASD symptoms, such as social communication deficits and repetitive, restrictive behaviors. Similar findings were corroborated in a small study

carried out by Filon et al. (2020), where hair analyses revealed that children diagnosed with ASD had arsenic and lead toxic overload.

Doherty at al. (2020), in a prospective pregnancy cohort, investigated associations between prenatal exposures to arsenic and neurodevelopmental outcome, reporting that exposures in mid- to late- pregnancy were more "impactful" than exposures earlier in pregnancy, concluding that "maternal postnatal toenail arsenic was associated with worse scores on the BASC-2 Internalizing Problems and Behavioral Symptoms Index". This study is insightful for the additional reason that it demonstrates the etiological relevance of pre-diagnosis arsenic exposure.

Skogheim et al. (2021) investigated the relationship between maternal levels of toxic metals and childhood diagnosis of ASD. They examined 397 ASD cases and 1034 controls in the Norwegian Mother, Father and Child Cohort Study. The authors identified positive associations between arsenic and ASD (increased risks) in the arsenic second quartile, showing associations between arsenic levels during gestation and ASD with negative impacts on neurodevelopment. This study, in addition to the study by Long, et al. (2019) discussed above, provides compelling evidence for the etiological relevance of arsenic exposure prior to disease onset.

Studies showing negative associations between arsenic exposure and ASD also exist. For example, Skalny et al. (2017) investigated hair trace elements content in 74 children suffering from ASD and 74 sex- and age-matched controls divided into two age groups (2-4 and 5-9 years). The authors note that levels of hair arsenic in children diagnosed with ASD were lower compared to matched control. And an ecological study by Dickerson et al. (2016) examining ambient arsenic levels across census tracts did not observe an association for ASD prevalence across the census tracts. A meta-analysis from 2017 by Saghazadeh and Rezaei found no difference in arsenic measurements of hair, urine, and blood between cases and controls.

However, given that the majority of the epidemiological studies I reviewed have reported positive associations between arsenic exposure and ASD, and considering that these effects were reported from multiple children cohorts from around the globe, emphasizing that these outcomes

are largely due to exposures *per se* and not genetic factors, notwithstanding negative studies, it is my opinion to a reasonable degree of scientific certainty that that arsenic exposure is a causal agent of ASD.

B. LEAD

The literature on the neurobehavioral effects of Pb in children is extensive, and leaves no doubt that Pb causes intellectual deficits, and most likely with no threshold (ATSDR, 2020).

Mechanistically, lead disrupts the nervous system at multiple levels. It can displace metal ion co-factors from protein, inhibit enzymes and ion transport, disrupt cell and mitochondrial membrane potentials as well as intracellular calcium homeostasis, induce oxidative stress and inflammation to name a few; and many of these adverse effects have been implicated in the development of both ASD and ADHD. Given that lead can mimic calcium, the latter being involved as a cofactor in many cellular processes, it is not surprising that Pb affects numerous cell-signaling pathways. One prominent pathway that affected by lead is related to the activation of protein kinase C (PKC), a serine/threonine protein kinase involved in many processes important for synaptic transmission, such as conductance of ionic channels, the synthesis of neurotransmitters, ligand-receptor interactions, and dendritic branching. Notably, the PKC γ-isoform is one of several calcium-dependent forms and is a likely target for lead neurotoxicity; it is neuron-specific and is involved in both learning and memory processes (ATSDR, 2020). In addition, Schneider et al. (2013) have shown altered DNA methyltransferase 1 (DNMT1), DNMT3a, and methyl-CpG Binding Protein 2 (MeCP2) expression profiles in postnatally lead-treated rats, suggesting potential epigenetic effects on DNA methylation through dysregulation of methyltransferases which are relevant to ASD etiology. Notably, these genes encode enzymes that transfer methyl groups to cytosine nucleotides of genomic DNA, thus maintaining methylation patterns following DNA replication. Methylation of DNA is an important component of mammalian epigenetic gene regulation, and abnormal methylation patterns have been shown to be associated with developmental abnormalities such as ASD. Therefore, as noted by these authors, lead may affect the dynamic modulation of DNA methylation during brain

development including processes such as learning and memory.

As succinctly summarized in the newly updated Toxicologic Profile of Lead ATSDR (2020), in children, consistent evidence of associations between decrements in cognitive and neuromotor/ neurosensory function with lead blood levels (PbBs) have been shown at the range from ≤10 to >50 μg/dL. The PbB-effect relationship for cognitive effects in children extends well below 10 μg/dL, with no evidence for a threshold. It is also noteworthy, several studies that have followed children to early adulthood establish associations between childhood Pb exposure (e.g., PbB) and behavioral and neuroanatomical changes, suggesting that exposures in childhood persist into adulthood. Other studies have reported on associations between cumulative Pb exposures (e.g., bone Pb) and neurological outcomes in adults.

It is now well accepted that even concentration of PbB ≤10 μg/dL are associated with decreased cognitive function, including full scale IQ (FSIQ), learning deficits, attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency. Neuromotor and neurosensory dysfunction, including gross and fine motor skills, visual-motor integration, and hearing threshold have also been documented at PbB ≤10 μg/dL.

The established effects of lead on neurological function in children are summarized in Table 2-28 (ATSDR, 2020). Taken together, these studies establish that lead affects cognitive function in children prenatally exposed to PbB ≤10 μg/dL, with similar effects occurring even at PbB ≤5 μg/dL. To summarize, neurobehavioral functions associated with PbB ≤10 μg/dL include, but are not limited to, decrements in cognitive function (learning and memory), altered behavior and mood (e.g., attention, hyperactivity, impulsivity, irritability, delinquency), and altered neuromotor and neurosensory function (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds).

The cognitive outcome of lead exposure in children that has been most extensively studied and compared across studies is full scale IQ. Tests of memory, learning, and executive function have also been utilized to assess cognitive function. For a summary, refer to Table 2-30, ATSDR, 2020). Collectively, these studies establish decrements in cognitive function in

association with increasing PbB. Several studies have utilized the Mental Development Index (MDI) score metrics from the Bayley Scales of Infant Development (BSID), allowing for comparison of results across different studies. All noted decreases in Mental Development Index scores measured from 6 to 36 months in association with increasing prenatal (e.g., maternal) or neonatal PbB. Furthermore, several studies have also established the persistence of these effects into adulthood.

Prospective studies initiated at birth have also consistently shown decrements in child full scale IQ in association with increased mean PbB <10 μg/dL measured at various stages of development (Table 2-30).

Modeling the effects of PbB of cognition effect, concurrent models predict a decrease of 6.2 points in FSIQ in children when PbB increases from 1 to 10 μg/dL irrespective of the exposure time. Academic performance for children with corresponding PbB data recorded in state or local blood Pb registries are also available. For example, Wechsler Intelligence Scales for Children-Revised [WISC-R]) in ~5,000 children 6–16 years of age (Lanphear et al., 2000) established that increasing PbB levels were significantly associated with decreased performance scores in reading in blood strata <5.0, <7.5, and <10 μg/dL.

Numerous studies have also examined possible associations between neonatal and child PbB risk of behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency (Table 2-30). Prospective studies have also provided evidence for associations between neonatal or early childhood PbB and other neurobehavioral outcomes, including neonatal behavior, emotional or temperament problems, anxiety or depression, sleep disorders, hyperactivity and impulsivity, delinquency, and, as discussed below, ASD.

Although I have only discussed the effects of lead on epigenetic changes, it should be noted that similar effects have been also reported for arsenic, and mercury. Therefore, epigenetic changes, such as DNA methylation, post translational histone modification and noncoding RNA-mediated gene silencing are effects inherent to all these metals, with outcomes consistent with

neurodevelopmental disabilities, including ASD (see review, Ijomone et al., 2020). When encountered as a mixture, one would further anticipate that these effects would be magnified in the course of an infant's neurodevelopment.

B.1 Lead and ASD

A large body of epidemiological data demonstrates the causal association between lead exposure and ASD. This data, importantly, is consistent with the toxicological profile of lead, and its capacity to injure the human brain, especially in children.

Kim, et al. (2016), addressed the relationship between low-level lead exposure and autistic behaviors in school-age children. In a prospective study, they studied 2,473 Korean children aged 7–8 years who had no prior history of developmental disorders, with two follow-up surveys conducted biennially through the age of 11–12. The authors reported "that blood lead concentrations at 7–8 years of age (geometric mean: 1.64 mg/dL), but not at 9–10 and 11–12 years of age, were associated with more autistic behaviors at 11–12 years of age", concluding that "*even low blood lead concentrations* at 7–8 years of age are associated with more autistic behaviors at 11–12 years of age." (emphasis added). Given its large scope and prospective design (exposure was assessed prior to outcome), this study lends strong support to the etiological relevance of lead exposure and the causal association between early life exposure to lead and ASD.

The association between lead exposure and ASD has also been observed in ecological data. Dickerson et al. (2016) addressed associations between lead, mercury, and arsenic and (ASD) in 4486 children with ASD residing in 2,489 census tracts in five sites of the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring (ADDM) Network. After adjusting for confounding factors, tracts with air concentrations of lead in the highest quartile had significantly higher ASD prevalence than tracts with lead concentrations in the lowest quartile (prevalence ratio (PR) = 1.36; 95 % CI: 1.18, 1.57). The authors suggest a possible association between ambient lead concentrations and ASD prevalence and demonstrate that exposure to multiple metals may have synergistic effects on ASD prevalence (see below).

Similarly, Roberts, et al. (2013) estimated associations between U.S. Environmental Protection Agency-modeled levels of hazardous air pollutants at the time and place of birth and ASD in the children of participants in the Nurses' Health Study II (325 cases, 22,101 controls). The authors note that perinatal exposures to the highest vs. lowest quintile of lead were significantly associated with ASD.

Arora, et al. (2017) analyzed tooth-matrix biomarkers, a correlate of temporal resolution of lead exposure during early development, to characterize levels of this metal in sample of twins and its association with ASD. They report significant differences between ASD cases and non-ASD controls during specific pre- and postnatal periods, with higher lead levels observed over the prenatal period and first 5 months postnatally in the ASD children. This study is particularly compelling because, in addition to observing a positive association between higher lead levels and ASD, it specifically demonstrates the etiological relevance of early life exposure to lead, notwithstanding the shared genetic risk factors of twins.

In a meta-analysis, Saghazadeh and Rezaei (2017) investigated differences in heavy metal measures between patients with ASD and control subjects, using different specimens (whole blood, plasma, serum, red cells, hair and urine). Of the 52 studies eligible to be included in the systematic review, 48 studies were included in the meta-analyses. Hair lead levels in ASD patients were significantly higher than those of control subjects (albeit this was limited to hair lead levels of children from developing as opposed to developed countries), and ASD patients had higher erythrocyte lead levels as well as higher blood lead levels, establishing a potential role for lead in ASD etiology.

In the same Norwegian Mother Father and Child Cohort Study discussed above (Skogheim et al., 2018), non-linear associations between ASD and lead were noted (in addition to those described for arsenic above).

Filon, et al. (2020) analyzed lead concentrations in the hair of children with ASD and controls. Hair samples were collected from 30 children diagnosed with ASD (case group) and 30 children randomly selected from the general population. The authors report that mean lead

concentration in the hair of children with ASD were statistically significantly higher than the mean concentration of this element in the hair of children without neurological disorders, concluding that increased lead burden may play the main role in the etiology of this disorder.

In another recent study, Fiore et al. (2020) performed a cross-sectional study in Catania to determine the relationship between the severity of autism symptoms and cognitive levels with heavy metal burdens. The authors note a significant and positive correlation between hair lead levels and the severity of ASD symptoms, as characterized by social communication deficits and repetitive, restrictive behaviors.

Frye et al. (2020) addressed neurodevelopmental regression (NDR) as a subtype of ASD, analyzing prenatal and early postnatal metal exposures in tooth-matrix biomarkers in 27 ASD cases (13 with NDR) and 7 typically-developing (TD) controls. In addition, mitochondrial respiration and glycolysis (endpoints of toxicity) were measured in peripheral blood mononuclear cells. The authors conclude that "children with ASD and NDR had greater metal-related disruption of cellular bioenergetics than children with ASD without NDR. Most notably, "*glycolysis decreased with increased exposure to prenatal lead*" (emphasis added), suggesting dysregulation of cellular bioenergetics.

As noted in the ATSDR document (2020), lead concentrations "≤10 µg/dL "may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency, as well as altered neuromotor and neurosensory function, including gross and fine motor skills, visual-motor integration, and hearing threshold". Furthermore, "altered mood and behavior includes hyperactivity, ADHD [see below], decreased adaptive skills and emotional functioning, externalizing behaviors, internalizing behaviors, social problems, delinquent behavior, impulsive behavior, irritability, autistic behavior, altered sleep, and associations between child PbB and adult behavior" (McFarlane et al. (2013). All of these identified symptoms are relevant to the manifestation of ASD. Moreover, a plethora of studies have addressed associations between neonatal and child lead blood risk of behaviors that may contribute to learning deficits, including autistic behaviors (ATSDR, 2020, see Table 2-30).

Not all studies have found a positive association between lead exposure and ASD. Abdullah et al. (2012) addressed possible links between lead (and other metals) and ASD, high levels of disruptive behavior (HDB), and typically developing (TD) children. The authors noted no significant differences in levels lead in children with ASDs compared with TD children. No significant differences were noted between children with HDB and TD children.

Doherty et al. (2020) also investigated the neurodevelopmental effects of prenatal metal exposures in the New Hampshire Birth Cohort Study, a prospective birth cohort. Lead levels (in addition to arsenic, see above), were analyzed in maternal prenatal and postnatal toenails and infant toenails, and mothers completed the Social Responsiveness Scale, 2nd ed. (SRS-2) and the Behavior Assessment System for Children, 2nd ed. (BASC-2) to assess their child's neurobehavior at 3 years. The authors note that lead levels were weakly or inconsistently associated with BASC-2 outcomes. A smaller 2021 study by Wahil et al. (2021) did not observe a significant difference in urine lead levels between cases and controls.

Guo et al. (2019) carried out a systematic review and meta-analysis to explore the association of hair lead levels with ASD in children. The authors identified 20 eligible studies involving 1,787 participants (941 autistic children and 846 healthy subjects). The authors note no statistically significant differences in the levels of hair lead between children with ASD and healthy individuals, concluding that there does not appear to be an association between hair lead levels with ASD. And, the authors of the Wang et al. (2019) meta-analysis concluded that the evidence for exposure to lead and ASD was "inconsistent". However, neither Wang or Guo included the large, prospective study of Kim et al. (2016), or the studies of Frye, et al. (2020), Fiore, et al. (2020), Filon, et al. (2020) or a recent smaller study Qin and colleagues (2018) which found that ASD cases had higher blood lead levels compared with controls, all of which support the causal association between exposure to lead and ASD. Additionally, following the performance of sensitivity analyses in Guo et (2019), a positive association was observed in the differences of hair lead levels between cases and controls that was statistically significant. The preponderance of epidemiological studies has established a causal association between lead

exposure in children and ASD. Given the reasons stated above, and notwithstanding the presence of some negative data, the literature consistently identifies positive associations between lead exposure and ASD. When this epidemiological data is considered within the toxicological context of what we know about how lead affects the human brain, especially in younger children, it is my opinion to a reasonable degree of scientific certainty that lead exposure is a causal agent of ASD.

B.2 Lead and ADHD

Even though no safe level of exposure exists for lead, there is evidence of a dose-response relationship between lead exposure and ADHD. Geier et al. (2017) relied upon the 2003–2004 National Health and Nutritional Examination Survey (NHANES) dataset, consisting of 2109 people aged 10-19. The authors observed a dose-response relationship between increasing blood lead levels and the risk of a reported ADD (per ug/dL, odds ratio (OR) = 1.237, $p = 0.0227$), and the dose-response relationship remained following adjustment for potential confounding variables. Collectively, the ADHD studies indicate that risk of childhood attention deficit hyperactivity disorder increases in association with increasing PbB within the range of PbB <10 μg/dL (Table 2-30, ATSDR 2020).

Other studies have examined possible associations between neonatal and child lead and neuromotor or neurosensory function (Table 2-30). For example, increased bone lead analyzed at age 24 months was shown to be associated with decreased cognitive development (Gomaa et al. 2002) and behaviors indicative of attention deficit hyperactivity disorder assessed at age 7–15 years (Xu et al. 2015). In another study (Zhang et al., 2015), the authors investigated ADHD in preschool-aged children in Guiyu, an electronic waste (e-waste) recycling town in Guangdong, China. The authors (Zhang et al., 2015) reported that 12.8% of children met the criteria for ADHD, of which the inattentive, hyperactive/impulsive and combined subtypes were 4.5%, 5.3% and 2.9% respectively. Of all children, 28.0% had BLLs ≥ 10 ug/dL and only 1.2% had BCLs ≥ 2 ug/L, levels conventionally considered high. Either modeled by univariate or multivariable analysis, the three ADHD scores (inattentive, hyperactive/impulsive and total scores) calculated

from the Parent Rating Scale showed strong positive correlations with BLLs but not with BCLs. In addition, high BLLs imparted a 2.4-fold higher risk for ADHD than low BLLs (OR: 2.4 [95% CI: 1.1-5.2]). When each of the 18 categories on the Parent Rating Scale was separately analyzed, it was found that children with high BLLs had significantly greater risks for positive ADHD symptoms than children with low BLLs in 12 of the 18 categories (ORs ranged from 2.1 [95% CI: 1.1-3.9] to 3.6 [95% CI: 1.7-7.5]). Taken together, this study suggests that environmental lead contamination due to e-waste recycling affects neurobehavioral development in preschool children in Guiyu, China.

The literature demonstrating the causal association between lead exposure and ADHD is abundant. I discuss some of the studies from this extensive dataset.

In a seminal study, Needleman et al. (1979) probed the neuropsychologic effects of unidentified childhood exposure to lead. Specifically, the performances of 58 children with high and 100 with low dentine lead levels were contrasted. The authors conclude that "children with high lead levels scored significantly less well on the Wechsler Intelligence Scale for Children (Revised) than those with low lead levels", and their poorer performance was also evident in other "verbal subtests, on three other measures of auditory or speech processing and on a measure of attention". None of these differences could be accounted for by 39 other variables studied. Significantly, the "frequency of non-adaptive classroom behavior increased in a dose-related fashion to dentine lead level". The authors conclude that "lead exposure, at *doses below* those producing symptoms severe enough to be diagnosed clinically appears to be associated with neuropsychologic deficits that may interfere with classroom performance." (emphasis added).

Tuthill et al. (1996) addressed the relationship between hair lead levels of children and their attention-deficit behaviors in the classroom, showing a striking dose-response relationship between levels of lead and negative teacher ratings which remained significant after controlling for age, ethnicity, gender, and socioeconomic status. The authors reported an even stronger relationship between physician-diagnosed ADHD and hair lead in the same cohort of children.

Wang et al. (2008) investigated the association between ADHD and blood lead levels in Chinese children, adjusting for known ADHD risk factors and potential confounding variables. The study included 630 ADHD cases and 630 non-ADHD controls 4-12 years of age. The authors noted a significant difference in blood lead levels between ADHD cases and controls with ADHD cases being more likely to have been exposed to lead during childhood than the non-ADHD control subjects. The authors concluded that "ADHD may be an additional deleterious outcome of lead exposure during childhood, even when BLLs are < 10 microg/dL."

Neugebauer et al. (2015) investigated low-level exposure in relation to children's attention. They studied attention of school-aged children (N=117) using a computer-based test battery of attention performance (and a parent rating questionnaire of behaviors related to ADHD, showing that questionnaire-based ADHD-related behaviors were increased with increased lead exposure.

He et al. (2019) reviewed and meta-analyzed case-control studies to assess the effects of blood lead levels in children on ADHD symptoms in seven relevant studies. The authors state that "low blood lead levels may be associated with ADHD symptoms in children", and "even children with blood lead levels <3 μg/dL exhibited significant increases in ADHD symptoms." (emphasis added).

In a study published in 2018, Ji, et al. investigated the prospective associations between early childhood lead exposure and subsequent risk of ADHD in childhood and its potential effect modifiers. The authors found that 8.9% of the children in the Boston Birth Cohort had elevated lead levels (5-10 μg/dL) in early childhood, which was associated with a 66% increased risk of ADHD (OR, 1.66; 95% CI, 1.08-2.56). Among boys, the association was significantly stronger (OR, 2.49; 95% CI, 1.46-4.26); in girls, the association was largely attenuated (P value for sex-lead interaction = .017). As a prospective cohort, the Ji, et al (2018) study reaffirms the causal association between lead exposure and ADHD as well as demonstrating the etiological relevance of lead exposure prior to ADHD diagnosis.

In a meta-analysis, Goodlad, et al. (2013) addressed the association between ADHD and

lead exposure in children and adolescents. They analyzed 33 studies published between 1972 and 2010 involving 10,232 children and adolescents. The authors report "small to medium association between inattention symptoms and lead exposure and a similar association between hyperactivity/impulsivity symptoms and lead exposure". Overall, the authors note a "relation between lead exposure and ADHD symptoms was similar in magnitude to the relation between lead exposure and decreased IQ and between lead exposure and conduct problems." This is particularly compelling because, as discussed above, decreased IQ exposure has also been consistently associated with low level lead exposure, lending further support to the causal association between lead exposure and ADHD.

Daneshparvar, et al. (2016), in a systematic review which included multiple cohort, case-control and cross sectional studies, examined the role of lead exposure in children with ADHD symptoms. Upon meeting study criteria, 18 articles were selected for the analysis. The authors note that blood lead level even at less than 10µg/dL in children were associated with ADHD. 16 of the 18 studies found a significant association between blood lead levels and ADHD.

Braun, et al. (2016) examined the association of exposures to tobacco smoke and environmental lead with ADHD. They analyzed data from the National Health and Nutrition Examination Survey 1999-2002, and of the 4,704 children 4-15 years of age identified, 4.2% were diagnosed to have ADHD Using multivariable analysis, the authors show that prenatal tobacco exposure and higher blood lead concentration were associated with ADHD. They further assert that lead exposure accounts for 290,000 excess cases of ADHD in U.S. children.

Lee, et al. (2018) addressed the relationships between several heavy metals, neurocognitive function, and ADHD symptoms noting that urinary lead levels were positively correlated with inattention and hyperactivity/impulsivity symptoms. Donzelli et al. (2019) performed a systemic review of the epidemiological literature (including cohort, case-control, and cross sectional studies) on the relation between lead exposure and diagnosis of ADHD, reporting that of the 17 of the studies that met the inclusion criteria, 12 showed positive associations between lead levels and ADHD, and the authors concluded that even low levels of

lead exposure increase risk of ADHD.

More recently, Tartaglione, et al. (2020) reported on the effects of lead on developing rodents. Pregnant rats were exposed via the drinking water to lead. Notably, offspring showed motor, emotional, and cognitive end points related to altered functioning of the synaptically distributed N-methyl-D-Aspartate receptor (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor in the hippocampus. These authors conclude that "lead exposure during development affects glutamatergic receptors distribution at the post-synaptic spine" and that these alterations may contribute to behavioral deficits, providing another line of evidence for the mechanism by which lead exposure can cause ADHD.

It is important to note that not all reported studies have established a positive association between lead exposure and ADHD. For example, the link between lead exposure and neuropsychological disorders and child behavior has been addressed by Abdullah et al. (2012). These authors analyzed in prenatal and postnatal enamel regions of deciduous teeth from children with disruptive behavior (HDB), and typically developing (TD) children as well as ASD, and reported on the absence of significant differences in levels of lead in these children compared with matched controls. And, in Kim, et al. (2010), the authors did not observe a significant difference between levels of blood lead between ASD cases and controls in an analysis limited to just girls, although the authors noted that the "probability of inattentive and hyperactive symptoms was increased with higher blood lead levels in boys."

The preponderance of studies, as evidenced by multiple meta-analyses and a prospective cohort study, has established a casual association between lead exposure in children and ADHD. Indeed, the epidemiological data is directly supported by what we know concerning the toxicological effects of lead on the human brain, especially in younger children (discussed above). Given the reasons stated above, and notwithstanding the presence of some negative data (indeed a recent systematic analysis conducted by Donzelli et al. (2019) found that most studies on lead and ADHD which did not establish a positive association were of poor quality, noting that the positive data primarily consisted of superior studies) the epidemiological literature

consistently identifies positive associations between lead exposure and ADHD. Accordingly, it is my opinion to a reasonable degree of scientific certainty that lead exposure is a causal agent of ADHD.

C. MERCURY

Mechanistically, methylmercury, disrupts/modulates brain cellular Ca^{2+}homeostasis. During critical brain developmental windows, methylmercury-induced disruption of neurotransmitter has been shown to interfere with cell proliferation and cell fate decisions. Furthermore, methylmercury blocks cell migration, and subsequently laminar cortical organization in the developing cerebellum *(part of the brain)*. Methylmercury interferes with neurotransmitter release, axonal growth, and gene expression and causes hippocampal-dependent memory deficits. Exceedingly low nanomolar concentrations of methylmercury affect proliferation and differentiation of embryonic stem cells, and reduce neural progenitor cell proliferation, expression of genes related to cell cycle regulation, cellular senescence, and mitochondrial function (Antunes dos Santos et al., 2016). In addition, low doses/concentrations of mercury have been shown to elicit oxidative stress (Aschner et al., 2007). For example, mercury induces ROS formation *in vivo* (rodent cerebellum), and *in vitro* (isolated rat brain synaptosomes), as well as in cerebellar neuronal cultures. Increased levels of reactive oxygen species have been noted in mitochondria isolated from MeHg-injected rat brains.

Most of the available information on methylmercury-induced humans neurotoxicity following exposure to organic mercury comes from studies in populations ingesting contaminated fish or fungicide-treated grains. Information on the doses at which the adverse effects of mercury are diagnosed is frequently limited, given difficulties in retracing prior exposures and uncertainties in estimating individual dose levels.

Select neurodevelopmental effects of methylmercury on brain development have been recently summarized by Gustin et al. (2017). The developing brain, both pre- and postnatally is considered to be the most sensitive organ and elevated exposure has been shown to affect child

development (Harada, 1995). For example, pre-natal mercury exposure is related to poorer estimated IQ (Jacobson et al., 2015).

Prospective studies in the Faroe Islands have established adverse effects of children's recent methylmercury exposure, characterized by hair and blood content, on visuospatial memory at 7 years of age, but not with any of the other developmental measures of functional domains such as language, attention, or motor skill (Grandjean et al., 2014). Epidemiological studies in the Faroe Islands have shown that *in utero* exposure to methylmercury caused decreased motor function, reduced verbal abilities, shortened attention span, altered memory and reductions in several other mental functions. Notably, these effects appear permanent and upon follow-up of these children at 22 years-of-age, these deficits persist (Debes et al., 2016; Landrigan et al., 2020). Further, methylmercury exposure in early life was shown to be associated with slowed processing of visual information, decreased IQ, diminished comprehension and perceptual reasoning, impaired memory, shortened attention span, and increased risk of attention deficit/hyperactivity disorder (ADHD) (Boucher et al., 2011, Boucher et al., 2012; Landrigan et al., 2020).

In the Seychelle Islands, where another extensive neurodevelopmental study has been carried out, no adverse associations were observed between children's hair mercury concentrations and neurodevelopment at 5.5 years of age (Myers et al., 2000). However, at a follow-up at 19 years of age, hair mercury concentrations were shown to be inversely associated with the Kaufman Brief Intelligence Test (van Wijngaarden et al., 2013). As noted by Sagiv et al. (2012), "findings underscore the difficulties of balancing the benefits of fish intake with the detriments of low-level mercury exposure in developing dietary recommendations in pregnancy."

C.1 Mercury and ASD

In one of the earlier studies on the association between heavy metals and ASD, Al-Ayadhi and collaborators (2005) enrolled 72 autistic children with confirmed diagnosis according to E-2 diagnostic criteria for autistic spectrum disorders, and compared their hair

heavy metal levels (lead, mercury, aluminum, arsenic, barium, cadmium, nickel, antimony and strontium) to controls. The authors noted significantly higher levels of toxic heavy metals mercury (as well as lead and arsenic children with ASD compared to controls children, suggesting "a possible pathophysiological role of heavy metals and trace elements in the genesis of symptoms of autism spectrum disorders, such as social withdrawal, eating and sleeping disorders."

Adams et al. (2007) investigated the level of mercury (as well as lead and zinc) in baby teeth of 15 children (aged 6.1 +/- 2.2 yr) with autism spectrum disorder (n = 15, age 6.1 +/- 2.2 yr) and 11 typically developing children (aged = 7 +/- 1.7 yr). The authors reported that "children with autism had significantly (2.1-fold) higher levels of mercury but similar levels of lead and similar levels of zinc."

Budtz-Jørgensen et al. (2007) applied structural equation modeling to data from a prospective study of developmental methylmercury exposure in the Faroe Islands, an Island characterized by a population with a relatively high fish consumption. The study adjusted for the benefits conferred from maternal fish consumption during pregnancy *vis-a-vis* increased prenatal methylmercury exposure, concluding that the "adverse effects of methylmercury exposure from fish and seafood are therefore likely to be underestimated by unadjusted results from observational studies, and the extent of this bias will be study dependent." Analogous to the findings by Sagiv et al. (2012) these studies strongly indicate that the detrimental effects of low-level exposure to mercury from fish is likely to exceed the beneficial effects inherent to fish consumption *per se* (omega 3 fatty acids, etc.).

Blanchard, et al. (2011), addressed risks associated with persistent low-level mercury exposure in the etiology of various developmental and neurodegenerative diseases, such as ASD and Alzheimer's disease. In their preliminary study, carried out at 2 locations (Bexar County Texas and Santa Clara County California), the authors suggest that the "occurrence of autism has a positive co-variation with the spatial structure of the distribution of mercury in ambient air." The authors note that where mercury air levels are higher the risk for ASD increases.

Yassa, et al. (2014) analyzed blood and hair samples from 45 autistic Egyptian children aged 2 and 10 years, and 45 controls in the same age range. The authors report significant differences between the two groups, with higher levels of mercury (as well as lead) in children with autism, concluding that "mercury [and lead should be] considered as one of the *main causes of autism*." (emphasis added).

In addition, the ecological study by Dickerson et al. (2016; see above in lead section) suggest that mercury concentrations above the 75th percentile (>1.7 ng/m(3)) are associated with significantly higher ASD prevalence (adjusted RR = 1.20; 95 % CI: 1.03, 1.40). Thus, exposure to multiple metals may have synergistic effects on ASD prevalence.

Ryu, et al. (2017) also noted that blood mercury levels at late pregnancy and in early childhood were positively correlated with more autistic behaviors in children when examined at 5 years-of-age, noting "that mercury concentrations at late pregnancy, in cord blood, and at 2 and 3 years of age were associated with autistic behaviors at 5 years of age." This a particularly compelling study given its large size, prospective design and the authors' adjustment for a wide range of potential confounding variables. The study also confirms the etiological relevance of mercury exposure in early life.

A prospective study was also conducted by Geier, et al. (2009) where they examined prenatal exposure to maternal dental amalgams (50% mercury) in relation to symptom severity in 100 autistic children. The study found that children born to mothers with 6 or more amalgams were 3.2-fold significantly more likely to be diagnosed with severe ASD than children born to mothers with 5 or fewer amalgams. This is further evidence linking mercury exposure to the development of ASD.

A systematic meta-analysis was performed by Jafari, et al. (2017) to evaluate a possible association between mercury in different tissues and ASD patients. The authors identified 44 studies that met criteria for meta-analysis and were included in the analysis. Mercury levels in whole blood, red blood cells, and brain were significantly higher in ASD patients than healthy controls, while mercury levels in hair were significantly lower in ASD patients than healthy

subjects. Notwithstanding the negative results in the hair samples, the authors concluded "that mercury is an important causal factor in the etiology of ASD."

Saghazadeh and Rezaei (2017) investigated differences in heavy metal measures between patients with ASD and control subjects, using different specimens (whole blood, plasma, serum, red cells, hair and urine). Of the 52 studies eligible to be included in the systematic review, 48 studies were included in the meta-analyses. The authors observed that erythrocyte mercury concentrations were higher in cases. Interestingly, ASD patients in developing, but not in developed countries, had increased hair mercury levels.

Li, et al. (2018) identified 180 children with ASD and 184 healthy controls and concluded that those with ASD had higher levels of mercury (and arsenic) and a lower level of cadmium. The levels of lead were statistically indistinguishable between the 2 groups. The authors noted that these findings "are consistent with numerous previous studies, supporting an important role for heavy metal exposure, particularly mercury, in the etiology of ASD."

El-Ansary, et al. (2017) probed the association between mercury (lead and selenium) and ASD in Saudi Arabian children (35 children with ASD and 30 age- and gender-matched healthy controls). A significant increase was reported in red blood cell levels of mercury (as well as lead) in patients with ASD compared to healthy controls.

In a Chinese study carried out by Qin and colleagues (2018), blood plasma metal levels were compared in children with ASD and unaffected children in Shenzhen (China). The results established that children with ASD had higher mercury (as well as lead levels) compared to the control group. The authors also note positive associations between levels of mercury or lead and seafood consumption.

Sulaiman and co-workers (2020) carried out a systematic review to determine the association between several metals and ASD. They reviewed 23 studies on mercury; while all the findings reported in each of the studies were not always in agreement, the review overall showed significant associations between mercury exposure and ASD. For mercury, increased levels in hair, urine, and blood were all positively associated with ASD.

Furthermore, a systematic review by Kern, et al. (2016) evaluated 91 studies and concluded that "[o]f 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*." (emphasis added).

As is the case for arsenic and lead, not all studies have shown a positive association between mercury exposure (characterized by hair or blood levels) and ASD. For example, Abdullah, et al. (2012) noted "no significant differences emerged between children with HDB and TD children". Some inconsistencies were noted in the meta-analysis by Saghazadeh and Rezaei (2017) as well as that of Jafari (2017). However, neither the Jafari nor Saghazadeh meta-analyses evaluated the results of the large prospective Ryu (2017) study. In any event, Jafari (2017) explicitly concluded that "mercury is an *important causal factor* in the etiology of ASD" (emphasis added).

The preponderance of studies has established a causal association between mercury levels in various biological media (such as hair and blood) in children and ASD. Indeed, this causal association is also directly supported by the toxicological profile of mercury and its known effects on the human brain, especially in younger children. Given the reasons stated above, and notwithstanding the presence of some negative data, the literature consistently identifies positive associations between mercury exposure and ASD. Accordingly, it is my opinion to a reasonable degree of scientific certainty that mercury exposure is a causal agent of ASD..

IX. ADDITIONAL CONSIDERATIONS

The strengths and limitations of epidemiological approaches were reviewed by Paddle and Harrington (2000). As noted in their publication "the great strength of environmental epidemiology is that it studies the most relevant populations at the most relevant exposure levels." Environmental epidemiology studies are generally designed to establish cause ± effect relationship, and where possible, a dose-response relationship between environmental exposures and health effects. As the topic under discussion is the impact of heavy metal exposures on ASD

and ADHD, it is highly advantageous to study children exposed to heavy metals at different levels and ages, analyze their metal levels in biological media (urine, hair, blood, etc.), and ascertain a possible association with ASD and ADHD. As noted by Paddle and Harrington (2000), advantages of environmental epidemiology studies mitigate the need to extrapolate across species and to extrapolate from high exposures, and when exposure levels are available based on routine measurements (such as those detailed above), recorded health effects (namely, ASD and ADHD) can be evaluated vis-à-vis exposures, and causality can be inferred. A second strength of environmental epidemiology studies is the "wide range of health conditions and exposure scenarios that can be studied".

Nonetheless, the limitations of environmental epidemiology studies must also be considered. Such studies are generally observational, as it is impossible "to locate two populations who differ from one another only inasmuch as one population is" exposed to mercury, lead or arsenic, and the other is exposed to a low level or none. "The populations will, inevitably, also differ genetically, socially, occupationally and psychologically". Some examples of limitations in the studies include, at times, small sample sizes (which were overcome in multiple meta-analyses), and the role of potential confounders (although many studies adjusted for potential confounders, and no actual confounders were noted to have caused systematic bias in the overall data). Methodological limitations such as low statistical power, exposure misclassification, and the effect of potential confounders might explain some the conflicting results found in the literature on the associations between the heavy metals discussed herein and ASD and/or ADHD. Although it must be noted that some potential confounders, such as fish consumption when considering mercury exposure and ASD, likely led to underestimations of the true associations (due to the protective effects of fatty acids from fish consumption).

It is important to note that many of the epidemiological studies discussed here concomitantly assessed exposure and outcome, raising the possibility of reverse causality, meaning that the associations we observe may be the result of disease status as opposed to exposure. However, when the totality of data is considered, and put into the context of the

known toxicological effects of these heavy metals on brain development, I do not believe the results seen in the studies with concomitant exposures and outcomes are the result of reverse causality.

First, the associations are replicated in prospective child cohorts from around the world which did assess exposure *prior* to outcome. In these studies, there is no risk of reverse causality. Moreover, these prospective data are further supported by the availability of studies examining prenatal heavy metals exposures and their impact on ASD and ADHD development, which as discussed above found consistent associations and demonstrate the etiological relevance of heavy metal exposure prior to diagnoses.

Second, studies analyzing baby teeth from early age, and prior to diagnosis, lend further support to a causal association, and undermine any concerns about reverse causality. For example, Arora et al. (2017) used validated tooth-matrix biomarkers to estimate pre- and post-natal exposure profiles of toxic metals, reporting divergences in their levels between ASD cases and their control siblings. Specifically, lead was reported to correlate with ASD severity and autistic traits, suggesting that specific developmental windows (pre- and or post-natal) can increase ASD risk and severity.

Finally, as documented in the preceding sections, arsenic, lead and mercury are able to readily accumulate in the brain tissue and to induce intracellular oxidative stress. Oxidative stress-induced aggregates of hyperphosphorylated tau has been associated with microtubule network degradation commonly associated with neurodevelopmental effects, specifically ASD and ADHD. Beyrent et al. (2020) have shown that increased oxidative stress led to increased overall neuronal tau expression, concomitant with decreased phospho-tau expression, suggesting that oxidative stress induces “changes in tau proteins that precede cytoskeletal degradation and neurite retraction”. These effects will have severe effects on normal brain development, as these organelles “provide structural integrity and support to maintain neural connectivity throughout development”, and abnormalities in neural migration and connectivity of MT-associated proteins, therefore, may lead to detrimental developmental disorders, including intellectual

disabilities and ASD (Lasser et al., 2018). Indeed, one of the prospective epidemiological studies discussed above (Kim, et al., 2016) provided a helpful summary of the myriad of mechanisms relevant to the potential for lead to cause ASD:

> First, lead exposure might affect the nervous system by hindering neurotransmitter release, interfering with energy metabolism, generating reactive oxygen species, and activating apoptosis…Second, lead might influence the nervous system by increasing the risks of conditions such as hypertension, vitamin D deficiency, and impaired thyroid or renal function…Third, the presence of lead might affect the nervous system by inhibiting the formation of key molecules during the mature differentiation of glial cells.

Having carefully considered the risk of confounding due to reverse causality, it is my opinion to a reasonable degree of scientific certainty, that the observed heavy metals in the participants at the time of diagnosis are likely suitable proxies for assessing a meaningful causal relationship and, as proxies, may in fact be underestimating the associations observed. The associations discussed in this report were observed in multiple children cohorts around the world, emphasizing that these outcomes are largely reflected by exposures *per se* to these metals, and likely less so by genetic susceptibility or selection bias. Concerns with reverse causality given the assessment of concomitant exposures and outcomes are largely diminished.

My independent review of the toxicological literature confirms the mechanisms identified by Kim and colleagues (2016) for the causative role of lead in ASD etiology. Moreover, the adverse effects of lead on neuroplasticity at key developmental life periods has been recognized as a plausible mechanism by which lead may cause ASD. As discussed above lead exposure causes neuroinflammation. Smith et al. (2018). This is due to its capacity of regulating multiple neuroinflammatory markers across brain areas, as recently observed by Bjorklund and colleagues (2018) and Kaur, et al. (2021). The available animal literature further supports the biologically plausible role of lead exposure in causing ASD. For example, Chen and colleagues (2019) observed that lead exposure in mice caused elevated pro-inflammatory cytokines – indicative of immune dysregulation associated with ASD. Notably, lead has been observed to have epigenetic

effects, affecting the expression of DNA binding proteins associated with ASD. Schneider, et al. (2012).

Multiple mechanisms have been postulated in understanding the mechanism by which lead can cause ADHD as well. For example, animal data indicates that lead-induced histone acetylation is key to the observed effect of lead exposure (hyperactivity) in rats. Luo, et al. (2014). Research has demonstrated lead-induced damage to the hippocampus, prefrontal cortex, basal ganglia, and the cerebellum, all of which are relevant to ADHD etiology. Goodlad., et al. (2013). For example, reduced volume and activity of the prefrontal cortex and cerebellum have been observed in individuals with ADHD. Karri, et al. (2016); Finkelstein, et al. (1998). Lead is known to interact with the NMDA receptor, thus leading to damage to the hippocampus. Given the tendency of lead (as well as mercury and arsenic) to cross the blood-brain barrier, it has been noted to affect neurotransmitter systems relevant to ADHD etiology, such as, specifically, the dopaminergic, cholinergic (attention, impulsivity, and memory), and glutaminergic systems. Cory-Slechta, et al. (1995); Goodlad, et al. (2013).

Mercury has been demonstrated to affect DNA methylation – a suspected mechanism of ASD – in rat models. Overall, the biologically plausible role of mercury in ASD etiology has been repeatedly verified, particularly with reference to oxidative stress. As Garrecht & Austin (2011) observed, "[mercury] has well-known effects relating to the disruption of sulfur chemistry leading to elevated oxidative stress which, in turn, results into broader physiological/organ affects, particularly to the CNS. Oxidative stress was consistently elevated in ASD… the *existing scientific literature supports the biological plausibility of a [mercury]-based ASD pathogenesis*." (emphasis added). As with lead, mercury exposure is a pathway to neuroinflammation, another recognized mechanism in ASD etiology. Garrecht & Austin (2011). And, as discussed further below, such mechanisms are especially pertinent when considering pediatric populations during key developmental windows, with Pletz, et al. (2016) noting that "the time window which encompasses the vulnerability of the brain to disturbances of all these processes is ample."

The plausible mechanistic role of arsenic exposure in ASD etiology has been

demonstrated by abnormal frontal cortex neurogenesis observed in animal studies. Zhou et al. (2018). As discussed above, Tolins, et al. (2014) noted that animal data have associated arsenic exposure with alterations in brain cells and neurotransmitters, with both processes implicated in ASD. Similar to lead and mercury, arsenic also causes oxidative stress (considered relevant to ASD development) and also affects epigenetic changes associated with ASD. As discussed above, arsenic exposure has further been associated with related neurodevelopmental deficits such as memory hyperactivity. Tolins, et al. (2014); Vahter, et al. (2020).

A recent article by Gibb et al., 2019, presents an overview of the burden of disease from arsenic, methylmercury and lead, and discusses these three metals in the context of the World Health Organization's initiative to estimate the global burden of foodborne disease. The results indicate that in 2015, ingestion these metals resulted in more than 1 million illnesses, over 56,000 deaths, and more than 9 million disability-adjusted life years (DALYs) worldwide. Notably, arsenic, methylmercury and lead were shown to have high DALYs per case in comparison with other foodborne disease agents, including infectious and parasitic agents. In addition, the authors (Gibb et al., 2019) reported that lead, arsenic, and methylmercury had high DALYs per 100,000 population in comparison to other foodborne disease agents.

When addressing foodborne diseases, consideration of the potential effects of arsenic, mercury, and lead on brain development in the early years of childhood is only complete if we consider the origins of this process during the prenatal months.

Brain development is a protracted process that starts about 2 weeks after conception and comprises a number of key stages that progress through the neonatal and infant period well into adolescence before the brain is fully mature. The brain continues to develop well into young adulthood (20 years). Brain development during the prenatal and post-natal months is largely subject to genetic control, although clearly the environment can play a role; for example, lack of nutrition (e.g., folic acid) and the presence of toxins, such as the one discussed herein, can both deleteriously influence the developing brain. Given the propensity of arsenic, mercury, and lead to adversely affect many processes responsible for the brain's growth and maturation, especially

during the sensitive developmental window when toddlers are undergoing critical growth, it is clear that these metals can have long-term negative consequences on the child's brain, resulting in a constellation of neurological impairments of which ASD and ADHD have also been recognized.

In addition, it needs to be considered that the current animal and human literature of metal-induced neurotoxicity is primarily confined to single metal exposures. The literature addressing the neurodevelopmental effects of metal mixtures is still emerging. However, studies have, for example, addressed the effects combined metal exposures, such as lead and mercury. Shah-Kulkarni and colleague (2020) addressed the effects of prenatal metal exposure in early pregnancy (12-20 weeks), late pregnancy (>28 weeks), and at birth on neurodevelopment of infants at 6-months-of-age. In this epidemiologic study of 523 eligible mother-child pairs, the authors have demonstrated "the effect of combined exposure to metals on the neurodevelopment of infants aged 6 months, with significant interaction between lead and mercury". Joint effects of prenatal exposure to metal mixtures on neurodevelopmental outcomes at 20-40 months-of-age have also been reported in children exposed to arsenic and manganese (Valeri et al., 2017). Moreover, Boucher, et al. (2012) observed a synergistic effect of lead and mercury mixtures on neurodevelopment following prenatal exposure. Namely, the combined effects of lead and mercury will be greater than the sum of their separate effects.

Therefore, exposure to multiple metals will lead to greater neurological effects than exposure to a single metal. It is my opinion to a reasonable degree of scientific certainty that oral metal mixtures will lead to additive and synergistic effects of these metals, given that they share common toxicological modes-of-action. Thus, neurotoxicity for these metals as mixtures will increase the cumulative risk for neurological dysfunction (Shah-Kulkarni et al., 2020; Valeri et al., 2017).

The developmental stage at which an infant/toddler is exposed to excessive levels of heavy metals should also be considered (see below; and, National Research Council (US) and Institute of Medicine (US) Committee on Integrating the Science of Early Childhood

Development, 2000). The human brain develops in a protracted fashion, starting in the third gestational week with differentiation of the neural progenitor cells and extending at least through late adolescence, and most likely through lifespan.

Notably, at birth, the average neonate's brain is about a quarter of the size of the average adult size (Stuart and Stevenson, 1950, 1959; Huelke, 1998). The first year is extremely dynamic, the brain doubling in size. By 3 years, the brain reaches about 75% of the adult size, and by the age 3 it is nearly full-grown, ~90% of adult brain size. Brain development is characterized as a complex series of dynamic and adaptive processes that synchronously operate throughout the course of development to enable the emergence and differentiation of new neural structures and functions. These processes operate within highly constrained and genetically organized, but constantly changing contexts that, over time, support the emergence of the complex and dynamic structure of the human brain (Stiles and Jernigan, 2010).

While the generation and migration of neurons occur largely in the prenatal period, proliferation and migration of glial progenitors continues for an extended period after birth, and the differentiation and maturation of these cells continue for a protracted period, throughout childhood (Stiles and Jernigan, 2010). The early childhood years are also highly crucial for synaptogenesis (connections between the various neurons). At least one million new neural connections (synapses) are made every second, more than at any other time in life. As described above, given their mode of action, arsenic, mercury, and lead will target critical neurodevelopmental processes – the interruption or disturbance of which are implicated in both ASD and ADHD – which are largely absent in the adult brain. Therefore, exposure to heavy metals will have a disproportionate adverse effect on the developing brain.

As pointed out in the ECP (2021; 2021a) reports, exposure to heavy metals during the developmental window can lead to long-lasting brain damage (Grandjean et al., 2014). For example, exposure to environmental chemicals, including lead, is estimated to cause a 40,131,518 total IQ points loss in 25.5 million children (or roughly calculated to correspond to 1.57 lost IQ points per child), exceeding the combined IQ losses due to preterm birth

(34,031,025), brain tumors (37,288), and traumatic brain injury (5,827,300) (Bellinger et al., 2011). Furthermore, it is estimated that for every one IQ point lost, it is estimated that a child's lifetime earning capacity will decrease by $18,000 (Bellinger et al., 2013). No published literature could be found addressing the combined effects on IQ of metal mixtures containing the three metals - arsenic, mercury and lead. Nonetheless, as noted above (Shah-Kulkarni et al., 2020; Valeri et al., 2017), the available scientific evidence indicates significant interaction between them, and likely underestimates the magnitude of the effect on a child's IQ.

One also needs to consider that neurological adverse effect of early life exposure to these metals may not be unmasked for years or decades to come (Arkadir et al., 2014).

The nervous system is highly redundant and with the ability to disguise the severity of an initial toxic insult. Take for example, Parkinson's disease, the second most common age-related complex, idiopathic neurological disorder in humans (Federoff, 2009; Harris et al., 2020). At the cellular and molecular level, the hallmark pathological features of Parkinson's disease include the loss of cells containing the neurotransmitter dopamine in the substantia nigra pars compacta, depletion of dopamine in the striatum, and development of Lewy bodies, which are an accumulation of misfolded proteins (including alpha-synuclein, phosphorylated tau, and amyloid beta) in intracellular spaces in the substantia nigra pars compacta (SNpc). Most notably, at the time of clinical presentation of Parkinson's disease, it has been estimated that 60-80% of dopaminergic neurons in the SNpc have already degenerated (Federoff, 2009).

Similarly, a child exposed to metals such as arsenic, lead, and mercury at, for example, 6-months of age may not reveal adverse health consequences for months or years. There are different mechanisms by which metal-induced neurological deficits could interact with age. For example, cumulative damage could eventually reach a detectable level, or otherwise latent damage may be unmasked only as age-related impairments further challenge functional difficulties (Newland and Rasmussen, 2000).

Importantly, the inability to detect heavy metals in hair, urine and/or blood of an individual does not exclude their persistence in the brain. For example, estimated half-lives of

brain inorganic mercury are several years to several decades, where it is basically trapped in the brain so levels in blood (or other biological media) would be expected to be very low (Rooney, 2013) or non-detectable. The half-life of lead in humans (bone) is estimated at a range of 15 to 20 years (ATSDR 2007), and will be a continued source of low-level exposure. The half-life of lead in brain is in the order of months (ATSDR 2007).

Blood levels of mercury decrease rapidly with half-life of three to five days.[8] The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of its methylated metabolites is 20 to 30 hours.[9] The half-life of lead is 1 to 2 months.[10]

As extensively documented herein, heavy metals are able to gain access to the developing brain and cause neurotoxic effects. A plethora of established animal models link prenatal and early postnatal exposure to these heavy metals and ensuing reduction in brain weight, reduction in numbers of glial and neuronal cells, and alterations in neurotransmitter systems, and neurogenesis, to name a select few effects, all of which have been recognized as modes of action that cause the manifestation of neurodevelopmental disorders such as ASD and ADHD. These effects may occur at levels of exposure below current safety guidelines, and some neurocognitive consequences may become manifest only later in life, weeks, months or years. Furthermore, levels of metals may persist months and years after exposure ceased, and their effects could be attributed to their persistence in the brain.

Finally, it is noteworthy that altered dopaminergic system functioning in response to heavy metal exposures has been implicated in the etiology of both ASD and ADHD. For example, lead exposure has been associated with the occurrence of ASD (Toscano and Guilarte, 2005; Kim et al., 2013; Moreira et al., 2001) as well as ADHD (Luo et al., 2014). Early postnatal exposure to mercury has been shown to cause lasting neurobehavioral impairments and neurochemical alterations in dopaminergic neurotransmission (Olczak et al., 2010). These

[8](https://www.atsdr.cdc.gov/toxprofiles/tp46.pdf).
[9](https://www.atsdr.cdc.gov/toxprofiles/tp2.pdf).
[10](https://www.atsdr.cdc.gov/toxprofiles/tp13.pdf).

findings are all consistent with observations that altered behaviors arise from a dysfunctional midbrain dopaminergic circuits originating in the midbrain, namely, the mesocorticolimbic and nigrostriatal pathways (Pavăl et al., 2021; Tripp and Wickens, 2008). It is thus plausible that exposure to heavy metals, such as arsenic, lead and mercury, alone or in mixtures, may disrupt dopaminergic functions, underlying the neurodevelopmental deficits inherent to ASD and ADHD.

Dated: November 12, 2021

Michael Aschner, Ph.D.

Dr. Aschner Reference List

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293.	Cory-Slechta	1995	Relationships Between Lead-Induced Learning Impairments and Changes in Dopaminergic, Cholinergic, and Glutamatergic Neurotransmitter System Functions
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295.	Cory-Slechta	2003	Lead-induced impairements in complex cognitive function: Offerings from experimental studies
296.	Cory-Slechta, et al.	1998	Nucleus accumbens dopaminergic medication of fixed interval schedule-controlled behavior and its modulation by low-level lead exposure
297.	Cory-Slechta & Widzowski	1991	Low level lead exposure increases sensitivity to the stimulus properties of dopamine D1 and D2 agonists
298.	Cory-Sletcha	1990	Exposure duration modifies the effects of low level lead of fixed - interval performance
299.	Cory-Sletcha, et al.	2002	Lead exposure and dorsomedial striatum mediation of fixed interval schedule - controlled behavior
300.	Cory-Sletcha, et al.	1996	The effects of dopamine agonists on fixed interval schedule - controlled behavior are selectively altered by low - level lead exposure
301.	Zhou, et al.	2018	Postnatal low-concentration arsenic exposure induces autism-like behavior and affects frontal cortex neurogenesis in rats
302.	Vahter, et al.	2020	Prenatal and childhood arsenic exposure through drinking water and food and cognitive abilities to 10 years of age: A prospective cohort study
303.	Pletz, et al.	2016	Dose-response analysis indicating time-dependent neurotoxicity caused by organic and inorganic mercury- Implications for toxic effects in the developing brain
304.	Garrecht & Austin	2011	The plausibility of a role for mercury in the etiology of autism: a cellular perspective

Dr. Aschner Reference List

#	Author(s)	Year	Title of Article
305.	U.S. Department of Health and Human Services	1999	Toxicological Profile for Mercury
306.	U.S. Department of Health and Human Services	2007	Toxicological Profile for Arsenic
307.	ATSDR	2020	Toxicological Profile for Lead

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Aschner, Michael

POSITION TITLE: Professor Molecular Pharmacology, Neuroscience and Investigator Kennedy Intellectual and Development Disabilities Research Center, Albert Einstein College of Medicine, Bronx, NY

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Rochester, Rochester, NY	BS	08/1980	Natural Sciences
University of Rochester, School of Medicine	MS	05/1983	Anatomy
University of Rochester, School of Medicine	PhD	12/1985	Neurobiology/Anatomy
University of Rochester, School of Medicine	PostDoc	12/1987	Toxicology
Fourth Military Medical School, Xi'an, China	Hon PhD	08/2012	Honorary

A. Personal Statement

My research interest is on the interaction between genetics and the environment in triggering disease both during CNS development and senescence. I have been interested in metal uptake and distribution in the brain, devoting the last 25 years of my research to the mechanisms of transport of methylmercury (MeHg) and manganese (Mn) across the capillaries composing the blood–brain barrier (BBB), as well as their cellular and molecular mechanisms of neurotoxicity. I have ample experience in both *in vivo* and *in vitro* models of BBB, and have tested the transport of several metals into the brain, including uranium, under the auspices of a DoD funded grant. Our studies address basic mechanisms in various experimental models (*C. elegans*, tissue culture and rodents), and they are designed to *(i)* increase the understanding of the genetic influences on health especially as it relates to neurological diseases; *(ii)* increase knowledge of the pathway involved in neurotoxicity as well as the impact of these processes on neurodegeneration; *(iii)* develop improved research models for environmental sciences and biology; and *(iv)* use environmental toxicants to understand basic mechanisms of neurobiology.

B. Positions and Honors

Positions

1988-1994 Assistant Professor (1988-1992); Associate Professor (1992-1994), Dept. of Pharmacology & Toxicology, Albany Medical College, Albany, NY.

1994-2004 Associate Professor (1994-1999); Professor (1999-2004), Dept. of Physiology & Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC.

2004-2013 Gray E. B. Stahlman Chair in Neuroscience, Professor of Pediatrics and Pharmacology, and Senior Scientist at the Kennedy Center for Research on Human Health, Vanderbilt University Medical Center, Nashville, TN.

2005-2013 Director, Division of Pediatric Clinical Pharmacology and Toxicology.

2011-2013 Director, NIEHS Molecular Toxicology Center P30ES000267.

2011-2013 Director, NIEHS Training Program in Environmental Toxicology 5T32ES007028.

2013-Pres. Harold & Muriel Block Chair in Molecular Pharmacology, Professor of Molecular Pharmacology, Pediatrics & Neuroscience, Investigator Kennedy Intellectual & Developmental Disabilities Research Center. Albert Einstein College of Medicine, Bronx, NY.

2017-Pres. Adjunct Professor and P30 Center Member, Department of Environmental Medicine & Public Health, Lautenberg Laboratory for Environmental Health, Icahn School of Medicine at Mount Sinai, New York, NY.

2017-Pres. Member, Institute for Exposomic Research at the Icahn School of Medicine at Mount Sinai. Icahn School of Medicine at Mount Sinai, New York, NY.

Honors

1995-Pres. Reviewer, multiple Special Emphasis Panels NIH, EPA, ATSDR, FDA, NSF.
1997-Pres. Member, Academy of Toxicological Sciences.
1997-1998 President (elected), Neurotoxicology Specialty Section of the Society of Toxicology.
1998-2001 Member, Committee on Health Effects Associated with Exposures Experienced During the Gulf War, Institute of Medicine, National Academy of Sciences, Division of Health.
1999-2000 Member, Committee to Review EPA's Maximum Contaminant Level Goal for Copper in Drinking Water, National Research Council, National Academy of Sciences.
2000-2001 Member, Committee to Review Navy's Proposed Submarine Escape Action Levels (SEALs) for Selected Chemicals, National Research Council, National Academy of Sciences.
2000 External Reviewer, National Academy of Science, Committee on Toxicological Effects of Mercury, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, National Academy Press, Washington DC
2001 External Reviewer, National Academy of Science, Committee on Thimerosal and Neurodevelopmental Outcomes, Institute of Medicine Immunization Safety Review Committee, National Academy Press, Washington, DC.
2002-2003 Chair, Alcohol and Toxicology (ALTX) 3 Study Section, NIH.
2006-2009 Consultant, the National Vaccine Injury Compensation Program, US Department of Justice
2006 Member, Joint Meeting of the Center for Radiological Health (CDRH) Dental Products Panel and the Center for Drug Evaluation and Research (CDER) Peripheral and Central Nervous System Drugs Advisory Committees. Safety of Dental Amalgams.
2007-2008 Member, Committee on Health Effects Associated with Exposures Experienced During the Gulf War, Institute of Medicine, Division of Health Promotion and Disease Prevention, National Academy of Sciences.
2008 Recipient, Vanderbilt University Medical Center Annual Postdoc Mentor of the Year Award
Sept. 2009 U.S. FDA, Advisory Committee Service Award, National Center for Toxicological Research.
2011 Society of Toxicology Merit Award in recognition of distinguished contributions to toxicology.
April 2012 Member, Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) meeting: Chlorpyrifos Health Effects, Environmental Protection Agency.
2012-Pres. Member, Neurotoxicology and Alcohol (NAL) Study Section, NIH
Nov. 2012 Fellow (Elected), American Association for the Advancement of Science
2013-2015 President (elected), International Society of Trace Element Research in Humans.
2014-Pres. Member, External Advisory Board, Mt. Sinai Medical School, Superfund Research Program, New York, NY.
2014-Pres. Member, External Advisory Board, University Of Washington, Superfund Research Program, Seattle, WA.
2014-Pres. Member, Scientific Advisor, UC Davis Center for Children's Environmental Health, Davis, CA.
2014-2019 Member, External Advisory Committee, Rhode Island IDeA Network of Biomedical Research Excellence, University of Rhode Island, Kingston, RI.
2014-2019 Member, External Advisory Committee, NIEHS P30 Center for Research on Environmental Disease (CRED), University of Kentucky, Lexington, KY.
2015-2018 Member, External Advisory Committee, The NIEHS Center for Environmental Health in Northern Manhattan, Columbia University, New York, NY.
2015-Pres. Member, T32 on Children's Environmental Health Research, National Institute of Child Health and Human Development (NICHD), Mount Sinai University School of Medicine.
2016-2019 Treasurer, and Council Member, Society of Toxicology
2016 Career Achievement Award, Metal Specialty Section, Society of Toxicology
2017-Pres. Member, Scientific Advisory Board, National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA), Jefferson, AR. Chair, 2019-2021.
2017 Programme Reviewer, Medical Research Council, Environmental Health, Pharmacology and Toxicology, London, UK.
2017 Chair, NIH - ZRG1 IFCN-J (02) special emphasis panel
2017 *Ad hoc* Member, W81XWH-11-D-0017, Department of Defense (DoD) Peer Reviewed Medical Research Program (PRMRP), Chantily, VA.

2019-2020 President of the Academy of Toxicological Sciences, Raleigh, NC.
March 2018 Peer reviewer, Eastern Research Group, Inc. (ERG). Reviewer of U.S. EPA's draft Provisional Peer-Reviewed Toxicity Values for Lanthanum (CASRN 7439-91-0).
2018-Pres. European Registered Toxicologist (ERT).
Sept. 2019 Center for Disease Control (CDC)/Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services**.** External Peer Reviewer of Toxicological Profile of Molybdenum**.** Agency for Toxic Substances and Disease Registry.
2020-2024 Vice-President-Elect, Vice-President, President and Past-President, Society of Toxicology
March 2020 Career Achievement Award, Neurotoxicology Specialty Section, Society of Toxicology.
Sept. 2020 *Ad hoc* Member, W81XWH-11-D-0020, Department of Defense (DoD) Peer Reviewed Medical Research Program (PRMRP).

Editor: Biomed Central Pharmacology and Toxicology (2012-2020); Adv in Neurotoxicology (2017-)

Associate Editor: Neurotoxicology (1995-), Toxicological Sciences (2005-2016), Neurochemistry Research (2011-), Biochemistry and Pharmacology (2013-), Section-Editor for Frontiers in Toxicogenomics (2014-2020), Toxicology Reports (2014-2020), Journal of Environmental Neuroscience and Biomedicine (2010-), Chemical and Food Toxicology (2017-) **Editorial Boards**: Toxicology (2005-), Clinical Nutrition (2005-), Acta Neurobiologiae Experimentalis (1999-present), Acta BioMedica (2007-), Environmental Bioindicators (2007-), Journal of Toxicology (2008-), Alcohol (2006-), Journal of Biomedicine and Biotechnology (2008-), Toxins (2009-), American Journal of Clinical Neurology (2009-), F1000 Research's Editorial Board (2013-), Chemical Research in Toxicology (2014-), Advances in Neurobiology (2015-), Archives Industrial Hygiene and Toxicology (2017-)

C. Contributions to Science

Over the last 3 decades, studies in our laboratory were designed to *(1)* shed novel mechanistic insight into metal-induced neurodegeneration; *(2)* identify targets for genetic or pharmacologic modulation of neurodegenerative disorders; *(3)* increase knowledge of the pathway involved in brain-induced oxidative stress; *(4)* develop improved research models for human disease using knowledge of environmental sciences. The following are deemed major thematic contributions to scientific understanding on multiple facets associated with environmental links to neurodegenerative diseases:

1. Our early work directly characterized the molecular mechanisms of methylmercury neurotoxicity, particularly in glial cells. This pioneer work has allowed a shift from the "neuronocentric" theory of neurotoxicity to the understanding of the importance of glial cells in modulating the neurotoxicity of this organometal. Indeed, an important theme that has emerged from this research is the role of glia in neurotoxicity. Notably, in the late 1980s and early 1990s, glial cells were still viewed as mere support cells for neurons; hence the findings that altered homeostatic control in glia secondary to methylmercury exposure is a trigger for neurodegeneration was deemed novel in the field. By providing evidence for the preferential accumulation of methylmercury in glia, next we could follow with molecular studies to characterize mechanisms of methylmercury-induced neurotoxicity (see 2., below). I was the PI on several NIH and EPA grants at the time, and this work has led to the following significant publications:
    a. **Aschner M**, Clarkson TW. Amino acid carrier-mediated uptake of methylmercury across the blood-brain barrier. Brain Res 1988; 462:31-39 (PMC unavailable).
    b. **Aschner M**, Clarkson TW. Distribution of 203 mercury in pregnant dams and their fetuses following systemic infusions with thiol-containing amino acids and glutathione, during late gestation. Teratology 1988; 38:145-155 (PMC unavailable).
    c. **Aschner M**, Eberle N, Goderie S, Kimelberg HK. Methylmercury uptake in rat primary astrocyte cultures: the role of the neutral amino acid transport system. Brain Res 1990; 521:221-228 (PMC unavailable).
    d. **Aschner M**, Eberle N, Kimelberg HK. Interaction of methylmercury with rat primary astrocyte cultures: methylmercury efflux. Brain Res 1991; 554:10-14 (PMC unavailable).
2. In addition to the contributions described above, with a team of collaborators, I directly documented molecular mechanisms of methylmercury-induced neurotoxicity, with major emphasis on the role of oxidative stress in this process. I also addressed potential neuroprotective mechanisms against metal-induced neurotoxicity, focusing on metallothionein and the role of astrocytic regulatory volume decrease in mediating brain-associated injuries. Fixation on transgenic models as early as the 1990s permitted initial characterization on the interaction between genes x environment, and was highly innovative for this time period. Ultimately these

translational studies characterized molecular mechanisms of neurotoxicity and potential targets for the mitigation of neurotoxic injuries.

a. Vitarella D, DiRisio D, Kimelberg HK, **Aschner M**. Potassium and taurine release are highly correlated with regulatory volume decrease in neonatal primary rat astrocyte cultures. J Neurochem 1994; 63:1143-1149 (PMC unavailable).
b. Dave V, Mullaney KJ, Goderie S, Kimelberg HK, **Aschner M**. Astrocytes as mediators of methylmercury (MeHg) neurotoxicity: Effects on D-aspartate and serotonin (5-HT) uptake. Develop Neurosci 1994;16:222-231 (PMC unavailable).
c. **Aschner M**. The functional significance of brain metallothioneins, FASEB J.1996; 10:1129-1136 (PMC unavailable).
d. Rising L, Vitarella D, Kimelberg HK, **Aschner M**. Metallothionein induction in neonatal rat primary astrocyte cultures protects against methylmercury cytotoxicity. J Neurochem 1995; 65:1562-1568 (PMC unavailable).

3. Given wide-spread usage of manganese and the recognition that excessive brain manganese resulting from occupational or environmental exposure, or disease (hepatic encephalopathy) may result in a Parkinsonism syndrome (see below), I focused since the 1990s on mechanisms of brain manganese uptake, its distribution, and molecular mechanisms that render excess brain manganese a risk factor for neurodegeneration. Early studies characterized transport mechanisms of manganese across the blood-brain barrier and identified the divalent metal transporter 1 (DMT1) as a putative carrier for manganese. Furthermore, given the transporter's propensity for shared transport of other divalent metals and the existing endemic deficiencies in global iron status (> 1 billion people), I have shown in cellular, molecular and magnetic resonance imaging studies that iron deficiency is a critical risk factor for increased manganese brain deposition and ensuing dopamine neurodegeneration. I have further characterized additional transporters for manganese, providing putative targets for pharmacological interventions and the maintenance of optimal manganese brain concentrations, thus reducing the risk for dopaminergic neurodegeneration.
    a. Milatovic D, Yin Z, Gupta RC, Sidoryk M, Albrecht J, Aschner JL, **Aschner M**. Manganese induces oxidative impairment in cultured rat astrocytes. Toxicol Sci 2007; 98:198-205 (PMC unavailable).
    b. Lee, ES, **Aschner M**. Estrogen and tamoxifen reverse manganese-induced glutamate transporter impairment in astrocytes. J Neurochem 2009; 110:530-544 (PMC unavailable).
    c. Sidoryk-Węgrzynowicz M, Lee E, Albrecht J, **Aschner M**. Manganese disrupts astrocyte glutamine transporter expression and function**.** J. Neurochem 2009; 110:822-830 (PMC2756186).
    d. Sidoryk-Węgrzynowicz M, Lee, E-S, **Aschner M**. Manganese-induced downregulation of astroglial glutamine transporter SNAT3 involves ubiquitin-mediated proteolytic system. Glia 2010; 58:1905-1912 (PMC unavailable).

4. Despite defined genetic and environmental factors we lack mechanistic understanding of the gene by environment interface of selective dopaminergic (DAergic) vulnerability. Accordingly, over the last decade I have focused our studies on understanding gene x environment interactions in the etiology of this disease, utilizing the nematode (*C. elegans*) as a model system. Our work has united state-of-the-art technological and scientific breakthroughs to perform studies that would not have been possible just a few years ago. The first breakthrough is the utilization of novel genetic tools for oxidative stress analysis in a transgenic worm line carrying P_{gst-4}::GFP along with transgenic animals selectively expressing green fluorescent protein (GFP) in DAergic neurons (P_{dat-1}::GFP). With my MPI collaborator, Dr. Bowman (Purdue University), we have also used human induced pluripotent stem cells (hiPSC) based technology and neurodevelopmental ontogeny recapitulating differentiation protocols, which enable the study of environmentally relevant toxicant exposures in an *in vitro* model of specific human neural lineages. In select studies, we have also used small molecule screens (library of 180,000 compounds). Combined, these studies have tested for genetic modifiers of methylmercury- and manganese-induced DAergic neurotoxicity, identifying potential targets for novel therapeutic approaches.
    a. Leyva-Illades D, Chen P, Zogzas CE, Swaim CD, Bowman AB, **Aschner M**, Mukhopadhyay S, Mutations in SLC30A10 block its intracellular trafficking and manganese efflux activity to cause a hereditary parkinsonian disorder. J Neurosci 2014; 34:14079-14095 (PMC4198546).
    b. Chen P, Bowman AB, Mukhopadhyay S, **Aschner M**. SLC30A10: a novel manganese transporter. Worm 2015; DOI: 10.1080/21624054.2015.1042648 (PMC4588552).
    c. Prince L, Bowman AB, Aschner M. Human-induced pluripotent stems cells as a model to dissect the selective neurotoxicity of methylmercury. Biochim Biophys Acta - Mol Basis Dis 2019; 1863:129300 (PMC6689259).

d. Caito SW, Newell-Caito J, Martell M, Crawford N, **Aschner M**. Methylmercury induces metabolic alterations in *Caenorhabditis elegans*: Role for C/EBP transcription factor. Tox Sci 2020; 174:112-123 (PMC7043228).

Complete List of Published Work:
Link to peer-reviewed publications: Citations: >45,000; h-index: 96; ORCID ID: 0000-0002-2619-1656
>700 PubMed publications; https://pubmed.ncbi.nlm.nih.gov/?term=aschner+m

D. Additional Information: Research Support and/or Scholastic Performance

Current

NIH R21 ES028960 (Zhang, Z.) 07/01/18-06/30/21 No Cost Extension through 06/30/21
Role of Autophagy in Manganese-Induced 1.2 cal mo
Neurotoxicity **(Aschner, M. - Co-Investigator)**
The proposal tests the hypothesis that Mn impairs autophagy by inhibiting TFEB activity, and that compromised autophagy contributes to the pathogenesis of Mn neurotoxicity. The proposed study will provide novel information about cellular and molecular mechanisms underlying Mn-induced neuropathology, which may serve as a foundation for generating efficacious therapeutic strategies to combat Mn toxicity.

NIH 1R01 ES024756 (Lee) 1/1/16-12/31/20 1.2 cal mo
Mechanism of manganese-induced impair-
ment of astrocytic glutamate transporters
(Sub - Florida A&M University) **(Aschner, M. - Co-Investigator)**
Project Goals: We will study the mechanism involved in Mn-induced repression of GLT-1 at the transcriptional level to identify the molecular target of Mn effect on GLT-1 by testing the role of the transcriptin factor yin yang 1 (YY1) in this Mn effect.

NIH 1R01 ES024812 (Mukhopadhyay) 01/01/16-12/31/20 0.6 cal mo
Regulation of Manganese Homeostasis and
Detoxificatin by SLC30A10 (Sub-U. Texas) **(Aschner, M. - Co-Investigator)**
This grant application will determine the process by which Mn is removed from human cells. These studies will lay the foundation for developing drugs that can treat Mn-induced Parkinsonism by increasing the removal of Mn from cells.

5 R01ES007331 (Aschner/Bowman) 03/01/96-05/31/21 3.0 cal mo Renewal of current grant
NIH/NIEHS - includes sub to Purdue U.
Mechanisms of Methylmercury Induced Neuron Toxicity
This study aims to (1) identify genetic modifiers of MeHg-induced neurotoxicity in C. elegans, (2) compare and contrast MeHg developmental neurotoxicological outcomes in human nigral versus cortical neural lineages, and (3) evaluate mechanisms by which genetic pathways modify MeHg developmental neurotoxicity.

5 R01 ES010563 (Aschner/Bowman) 07/01/00-03/31/23 2.4 cal mo
NIH/NIEHS
Mechanisms of Manganese Neurotoxicity
Subcontract with Purdue ($290,163)
In the third competitive renewal, this program is testing the hypothesis that threshold-level Mn neurotoxicity occurs via alteration of Mn-dependent/-activated biological functions such as insulin/insulin-like growth factor and related metabolic signaling pathways and dopamine neuronal function in worms and mammalian systems.

NIH R01 NS110760 (Ballabh) 05/15/19-02/29/24 0.5 cal mo
Intraventricular Hemorrhage Affects
Production of Cortical Interneurons **(Aschner, M. - Co-Investigator)** .
Even though IVH results in neuro-psychiatric disorders, there is no information on how hemorrhage affects production of interneuron progenitors, fate of progenitors and their positioning in the cortical layers. It is unknown if minimizing oxidative stress will restore neurogenesis and density in the cortical interneurons in the survivors of IVH. It is also unclear how effectively a specific interneuronal deficit can be normalized in a developmental model of perinatal insult.

Dr. Aschner Peer-Reviewed Publications, 2011-2021

Schusheim S, Aschner M, Brodsky B, Proscura E, Erlanger-Rosengarten A, Feldman R, Shapira E, Wormser U. Anti-inflammatory effects of novel peptides. Peptides 2011; 32:125-30.

Meinerz DF, Sudati JH, dos Santos DB, Frediani A, Alberto EE, Allebrandt J, Franco JL, Barbosa NBV, Aschner M, Rocha JBT. Evaluation of the biological effects of (*S*)-dimethyl 2-(3-(phenyltellanyl) propanamido) succinate, a new telluro amino acid derivative of aspartic acid. Arch Toxicol 2011; 85:43-9.

Aitlhadj L, Ávila DS, Benedetto A, Aschner M, Sturzenbaum SR. Environmental exposure, obesity and Parkinson's disease: Lessons from fat and old worms. Environ Health Perspect 2011; 119:20-8.

Dydak U, Jiang Y, Long L, Zhu H, Li WM, Chen J, Long Z, Fu X, Hu S, Edden RAE, Meier D, Aschner M, Harezlak J, Murdoch J, Zheng W. Alteration in brain GABA concentrations by magnetic resonance spectroscopy in smelters occupationally exposed to manganese. Environ Health Perspect 2011; 119:219-24.

Shelton R, Sidoryk-Węgrzynowicz M, Reddy R, Aschner M, Lewis DL, Mirnics K. Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. Mol Psychiat 2011; 16:751-62.

Sidoryk-Węgrzynowicz M, Węgrzynowicz M, Lee, E-S, Bowman AB, Aschner M. Role of astrocytes in nervous system disease. Toxicol Pathol 2011; 39:115-23.

Fitsanakis V, Zhang N, Erikson KM, Avison MC, Gore JC, Aschner M. Changes in dietary iron exacerbate regional brain manganese accumulation as determined by magnetic resonance imaging. Toxicol Sci 2011; 120:146-53.

Martinez-Finley E, Chakraborty S, Ávila DS, Aschner M. Insights from *C. elegans* on the role of metals in neurodegenerative diseases. Metallomics 2011; 3:271-9.

Dos Santos APM, Santos ML, Dias D, Aschner M, Batoréu CM. Search for biomarkers to control and prevent the risk of neurotoxicity induced in rats sub-acutely exposed to $MnCl_2$. Brain Res 2011; 1382:282-90.

Roos DH, Puntel RL, Farina M, Aschner M, Bohrer D, Rocha JBT, Barbosa NBV. Modulation of methylmercury uptake by methionine: Prevention of mitochondrial dysfunction in rat liver slices by a mimicry mechanism. Toxicol Appl Pharmacol 2011; 252:28-35.

Zhaobao Y, Lee ES, Ni M, Jiang H, Milatovic D, Farina M, Rocha JBT, Aschner M. Methylmercury-induced alterations in astrocyte functions are attenuated by ebselen. Neurotoxicology 2011; 32:291-9.

Ni M, Li X, Yin Z, Sidoryk-Węgrzynowicz M, Jiang H, Farina M, Rocha JBT, Syversen T, Aschner M. Comparative study on the response of rat primary astrocytes and microglial cells to methylmercury toxicity. Glia 2011; 59:810-20.

Milatovic D, Montine TJ, Aschner M. Prostanoids signaling: dual role for PGE_2 in neurotoxicity Neurotoxicology 2011; 32:312-9.

Caito SW, Milatovic D, Hill KE, Aschner M, Burk RF, Valentine WM. Progression of neurodegeneration and morphologic changes in the brains of juvenile mice with selenoprotein P deleted. Brain Res 2011; 1398:1-12.

Aschner M. Volume measurements in cultured primary astrocytes. In: *In vitro* neurotoxicology – methods and protocols. Method Mol Biol 758:391-402.

Milatovic D, Montine TJ, Aschner M. Measurement of isoprostanes as markers of oxidative stress. In: *in vitro* neurotoxicology – methods and protocols. Method Mol Biol 758:195-204.

Sidoryk-Węgrzynowicz M, Lee ES, Ni M, Aschner M. Protein kinase Cδ is involved in manganese-mediated disruption of glutamine turnover in astrocytes. Glia 2011; 59:1732–1743.

Farina M, Rocha JBT, Aschner M. Mechanisms of methylmercury-induced neurotoxicity: evidence from experimental studies. Life Sci 2011; 89:555-63.

Albrecht J, Sidoryk-Węgrzynowicz M, Zielińska M, Aschner M. Role of glutamine in neurotransmission. Neuron Glia Biol 2011; Neuron Glia Biol 21:1-14.

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Le TM, Jiang H, Cunningham GR, Magarik JA, Barge WS, Cato MC, Lee ES, Farina M, Rocha JBT, Milatovic D, Lee ES, Summar ML, Aschner M. γ-glutamylcysteine ameliorates oxidative injury in neurons and astrocytes *in vitro* and increases brain glutathione *in vivo*. Neurotoxicology 2011; 32:518-25.

Milatovic D, Jenkins JW, Hood J, Yu Y, Rongzhu L, Aschner M. Mefloquine neurotoxicity is mediated by non-receptor tyrosine kinase. Neurotoxicology 2011; 32:578-85.

Milatovic D, Aschner M. Response to Nevin, RL: Mefloquine neurotoxicity and gap junction blockade: Critical insights in drug repositioning. Neurotoxicology 2011; 32; 987.

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Owens SE, Summar ML, Ryckman KK, Haines JL, Summar SR, Aschner M. Polymorphisms in four heavy metal regulatory genes do not associate with autism. Neurotoxicology 2011; 32; 769-775.

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Bowman AB, Kwakye G, Herrero Hernández E, Aschner M. Role of manganese in neurodegenerative disease, J Trace Elem Med Biol 2011; 25:191-203.

Ávila DS, Au C, Benedetto A, Aschner M. The role of *smf* transporters and dopamine in manganese-induced neurodegeneration in *C. elegans*. Proceedings of the 11th International Symposium on Metal Ions in Biology and Medicine, Pele L, Powell JJ, Kinrade S, Jugdaohsingh R,

Collery P, Maymard I, Badawi A, Eds. Cambridge, UK, John Libbey Eurotext, Paris; ISBN: 978-2-7420-0809-4, 2011.

Antonelli M, Guillemin GJ, Raisman-Vozari R, Del-Bel EA, Aschner M, Collins MA, Tizabi Y, Moratalla R, West AK. New strategies in neuroprotection and neurorepair. Neurotox Res 2012; 21:49-56.

Martins EN, Pessano NTC, Leal L, Roos DH, Folmer V, Puntel GO, Rocha JBT, Aschner M, Ávila DS, Puntel RL. Protective effect of *Melissa officinalis* aqueous extract against Mn-induced oxidative stress in chronically exposed mice. Brain Res Bull 2012; 87:74-9.

Li Z, Chadalapaka G, Ramesh A, Khoshboue H, Maguire M, Safe S, Rhoades RE, Clark R, Jules G, McCallister M, Aschner M, Hood DB. PAH particles perturb prenatal processes and phenotypes: Protection from deficits in object discrimination afforded by dampening of brain-oxidoreductase following *in utero* exposure to inhaled benzo(a)pyrene. Toxicol Sci 2012; 125:233-47.

Marreilha dos Santos AP, Lucas RL, Andrade V, Mateus ML, Milatovic D, Aschner M, Batoreu MC. Protective effects of ebselen (Ebs) and para-aminosalicylic acid (PAS) against manganese (Mn)-induced neurotoxicity. Toxicol Appl Pharmacol 2012; 258:394-402.

Santos D, Milatovic D, Sidoryk-Wegrzynowicz M, Andrade V, Batoreu MC, Aschner M, Marreilha dos Santos AP. The inhibitory effect of manganese on acetylcholinesterase activity can enhance oxidative stress and neuroinflammation in rat brain. Toxicology 2012; 292:90-8.

Skowrońska M, Zielińska M, Wójcik-Stanaszek L, Ruszkiewicz J, Milatovic D, Aschner M, Albrecht J. Ammonia increases paracellular permeability of rat brain endothelial cells by a mechanism encompassing oxidative/nitrosative stress and activation of matrix metalloproteinases. J Neurochem 2012; 121:125-34.

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