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. HANNAH GARDENER, SC.D IN SUPPORT OF GENERAL CAUSATION

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I. Qualifications

I have worked as an epidemiologist at the University of Miami Miller School of Medicine for over 14 years. I received my Doctorate in Epidemiology, with a minor in Biostatistics from the Harvard School of Public Health in 2007. My doctoral work focused on prenatal, perinatal, and neonatal risk factors for autism spectrum disorder (ASD).

I successfully defended my dissertation in August 2007 and in September 2007 started as a post-doctoral fellow at the University of Miami. I gained a faculty appointment at the start of 2009. I have primarily worked as an epidemiologist in the Neurology Department at the University of Miami, but also spent a year on the faculty in the Department of Pediatrics.

I have over 100 peer-reviewed manuscripts published in the medical literature, and my research focuses on modifiable risk factors for a range of neurological outcomes. More specifically, much of my work has centered around diet and other environmental causes for neurological diseases. I have also contributed to over 100 abstracts presented at major medical conferences. I have authored three book chapters, including "Pre-, Peri- and Neonatal Factors in Autism Etiology" in the Comprehensive Guide to Autism.

In addition to my faculty position I am also a consulting epidemiologist for several organizations including the Alzheimer's Prevention Clinic at Cornell Medical School, the Intersocietal Accreditation Commission, and the Clean Label Project. I serve as an Associate Editor of the Journal of Alzheimer's Disease, and I am on the Editorial Board of Stroke. I serve as a frequent ad hoc reviewer of many major high impact medical journals including JAMA, Pediatrics, Journal of Autism and Developmental Disorders, Pediatric and Perinatal Epidemiology, Molecular Autism, Neurology, Environmental Research, International Journal of Epidemiology, Nature Reviews, and the Journal of Epidemiology and Community Health.

I have been studying the burden of heavy metals in products since 2015. In 2017 I published data on the concentrations of heavy metals in baby foods and infant formulas, and I am currently working on studies looking at heavy metals in prenatal vitamins, CBD, and pet food.

My areas of expertise include risk factors for neurological outcomes, environmental

health, and epidemiological methods. This year I am co-teaching a course on biostatistics and epidemiological methods at the University of Miami Miller School of Medicine.

II. Prior Expert Testimony and Compensation

I have not testified as an expert consultant in litigation in the past four years. I am being compensated for my time at a rate of $600/hour.

III. Charge

I have been asked to provide my opinions regarding whether early life exposure to lead, arsenic, and mercury can cause, i.e., are causally associated with, autism spectrum disorder (ASD) and whether exposure to lead can cause attention-deficit hyperactivity disorder (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 to add new opinions regarding baby foods that contain lead, arsenic, and mercury and their ability to cause ASD or ADHD, 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

- After reviewing the peer-reviewed scientific literature on the relationship between exposure to lead and ASD, followed by consideration of the Hill criteria, I conclude to a reasonable degree of scientific certainty that lead accumulation in the body is causally associated with ASD, and that early life postnatal lead exposure can cause the development of ASD.
- After reviewing the peer-reviewed scientific literature on the relationship between exposure to arsenic and ASD, followed by consideration of the Hill criteria, I conclude to a reasonable degree of scientific certainty that arsenic accumulation in the body is causally associated with ASD, and that early life postnatal arsenic exposure

can cause the development of ASD.

- After reviewing the peer-reviewed scientific literature on the relationship between exposure to methylmercury and ASD, followed by consideration of the Hill criteria, I conclude to a reasonable degree of scientific certainty that methylmercury accumulation in the body is causally associated with ASD, and that early life postnatal methylmercury exposure can cause the development of ASD.
- After reviewing the peer-reviewed scientific literature on the relationship between exposure to lead and ADHD, followed by consideration of the Hill criteria, I conclude to a reasonable degree of scientific certainty that lead accumulation in the body is causally associated with ADHD, and that early life postnatal lead exposure can cause the development of ADHD.

V. Overview of Epidemiological Principles and Terms Discussed in this Report

Adjustment: An adjusted analysis is one that involves statistical techniques or design techniques to control for other variables that could be potential confounders. In other words, an adjusted analysis is intended to remove confounding bias by the included models. When reviewing the literature and interpreting the results across studies I gave careful consideration to the variables included in adjusted models and other methods used to statistically control for confounding.

Bradford Hill Criteria (Hill criteria): The evaluation of whether lead, arsenic, and mercury can cause ASD and whether lead can cause ADHD in humans requires the review and synthesis of scientific evidence from studies of human populations (epidemiology), animal studies, and studies investigating the mechanisms through which metals cause neurotoxicity. Once the quality of the individual studies has been assessed, a judgment needs to be made concerning the degree to which the studies support a finding of ASD/ADHD in humans, specifically children. To do this, scientists often rely upon aspects of the criteria for causality developed by the British epidemiologist, Sir Bradford Hill (1965). This approach is commonly used by epidemiologists to determine whether an observed association may be causal. Hill listed

nine aspects of epidemiological studies and the related science that one should consider in assessing causality. Although these are called "criteria" the elements are really factors. The presence or absence of any of these factors is neither sufficient nor necessary for drawing inferences of causality. Instead, the nine aspects serve as means to answer, holistically, the question of whether other explanations are more credible than a causal inference. As noted by Hill: "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" The nine aspects cited by Hill include consistency of the observed association, strength of the observed association, biological plausibility, biological gradient, temporal relationship of the observed association, specificity of the observed association, coherence, evidence from human experimentation, and analogy. The most logical approach to developing an inference of causality is to consider each of the aspects of causality developed by Hill (1965) and apply them to the available data for heavy metals. This is done in the sections that follow.

Case-control study: A case-control study is a study where the subjects are selected for inclusion based on their disease status. In other words, study subjects referred to as cases are enrolled because they have the outcome of interest (in this case, ASD or ADHD) and controls are subjects who at the time the cases are diagnosed are not affected by the outcome of interest; additionally, a study is considered population-based if the controls are selected without bias from the same population from which all cases arose. After study enrollment, everyone is assessed for the exposures of interest or – if possible – exposures are reconstructed from a record system (e.g., medical records) or from stored biospecimens. Like any study type, there are benefits and limitations with case-control studies, and I have considered and weighed those issues in reviewing the relevant case-control studies in this report.

Causal inference: Causal inference refers to the process of determining the causal

relationship between an exposure and outcome.

Cohort study: In a cohort study, subjects are enrolled in the study and assessed for their exposures (in this case, to heavy metals), and followed over time to determine who develops the outcome(s) of interest. In some cohorts, exposure is only assessed at enrollment (baseline) while in other cohorts exposures continue to be assessed throughout follow-up until disease occurs. Like any study type, there are benefits and limitations with cohort studies, and I have considered and weighed those issues in reviewing the relevant cohort studies in this report.

Confidence interval (CI): A confidence interval, or CI, is provided around an odds ratio or a relative risk to give the likely interval which potentially includes the unobservable true measure of effect. In other words, it is an interval estimate (as compared to a point estimate) of the true underlying relationship between exposure and disease, in a given study. In practice, most published estimates are 95% confidence intervals, which means that in 95 out of 100 times when sampling your study subjects, you will find the true result (effect estimate) within the given confidence interval. When a (95%) confidence interval excludes 1.0 (such as OR=2.0, 95% CI=1.2- 2.8) – because 1.0 (the null value) is outside of the confidence interval – it would be considered "statistically significant". It is inappropriate to disregard the relevance and importance of any result merely because the confidence interval crosses 1. Likewise, an association with a confidence interval that does not include 1 does not always reflect clinical significance, as statistical significance and clinical significance are not the same. The confidence interval reflects the strength of the association as well as the sample size, the frequency of the exposures and outcomes of interest, the inclusion of covariates, and other complex methodological issues. Therefore, in considering and analyzing the results across studies I focus on the strength of the effect estimates, the width of the confidence intervals, whether they overlap 1, and all associated methodological strengths and weaknesses.

Confounding: Confounding is a bias that occurs because a risk factor for the outcome is also a cause or precursor of the exposure of interest such that the outcome is caused by this confounder and not by the exposure one is trying to assess. For example, if sex is a risk factor for

ASD ***and*** sex is also associated with exposure to heavy metals, we would want to adjust all effect estimates for heavy metals by sex to remove potential confounding bias. In considering and analyzing the studies listed in this report and reference list, I have given careful consideration to potential biases due to confounding.

Control: In case-control studies, the controls represent the participants that the outcome cases are compared to. The controls are selected to represent the exposure distribution in the underlying population that gave rise to the cases. Therefore, we compare the exposure distribution in the cases and controls to determine if a relationship exists between the exposure and outcome of interest. When interpreting the results across studies I have given careful consideration to the appropriateness of the control selection and whether the selection of controls could introduce bias.

Cross sectional: In a cross-sectional study the exposures and the outcomes of interest are identified simultaneously in a given study population. Like any study type, there are benefits and limitations with cross-sectional studies, and I have considered and weighed those issues in reviewing the relevant cross-sectional studies in this report.

Data pooling or pooled analysis: To pool data is to use the raw (un-analyzed or non-summarized) data from several studies and merge them together to conduct analyses. Data pooling is often done when there have been multiple small studies on a topic, because the pooling allows for larger sample sizes and a uniform approach to the analysis of the pooled data. Pooled studies have greater statistical power than the original studies from which they draw. Like any study type, there are benefits and limits with pooling data across studies, and I have carefully considered and weighed those issues in reviewing the relevant pooled analyses in this report.

Dose response: A dose-response association represents an increasing risk with an increasing dose and/or exposure, such as a higher blood heavy metal concentration, being related to higher Odds Ratios.

Ecological: In an ecological study, multiple populations are compared in relation to both

the distribution of the exposure of interest and the frequency of the outcome of interest. In this study design the unit of measurement is the population or region rather the individual. The frequencies of the exposures and outcomes are determined but not the cross-frequencies of the exposures and outcomes. In other words, the investigator does not know if the individuals who were exposed were the same as those who had the outcome. Like any study type, there are benefits and limitations with ecological studies, and I have carefully considered and weighed those issues in reviewing the relevant ecological studies in this report.

Effect modification: Effect modification is also referred to as an interaction in epidemiology between the exposure of interest and another variable (the effect modifier) in relation to the outcome of interest. It refers to the impact of a factor (a separate variable) on the relationship between the exposure and outcome of interest. It is not a variable on the causal pathway between an exposure and outcome of interest, but rather an external factor that influences the effect of the exposure. Effect modification does not reflect bias, but instead a causal phenomenon. When interpreting the results across studies and within studies I gave careful consideration to the potential influences of effect modification.

Epigenetics: Epigenetics refers to changes in gene expression rather than changes to the actual genetic code. Environmental exposures can cause outcomes by impacting the expression (turning on and off) of relevant genes.

Forest plot: A Forest Plot is a visual representation of the main results of all studies on a topic. The purpose of grouping them all together visually is to give the reader a sense of the overall size of the effect estimates and the direction of the associations in the existing literature.

In vitro: "*In vitro*" refers to medical procedures, tests, and experiments that researchers perform outside of a living organism. An *in vitro* study occurs in a controlled environment, such as a test tube or petri dish.

In vivo: "*In vivo*" refers to tests, experiments, and procedures that researchers perform in or on a whole living organism, such as a person, laboratory animal, or plant.

Meta-analysis: In some instances, scientists are interested in pooling data but do not

easily have access to the raw data from each study. This is, typically, because the studies were conducted many years earlier, or perhaps because the investigators do not know/trust each other or human subject restrictions do not allow for the sharing of raw data; it is quicker and more efficient to conduct a meta-analysis based on summary estimates from published reports. A meta-analysis uses the odds ratios or rate ratios (see below definitions) and confidence intervals which were published in the original studies and comes up with a summary estimate of the relationship between exposure and disease. Similar to pooled analyses, meta-analyses also have much greater statistical power than each study does on its own. Like any study type, there are benefits and limitations with using meta-analyses, and I have carefully considered and weighed those issues in reviewing the relevant meta-analyses in this report.

Misclassification: misclassification bias is characterized as mismeasurement of exposures or outcomes which can severely distort results in both case-control and cohort studies. As long as mismeasurement is non-differential/random (i.e., the same for cases and controls or for exposed and unexposed), such biases most often cause underestimation of true effect sizes i.e., bias results towards the "null" (see below definition) that can be severe. When reviewing the literature and interpreting the results across studies I carefully considered the methods used to measure exposures, covariates, and outcomes and therefore the possibility of bias due to misclassification.

Null: The null represents no association between the exposure and outcome of interest. An odds ratio or relative risk (see below definitions) of 1 represents the null. And the null hypothesis is that there is no association between the exposure and outcome of interest.

Observational: In an observational study the participants' exposures are not determined by the investigators – i.e., they are not randomly assigned but rather determined based on the choices or the life circumstances of the participants.

Odds Ratio (OR): An odds ratio, or OR, is a measure of association between an exposure and an outcome. It represents the odds that the outcome will occur in a group of people given a particular exposure, in comparison to the odds of the outcome in a group of people without the

exposure, or it represents the increased odds of an outcome with a one unit increase in the exposure. An OR of 1.00 is the null, meaning no effect. Thus, an OR of 1.237 as reported in one of the studies below, for example, represents a 23.7% increase in ADD with each ug/dL (micrograms per deciliter) of blood lead. An odds ratio is a "point estimate" or the "central" estimate of the relationship between exposure and outcome, in a given study (note: the OR is between the upper and lower confidence limit boundaries, see above). Odds Ratios are the statistics that are used most often to analyze case-control studies, and they are often calculated using a statistical technique called logistic regression but can also be derived by simple calculations based on a 2x2 table of data.

Oxidative stress: Oxidative stress is cell and tissue damage resulting from an imbalance between the production and accumulation of reactive oxygen species and the body's ability to detoxify them.

Polymorphism: A polymorphism is a variant of a particular DNA sequence (a genetic variant).

Prospective: In a prospective study, data on the exposures is collected prior to the occurrence of the outcomes of interest.

P-value: The p-value is the probability of obtaining an estimate at least as far from a pre-specified value (in case of the null hypothesis the "null" value) as the estimate we have obtained, if the specified value were the true value (note: no p-value, for the null hypothesis or any other hypothesis, is the probability that the specified hypothesis is true). For example, a p-value of 0.04 means that, given the null hypothesis is true, if you repeatedly conducted 100 tests of samples drawn from the same population (people), then in 4% of your tests, you would obtain the results you got solely due to random error (chance). It is a metric intended to show the likelihood of random error. It should not be interpreted as the probability that an agent causes an outcome. Statistical significance refers to a p-value less than 0.05, which is typically used to reject the null hypothesis of no association. In other words, a statistically significant association with $p<0.05$ is intended to reflect an association that exists and is unlikely to be observed due to

chance alone. The use of the $p<0.05$ to establish statistical significance reflects convention. It is inappropriate to disregard the relevance of any result merely because of its p-value. The p-value is not truly a representation of the strength of the association, but rather a combination of many factors that include (but are not limited to) sample size, frequency of the exposure and the outcome, the variables included and adjusted for in the statistical analyses, statistical techniques, and the strength of the association. The p-value is truly a statistical artifact, and statistical significance does not always equate to clinical significance. Therefore, the weight of reliance on the p-value must take into consideration many complex methodological factors, especially when inferring causality. When reviewing the literature and interpreting the results across studies I gave careful consideration to statistical significance and its associated issues.

Relative Risk (RR): Risk Ratio (or Relative Risk) is a ratio of the risk in the exposed divided by the risk in the unexposed in a cohort - where risks are defined as the number of (un)exposed cases divided by the total number of (un)exposed. Note: under certain circumstances often met especially for rare diseases, the odds ratio (OR), risk ratio (RR) and rate ratio (RR) are the same (albeit calculated as the ratio of odds, risks, or rates) and the interpretation of the estimates is also the same.

Retrospective: In a retrospective study, data on the exposures is collected after the outcomes of interest have already occurred.

Reverse causality: Reverse causality refers to the type of bias in any study that isn't prospective where an exposure and outcome of interest are associated not because the exposure causes the outcome, but rather the outcome impacts the probability of the exposure. In considering and analyzing the studies listed in this report and reference list, I have given careful consideration to the possibilities of reverse causality.

Statistical power: Statistical power is the ability of a study to estimate an effect. In essence, it is a reflection of the sample size (number of subjects in a study; also the number of cases), the prevalence of exposure, and the expected effect size. Large sample sizes give us generally higher statistical power, which means they have narrower and more stable confidence

intervals around point estimates. Smaller sample sizes have wider confidence intervals. Thus, larger studies are much more able to find statistically significant results especially when exposures or outcomes are rare and the expected size of the effect moderate or small in size. In considering and analyzing the literature I have carefully interpreted the results across studies while considering their statistical power.

VI. Methodology and Literature Review Process

To arrive at my opinions, I searched the PubMed database (the online database of the peer-reviewed medical literature) for peer-reviewed studies on lead, arsenic, and mercury in relation to ASD and for peer-reviewed studies on lead in relation to ADHD. I reviewed epidemiological studies of all types. I reviewed studies that used ASD and ADHD diagnoses as the outcomes as well as studies that looked at ASD and ADHD behaviors or traits. I focused on studies that measured heavy metals from the postnatal period through childhood, but I also reviewed studies relating to prenatal heavy metal exposures. The use of the PubMed database and searching for relevant literature represents the process through which epidemiologists access the complete medical literature on a topic and review it to assess causality.

In order to reach my opinions about whether these heavy metals likely cause ASD and ADHD I also reviewed studies in animal models, as well as *in vivo* and *in vitro* studies that examined the underlying biological mechanisms. Epidemiologists consider both *in vivo* and *in vitro* studies when assessing causality. I reviewed original studies as well as reviews and meta-analyses. In addition to identifying the relevant literature on PubMed, I also reviewed the reference lists of the studies to identify other relevant studies on the relationship between lead, arsenic, and mercury and ASD, and lead and ADHD. This approach is also commonly used by epidemiologists to make sure they have reasonably captured the body of literature needed when assessing causality.

I reviewed the literature on lead, arsenic, and mercury separately in relation to ASD as well as the literature on the relationship between lead and ADHD, and for each association I determined whether the metal is a causal agent for the outcome based on my review of the

literature and my understanding of the strengths and weaknesses of the available data. Specifically, I relied on the Hill criteria to determine whether the existing literature at this time supports a causal effect. The Hill criteria are composed of the following: (1) the strength of the associations in the literature; (2) the consistency of the associations observed across studies; (3) the specificity of the exposure and outcome relationship; (4) the temporality of the exposure and outcome assessment; (5) the biological gradient, or dose-response relationship; (6) the biological plausibility of the exposure causing the outcome; (7) the coherence with other lines of experimental evidence; (8) the existence of experimental evidence (such studies on heavy metals would not be ethical in humans); (9) whether analogous/similar agents have similar outcomes. This approach is commonly used by epidemiologists to determine causality.

Experimental randomized controlled trials represent the gold standard for assessing causality in epidemiology. However, such studies on heavy metals would be highly unethical—because the intentional exposure of a baby to known neurotoxic heavy metals would constitute human experimentation—so we rely on observational epidemiological studies to inform our opinions, with additional evidence from experimental studies in animals and translational work on the underlying biological mechanisms. Observational epidemiological studies include cohort studies, case-control studies, and cross-sectional studies. These designs vary in their methodological strengths and weaknesses, and I reviewed the existing literature while considering the various strengths and weaknesses across studies. It is important to note that the chronic nature of both ASD and ADHD and the frequency of their associated traits make cross-sectional studies a suitable design for assessing the association between heavy metals and the two disorders, in addition to the more common case-control and cohort design. Carefully considering all data related to the etiology of a disease, as described above, is a widely accepted approach used by epidemiologists when assessing causality.

A primary weakness in this field relates to the timing of the assessment of exposure to heavy metals. In an ideal world we would assess heavy metal exposure in very early life when there were no clear signs of ASD/ADHD diagnosis and then follow children up until the time of

diagnosis with repeated heavy metal assessments. Such studies, to the extent they could be accurately conducted, would be extremely expensive and time-consuming and would require very large samples due to the rarity of these outcomes. Therefore, most studies relating heavy metal exposure to ASD/ADHD in fact assessed heavy metal exposure simultaneously with ASD/ADHD assessment in case-control and cross-sectional designs. As such they would not be considered prospective. This raises concerns about temporality, i.e., whether the exposure occurred prior to the disease. In other words, it forces us to ask whether heavy metal exposures we observe in the sample reflect heavy metal exposures prior to the diagnosis or disease onset. Additionally, due to the fact that most studies assessed the exposures and outcomes simultaneously we need to consider the plausibility of reverse causality: the notion that an association between heavy metals and ASD/ADHD would be due to the diagnosis causing the exposure rather than the reverse – this is discussed further below. However, such important concerns can be addressed by considering those studies in connection with related prospective human data and/or experimental data in animal models. If the prospective data is consistent with the data observed in retrospective and cross-sectional studies, then reverse causality becomes an unlikely explanation for the associations observed, and concerns about temporality in cross-sectional studies are ameliorated. The retrospective and cross-sectional studies become valuable in forming opinions about causality, especially when the exposure assessments represent long-term exposure levels and when the possibility of the outcome itself increasing the exposure is remote. The fact that some of the biospecimens (e.g., hair) used to measure heavy metals represent very long-term heavy metal exposure helps support inferences about causality and helps overcome the weakness inherent in the simultaneous exposure/outcome data collection. ASD.

Furthermore, we must consider whether it is plausible that increased oral activity that many ASD/ADHD children exhibit (sometimes referred to as “PICA”) could in fact increase exposure to lead in the environment, even though the likelihood for this phenomenon in relation to certain heavy metals (e.g., arsenic, mercury) is far less likely. Following review of the data, it

does not appear that PICA explains the causal association between exposure to lead and ASD/ADHD. One study that incorporated an analysis of PICA in their small study of hair heavy metal levels in relation to ASD observed no significant difference in hair lead and mercury levels between children with and without PICA, while children with PICA were observed to in fact have lower arsenic levels. Adams, et al. (2006). As discussed below, the availability of prospective studies, data on prenatal exposure, studies on early life (pre-diagnosis) exposure to heavy metals via analysis of baby teeth, and translational research all demonstrate the etiological relevance of heavy metal exposure ***prior*** to manifestation of disease.

It important to note that the two outcomes of interest in this report (ASD and ADHD) are rare. The rarer a disease, the harder it is for a scientist to create a large enough study with a sufficient number of ASD/ADHD cases enrolled to have adequate statistical power. This is why it is challenging to study ASD and ADHD diagnoses with a cohort study design. An investigator would have to follow hundreds of thousands of people for many years to achieve adequate statistical power to identify moderate risk factors. This is the main reason why most of the reviewed studies employed a case-control design which is much more efficient in terms of the necessary sample size for sufficient statistical power, as well as being less costly. Many of the case-control studies discussed in this report, particularly those that tried to recruit cases in areas with low population density, had a limited sample size simply because there are a finite number of cases in these areas. This limitation is especially important to consider when there is inconsistency in results across studies, including multiple studies that fail to find statistically significant associations. In other words, a small sample size is a frequent explanation for a failure to observe a significant association even when the effect estimate appears to be moderate. This limitation can be overcome by formally pooling or meta-analyzing data, as researchers have done on the metals discussed here, and by reviewing the complete volume of literature and identifying consistencies across small studies. As such, these small studies contribute to my assessment of causality.

Moreover, it is important to consider that ASD and ADHD are a “spectrum” disorders,

meaning that they are composed of a variety of behavioral manifestations and symptoms as well as varying degrees of severity. As such, a binary interpretation of the epidemiological literature on heavy metals and ASD/ADHD is not appropriate, i.e., limiting the enquiry to whether cases have a "formal" ASD/ADHD diagnosis or not. For example, many of the ADHD – and some of the ASD – studies discussed in this report evaluated the relationship between exposure to heavy metals and ASD/ADHD "diagnoses" as well as "behaviors" and "traits". To properly assess causation, an epidemiologist must consider the totality of this literature.

VII. Autism Spectrum Disorder and Attention-Deficit Hyperactivity Disorder

A. Autism

Autism, or autism spectrum disorder (ASD), is a condition characterized by chronic disabilities in the areas of communication and behavior that is typically diagnosed in early childhood. ASD includes a broad spectrum of symptoms, skills, and severity. ASD is characterized by persistent differences in communication, interpersonal relationships, and social interaction across different environments, with restricted and repetitive behavior, patterns, activities, and interests. It is currently estimated that 1 in 54 children in the United States are autistic, and ASD affects boys more frequently than girls. ASD is understood to be caused by both genetics and environmental factors and their interaction.

B. Attention-Deficit Hyperactivity Disorder

ADHD is a common neurodevelopmental disorder, affecting approximately 8.4% of children and 2.5% of adults. It is typically diagnosed in childhood and often persists into adulthood. ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. ADHD is understood to be caused by both genetics and environmental factors and their interaction.

VIII. Overview of Toxic Heavy Metals

A. Lead

Lead is a heavy metal found in many sources including paint, pipes, ceramics, bullets, crystal, solders, gasoline, antiques, and cosmetics, and contaminates soil, dust, water, and food.

People are exposed to lead primarily through ingestion and inhalation, and young children under age 6 are at an increased risk of lead exposure. It is widely understood by many agencies (e.g., the Food and Drug Administration, Environmental Protection Agency, Centers for Disease Control and Prevention, American Academy of Pediatrics, World Health Organization) that lead is a human neurotoxin and that there is no safe level of lead exposure for children.

B. Arsenic

Arsenic is a heavy metal, naturally found in the Earth's crust and prevalent in air water and land across the Earth. It is found in both the organic and inorganic form, with the inorganic form being highly toxic. Exposure to inorganic arsenic occurs primarily due to drinking contaminated water, using contaminated water in food preparation and irrigation of food crops, industrial processes, eating contaminated food and smoking tobacco. Arsenic is used industrially as an alloying agent, as well as in the processing of glass, pigments, textiles, paper, metal adhesives, wood preservatives and ammunition. Arsenic is also used in the hide tanning process and, to a limited extent, in pesticides, feed additives and pharmaceuticals. Grains, and particularly rice, are significant sources of dietary arsenic, as arsenic in soil is readily absorbed by the rice/grains. Arsenic, specifically inorganic arsenic, is deemed by many agencies to be both neurotoxic and carcinogenic (e.g., CDC, WHO, FDA).

C. Mercury

Mercury is a naturally occurring toxic heavy metal that comes in many forms including elemental (metallic) mercury, inorganic mercury, and organic mercury (including methyl mercury). According to the EPA, elemental or metallic mercury is a shiny, silver-white metal, historically referred to as quicksilver, and is liquid at room temperature. It is used in older thermometers, fluorescent light bulbs and some electrical switches. In its inorganic form, mercury occurs abundantly in the environment, primarily as the minerals cinnabar and metacinnabar, and as impurities in other minerals. Mercury can readily combine with chlorine, sulfur, and other elements, and subsequently weather to form inorganic salts. Inorganic mercury salts can be transported in water and occur in soil. Dust containing these salts can enter the air

from mining deposits of ores that contain mercury. Emissions of both elemental or inorganic mercury can occur from coal-fired power plants, burning of municipal and medical waste, and from factories that use mercury. Inorganic mercury can also enter water or soil from the weathering of rocks that contain inorganic mercury salts, and from factories or water treatment facilities that release water contaminated with mercury. Human exposure to inorganic mercury salts can occur both in occupational and environmental settings. As it cycles between the atmosphere, land, and water, mercury undergoes a series of complex chemical and physical transformations, many of which are not completely understood. Microscopic organisms can combine mercury with carbon, thus converting it from an inorganic to organic form. Methylmercury is the most common organic mercury compound found in the environment and is highly toxic. Diet, including fish consumption, is the primary source of mercury exposure. Mercury is a known potent human neurotoxin, recognized by many government and scientific agencies (e.g. EPA, CDC, FDA, WHO).

IX. Opinions

A. Lead and ASD

A very large number of studies have examined the question of whether a higher body burden of lead during infancy/childhood predicts ASD, and the overwhelming majority of those studies show that lead was measured at higher levels in children with ASD than in children without ASD. The consistency of findings across studies was apparent, though not every study showed that lead levels were higher in children with ASD. Some inconsistency across studies is always expected in epidemiology, but overall, the conclusions across studies were consistent. Lead levels were most commonly measured in blood, but also measured in hair, urine, and teeth, as well as ambient environmental levels.

Out of 14 studies that examined blood lead levels in relation to ASD, 8 showed that blood lead levels were significantly associated with ASD risk. The other 6 studies showed no statistically significant association (in 3 of these the mean lead levels were non-significantly higher in cases), and no studies showed that lead levels were associated with a decreased risk of

ASD. Out of 17 studies that examined hair lead levels in relation to ASD, 12 concluded that lead levels in hair were higher in autistic participants, while only 1 study showed that autistic participants had lower hair lead levels, and 4 showed no significant difference (in 1 of these the mean lead levels were non-significantly higher in cases). In 7 studies that examined urine lead excretion levels, 3 showed an association between urinary lead excretion and increased ASD risk, while 1 study showed that urine lead was inversely related to ASD, and 3 showed no significant association (in 1 of these the mean lead levels were non-significantly higher in cases). It is important to note that in the large body of observational data, lead was associated with ASD risk in diverse study populations with varying levels of lead burden in the overall study population. This is important because it indicates that the results seen are less likely the result of bias.

In 2019 a systematic review and meta-analysis was published on the relationship between lead and ASD in the available literature through 2018, which included 37 studies on lead and ASD. Wang, et al. (2019). The authors noted that 51.3% of studies included in this meta-analysis showed an increased risk of ASD associated with higher lead levels, and no studies showed an inverse association (lower lead levels in ASD). Seventeen of the 37 studies provided the data necessary to be included in the meta-analysis. In the meta-analysis portion the authors observed a statistically significant higher level of lead in the hair of ASD cases as compared to non-ASD controls, and the mean hair levels of lead were 115% higher in the cases as compared to the controls. Four of the six reviewed studies on urine lead levels and ASD showed that ASD cases had higher lead levels than the controls, but the difference between cases and controls in urine lead levels was not statistically significant in the meta-analysis. The authors reported that the blood lead levels were in fact 38% higher in the controls than the cases, and though this difference may appear to be small it did reach statistical significance. This observation of a higher level of blood lead in the controls than in the cases in this meta-analysis contradicts the literature that it was intended to capture. Only 7 studies on blood lead levels and ASD risk were included in the quantitative meta-analysis, and of these individual studies 5 showed higher blood

lead in ASD cases compared to non-ASD controls (2 being statistically significant), and no individual studies had a statistically significant higher blood lead level in controls. In comparison, 6 studies on blood lead in relation to ASD in this systematic review were not included in the quantitative meta-analysis, and of these 6 studies 4 showed that ASD cases had higher blood lead levels as compared to controls, and 2 showed no association (one of these had non-significantly higher blood lead levels in the cases).

Although, at the time, the Wang authors in their meta-analysis characterized the association between lead and ASD as "inconsistent" compared with arsenic exposure and ASD, the meta-analysis did not include additional data which, following my review, provides further evidence in support of a causal association between lead exposure and ASD. For example, a notable large prospective cohort study was not included in Wang's systematic review, including 2473 Korean children. Kim, et al. (2016). This study showed that blood lead levels measured at age 7-8 were associated with the score on the ASD Spectrum Screening Questionnaire at ages 11-12, even after taking into account a wide range of potential explanatory factors including socioeconomic and environmental factors. This important study demonstrated that lead is also associated with ASD behaviors even in the absence of a formal diagnosis. In addition, a 2018 case control study by Qin et al was not included in Wang's meta-analysis. This study included 34 ASD cases (age 3-5) and 34 controls and found that cases had higher blood lead levels (median: 31.9 μg/L in cases vs 18.6 μg/L in controls).

A more formal and methodologically rigorous meta-analysis on the relationship between lead and ASD also came to a different conclusion than Wang et al. and provided more support for a strong and consistent association between lead and ASD. Specifically, an earlier meta-analysis from 2017 by Saghazadeh and Rezaei included 48 studies published through the end of 2016 with lead measurements conducted in whole blood, plasma, serum, red cells, hair and urine. A meta-analysis of the 3 studies that measured erythrocyte lead levels in patients with ASD (n = 138) and controls (n = 91) showed that ASD cases had higher erythrocyte lead levels than controls (summary effect size=1.55, Z = 2.26, p = 0.024). A meta-analysis of 9 studies on blood

lead levels also showed increased lead levels in blood and plasma in ASD cases compared to controls. Also, in 20 studies that measured hair lead, they found lead levels also to be higher in cases than control children. No statistically significant difference was seen in relation to urine lead measures between cases and controls in the meta-analysis of data from 5 studies.

And, prior to publication of the Wang, et al. (2019) meta-analysis, Guo and colleagues (2019) published a smaller meta-analysis only evaluating hair lead measurements based upon 20 studies published between 1982 and 2017. Overall, this meta-analysis did not find statistically significant differences in the levels of hair lead in autistic compared with control individuals (Hedges' g=0.251; 95% CI: −0.121, 0.623; P=0.187). However, the authors did note heterogeneity across included studies, and following a sensitivity analysis which removed one study with a larger sample size but smaller effect size (Yasuda, et al. (2005)), the overall estimate was positively associated with hair lead levels and became statistically significant.

Since the time the Wang and Guo meta-analyses and reviews were completed, the data that supports a causal association between hair lead levels and ASD has only become stronger, with one additional case control study showing a 77% higher level of lead in the hair of ASD cases compared to controls. Filon, et al. (2020), and another study of 48 autistic children showing that hair lead levels were associated with greater ASD symptom severity. Fiore, et al. (2020). However, it should also be noted that a 2021 study on urine lead levels in relation to ASD (Wahil, et al (2021)) showed no significant difference in adjusted urine lead levels between cases and controls.

The observed associations between lead levels and ASD in the literature are compelling. Of the 6 case control studies reviewed by Wang, et al. (2019) that showed statistically significant higher blood lead levels in ASD cases than controls, the blood lead levels in cases were between 18% and 467% higher in the ASD cases compared to the non-ASD controls, with three studies showing that ASD cases had a greater than double blood lead level compared to controls. As mentioned above, the mean hair levels of lead were 115% higher in the cases as compared to the controls in Wang's 2019 meta-analysis.

There are a few limitations common in the literature on lead burden as a risk factor for ASD. The first is the small sample size in most of the studies. A small sample size makes it difficult to observe a statistically significant association when one exists. The fact that most of the studies that have looked at lead burden in relation to ASD show significant associations ***despite*** the challenges of the small sample sizes is due to the strength of the association. Given the fact that most studies did in fact show significant associations, the small sample sizes become less relevant. If the associations had been mostly shy of statistical significance the small sample sizes could be considered as a likely explanatory factor. This remains relevant when considering the fact that many small studies failed to reach statistical significance, but the trends were in the direction of showing higher levels of lead in ASD cases as compared to controls.

A second limitation is the fact that the case control and cross-sectional studies measured lead levels during childhood rather than in infancy, after the ASD diagnoses had been made, and following the presumed etiologically relevant period (prenatal and within the first year of life). When the exposure and outcomes are assessed simultaneously, inferences about causality are challenged, so we need to look for prospective data to help elucidate the assumed temporality. One study (Kim, et al. (2016)) was prospective in that the blood lead levels were collected years before the ASD traits were measured, and ASD traits were found to be greater among those with higher blood lead levels. The results of this study, when interpreted in light of the totality of the available literature, demonstrates that exposure to lead is associated with a diagnosis of childhood ASD in the future.

I have also considered whether the body burden of lead, measured in blood, hair and urine, may be due to increased exposure and/or differences in excretion/detoxification. It is possible that some of the differences observed in lead levels in blood, hair, and urine between ASD cases and controls could be due to differences in the ability to efficiently detoxify and remove lead from the body, and that can be controlled by genetic factors that in turn impact ASD risk. There may be genes that impact ASD risk by increasing the adverse effects of lead exposure. It is crucial to emphasize that this potential mechanism does not reflect bias and would

not suggest that an association between lead and ASD is spurious. Rather, it would simply reflect the fact that certain genes may also be involved in modifying the relationship between lead exposure and ASD. In other words, such a scenario would in fact support a causal association between lead exposure and ASD risk because the child's ability to detoxify or chelate the lead (or other heavy metal) exposure presumes the exposure is causing ASD. Genome-wide data have revealed that several candidates containing genetic polymorphisms modified the response to early life lead exposure on neurodevelopmental outcomes, and the data suggest that some of these candidates impact lead-induced oxidative stress. In other words, recent data suggests that certain genetic polymorphisms in genes that play a role in neurodevelopment modify the toxic effects of lead exposure on oxidative stress. Wang, et al. (2017).

The lead exposure levels in childhood may not be a perfect proxy measure for lead levels in infancy, during the etiologically relevant period. Lead measured in blood and urine reflects short-term, recent exposure. Hair lead levels are more representative of longer-term exposure levels and are recognized as a particularly reliable measure of cumulative chronic exposure. The fact that hair lead levels during early childhood are more associated with ASD risk than blood and urine lead levels supports the understanding that lead exposure during earlier life periods would be more etiologically relevant, and that long-term exposure would be more etiologically relevant than brief recent exposures during childhood. In the Wang, et al. (2019) meta-analysis, the authors stated: "Hair measurement of heavy metal is more relevant to long-term exposure and thus a more suitable marker and an indicator of accumulative exposure. For this reason, we view the strength of the evidence from hair assessment as stronger than the evidence obtained from blood and urine evaluation." This is a reasonable observation, however, in order to arrive at a meaningful conclusion regarding causation, the totality of the data, including evaluation of multiple biomarkers such as, where available, hair, urine, and blood, should be considered in conjunction with any prospective and early life data.

Moreover, if current lead levels measured during childhood (post-diagnosis) in cross-sectional and case-control studies are used as a proxy for earlier life exposure levels during the

etiologically sensitive period then we would expect some random misclassification as they would not be perfectly correlated. Some children with high levels of lead in their system today may not have had high levels of lead in their system before, and vice versa. This degree of random misclassification of the intended exposure period would be expected to bias results in the direction of not observing a significant exposure even if a causal association truly exists. In other words, this type of bias would not mean that the strong associations observed in this literature do not in fact exist, but rather the opposite. Thus, the fact that we observe a consistent association between lead exposure and ASD risk so frequently suggests that the true association may in fact be much stronger than what the current literature demonstrates.

There is not a lot of data on the relationship between lead exposure in utero and ASD risk, but one study showed a significant association between prenatal lead exposure (lead levels measured in pregnant women) and offspring autistic behaviors. Alampi, et al. (2021). The findings of Alampi, et al. (2021) support the presumed temporality that lead exposure predicts future ASD risk. In addition, a smaller Danish study (Long, et al. (2019)) evaluated amniotic fluid to determine whether prenatal lead levels contribute to ASD development. The authors selected 37 cases born between 1995 and 1999 and clinically diagnosed with ASD and a matched set of 50 controls (matched on child age, gender, and maternal age). The authors found a suggestive but not statistically significant increase in ASD with increased lead exposure when comparing cases to controls: OR=1.30 (95% CI: 0.66–2.58) per 1 mg/L increase in lead. The results did not reach statistical significance and the study was not adequately powered to detect moderate effects, however, the authors suggested that prenatal lead exposure contributes to autism risk.

Another line of evidence that refutes the potential for reverse causality is ecological data demonstrating increased rates of ASD in regions with increased ambient lead levels. Such associations cannot be explained by genetics or reverse causality (because there is no reason to believe that autistic children would disproportionally select to live in places with greater environmental lead exposure), but instead support the understanding that increased lead exposure

increases the risk of ASD in a causal manner on a population-wide level. Dickerson, et al. (2016) studied 2558 census tracts across 5 states and found that children living in census tracts in the top quartile for ambient lead had a 36% increased ASD prevalence compared to census tracts in the bottom quartile for ambient lead, a difference that was statistically significant. These findings accounted for differences in neighborhood race, urbanicity, and socioeconomic status. Such associations, on their own, cannot establish causation, but they do support the overall evidence and conclusion that lead exposures are causally associated with ASD risk rather than the reverse. Moreover, perinatal exposures to the highest versus lowest quintile of air pollution from lead, mercury, manganese, diesel, methylene chloride, and an overall measure of metals were significantly associated with ASD risk in a large US-based study of 325 ASD cases and 22,101 controls. Roberts, et al. (2013). This study is noteworthy not just because of its size and examination of multiple metals and pollutants, but also because it controlled for confounding by family-level socioeconomic status (maternal grandparents' education) and census tract-level socioeconomic measures (e.g., tract median income and percent college educated), as well as maternal age at birth and year of birth. This data is important as it suggests that perinatal exposure to multiple metals may increase the risk of ASD.

Furthermore, a 2017 study on monozygotic and dizygotic twin pairs discordant for ASD (meaning one twin had ASD and the other did not) provided important insight about the ability of lead exposure during infancy to cause ASD. Arora, et al. (2017). This study specifically tested the hypothesis that early life lead exposure predicted ASD risk in a novel study design that utilized baby teeth from 32 twin pairs. Tooth matrix biomarkers obtained by drilling cores from the baby teeth allowed the investigators to identify and quantify metal exposures during the sensitive periods during development from the prenatal period through childhood during which metal uptake was associated with ASD risk. Using this study design with twins discordant for ASD, the investigators were also able to reduce the impact of other shared genetic and environmental exposures. They correlated the tooth matrix biomarkers with the severity of ASD and autistic traits. They found that lead levels were consistently higher in ASD cases compared

to their non-ASD co-twins from 20 weeks before birth to 30 weeks after birth. After adjusting for intra-twin correlations, this association was evident between weeks 10 to 20 postnatally. At 15 weeks postnatally, lead levels in ASD cases were 1.5 times higher than in their non-autistic co-twins. This study provided important evidence not only for a strong relationship between lead exposure and ASD risk, but specifically implicated the first year of life as being etiologically relevant, even in twin pairs that share substantial genetic and environmental risk factors.

It is important to note that children with ASD often exhibit increased oral tendencies which could theoretically increase exposure to household items, toys, paint, and dust contaminated with lead. As such, ASD behaviors themselves may cause increased lead exposure. Because of this possibility, prospective data, data on prenatal exposure, the study on baby teeth by Arora et al (2017), and translational research outlined below are very helpful for elucidating the fact that lead exposure can cause ASD, and that lead exposure is increased ***before*** the ASD behaviors become apparent.

There is strong biological plausibility to support lead exposure as a causal risk factor for ASD. Lead is a known neurotoxin with well-recognized impacts on child cognition, behavior, and neurodevelopment. In the medical literature lead exposure early in life is consistently associated with impaired neurological development, impaired cognitive function, antisocial behavior, and delinquent behavior. Multiple mechanisms through which lead exposure in babies and children can impact ASD risk have been discussed in the peer-reviewed medical literature. Lead exerts a variety of direct neurotoxic effects in the brain including oxidative stress and cell death, and it interferes with the storage and release of neurotransmitters that are critical for brain function. Lead is believed to cause ASD as it suppresses brain plasticity at a critical period of neurodevelopment. Smith, et al. (2018). Lead is able to cross the blood brain barrier by mimicking calcium and zinc. Lead affects neuroinflammation as it regulates several neuroinflammatory markers in multiple brain areas. Bjorklund, et al. (2018); Kaur, et al. (2021). Moreover, lead has been shown to inhibit the NMDA receptor in brain cells, a receptor that is critical for brain development and function, and lead exposure has been shown to affect the

expression of genes involved in neurodevelopment. Wagner, et al. (2017).

Kim, et al. (2016) provided a relevant summary of the proposed mechanisms by which lead exposure during early childhood may 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 (Brookes et al., 2004; Markovac and Goldstein, 1988). 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 (Abadin et al., 2007). Third, the presence of lead might affect the nervous system by inhibiting the formation of key molecules during the mature differentiation of glial cells (Bressler and Goldstein, 1991; Silbergeld, 1992).

Experimental data in animals has also supported a causal role for lead exposure in ASD risk. Lead exposure has been associated with ASD-like phenotypes, development, and behavior in animal experimental studies. For example, lead exposure resulted in repetitive stereotyped behavior and spatial learning impairment in mice, effects that coincided with elevated pro-inflammatory cytokines which are markers of immune dysregulation associated with ASD in humans as well as brain pathology. Chen, et al. (2019). In utero exposure to lead in mice caused abnormalities in social interaction. Hill, et al. (2015). Lead exposure in rats through drinking water has resulted in impaired explorative behavior, spatial learning and memory, and higher anxiety. Tartaglione, et al. (2020). Animal data have also shown that lead exposure has epigenetic effects, impacting gene function and expression, including impacting the expression of DNA binding proteins associated with ASD. Schneider, et al. (2012). Although studying a neurological disorder like ASD is difficult in animals, the data that does exist is, again, consistent with the human data indicating that lead causes ASD.

Having reviewed the literature and assessed the quality of the studies, I turn to the Hill criteria to consider the burden of evidence to support causality.

Hill Criteria	**Evidence**
Strength	The observed associations between lead levels and ASD in the literature are

Hill Criteria	Evidence
	strong. Of the 6 case control studies reviewed by Wang, et al. (2019) that showed statistically significant higher blood lead levels in ASD cases than controls, the blood lead levels in cases were between 18% and 467% higher in the ASD cases compared to the non-ASD controls, with three studies showing that ASD cases had a greater than double blood lead level compared to controls. The mean hair levels of lead were 115% higher in the cases as compared to the controls in Wang's 2019 meta-analysis. The association between lead and ASD behaviors was also shown to be strong in a prospective cohort study. Kim, et al. (2016).
Consistency	A very large number of studies have examined the question of whether a higher body burden of lead predicts ASD, and the overwhelming majority of those studies showed that lead was measured at higher levels in children with ASD than in children without ASD, further supported by a prospective cohort study and a study on monozygotic and dizygotic twin pairs which demonstrated a higher risk of ASD following lead exposure in early infancy. Arora, et al. (2017). This consistency is further supported by the fact that these studies involved diverse populations. The consistency of findings across studies was apparent, even though not every study showed that lead levels were higher in children with ASD (which would be expected).
Specificity	Does not apply – lead exposure causes a wide range of neurological and developmental impairments, including ASD.
Temporality	Prospective data confirms an association between lead exposure and ASD risk, lending support to a temporal relationship consistent with causality.
Biological gradient	Formal tests of a dose-response relationship are lacking in the literature though linear associations are presented in studies, without an apparent threshold effect, and significant associations between lead and ASD are shown across populations and time periods with varying population-wide exposure levels.
Biological plausibility	There are multiple plausible biological mechanisms, supported by *in vitro* and *in vivo* human and animal studies, that support a causal relationship

Hill Criteria	Evidence
	between lead and ASD.
Coherence	The existence of a causal association is coherent. Not only is there experimental data in animals that supports a causal role for lead exposure to ASD risk, lead exposure has been associated with ASD-like phenotypes, development, and behavior in animal experimental studies as well. Lead is a well-established neurotoxin.
Experimental Evidence	Intentional exposure of humans to heavy metals in experimental studies is not ethical. However, animal studies support a casual association.
Analogy	As discussed below, other neurotoxic metals have also been shown to cause ASD and related neurodevelopmental abnormalities.

Overall, the weight of the scientific evidence – taken in totality – demonstrates that lead exposure in infancy and early childhood can cause ASD. The associations observed in the observational epidemiological literature are reasonably strong and consistent. Data shows that lead exposure ***prior*** to ASD diagnosis is specifically associated with higher risk. The association appears in different study populations and across the range of exposure levels without an apparent threshold effect shown. There are multiple underlying biological mechanisms that support a causal relationship. The association is supported by experimental evidence in animal models and in translational research. Lastly, the association between lead and ASD risk is consistent with a well-recognized and extensive body of literature that has also shown that lead exposure early in life causes related behavioral, cognitive, and developmental deficits.

After reviewing the peer-reviewed scientific literature on the relationship between exposure to lead and ASD, followed by consideration of the Hill criteria, I conclude to a reasonable degree of scientific certainty that lead accumulation in the body is causally associated with ASD, and that early life postnatal lead exposure can cause the development of ASD.

B. Arsenic and ASD

Inorganic arsenic tops the EPA's priority list of hazardous substances.

As with lead, the postnatal body burden of arsenic has been examined in blood, hair, and urine and compared between ASD and non-ASD children. Out of 6 studies that have analyzed blood arsenic in relation to ASD, 3 showed that arsenic levels were higher in autistic cases and 3 showed no significant difference (in all of these studies arsenic was non-significantly higher in controls). Out of 12 studies that have evaluated hair arsenic levels, 5 studies also showed a positive association between arsenic and ASD, 6 studies showed no significant association (in 3 of these studies arsenic was non-significantly higher in cases), and one study showed an inverse association. In addition, 3 studies examined urine arsenic levels and ASD, and in all of them arsenic was non-significantly higher in cases compared with controls. Overall the epidemiological literature on the relationship between arsenic and ASD has been relatively more mixed compared with that of lead and ASD, but a large number of studies have shown a significantly increased risk of ASD among individuals with higher arsenic levels.

A primary limitation common across the epidemiological studies on arsenic and ASD are small sample sizes with limited statistical power to detect statistically significant associations. In fact, none of the studies included more than 100 cases. In this case, nonsignificant findings should be interpreted cautiously and a pooled or meta-analysis approach is particularly valuable. In 2019, Wang and colleagues combined all of the data on inorganic arsenic in relation to ASD published through 2018. The meta-analysis included 14 studies on the association between inorganic arsenic and ASD, of which 8 were included in the quantitative meta-analysis. The meta-analysis of blood inorganic arsenic included 318 autistic cases and 304 controls and showed a substantial increased level of inorganic arsenic in the blood of autistic cases (mean=1.95±1.49 ug/dL) compared to non-autistic controls (mean=0.37±0.05 ug/dL). This difference was strong in both the absolute difference and statistical significance ($p<0.0001$). Similar results were observed when hair arsenic levels were compared between 168 autistic cases (mean=0.52±0.42 ug/g) and 183 non-autistic controls (mean=0.10±0.05 ug/g), $p<0.0001$ in this

meta-analysis of 4 studies. Of the comparisons that were included in the meta-analysis, 5 showed that arsenic levels were higher in ASD cases, while 3 showed no significant difference. Of the comparisons not included in the meta-analysis, 3 showed that arsenic levels were higher in ASD cases and 4 showed no significant difference. Across the literature, the association between arsenic and ASD has been modeled as a continuous linear association rather than as a threshold effect.

An older meta-analysis by Saghazadeh and Rezaei in 2017 showed that patients with ASD and control subjects did not differ in arsenic measurements of hair, urine, and blood.

Following publication of the 2019 Wang et al meta-analysis and review, the data that supports a strong association between hair arsenic levels and ASD has only become stronger, with one additional case control study showing a higher level of arsenic in the hair of ASD cases compared to controls (0.216 ± 0.09 mg kg-1 vs 0.061 ± 0.03 mg kg-1 (Filon, et al. (2020)), and another study of 48 autistic children showing that hair arsenic levels were associated with greater ASD symptom severity. Fiore, et al. (2020).

A second limitation in the current body of literature is the fact that arsenic in children's bodies were measured after the diagnosis had already occurred, challenging assumptions about temporarily and causality. However, as explained above with respect to lead, reverse causation, such that ASD characteristics would increase arsenic exposure, is not a likely explanation of the observed associations.

Associations observed between maternal arsenic levels during pregnancy and an increased risk of ASD following birth supports the understanding that arsenic levels early in life, prior to an ASD diagnosis, are in fact etiologically relevant, rather than increased arsenic levels being observed as a consequence of ASD. A recent Norwegian study with 397 ASD cases and 1034 controls observed a non-linear association between maternal blood arsenic during pregnancy and offspring ASD risk. Skogheim, et al. (2021). Moreover, a smaller Danish study published in 2019 evaluated amniotic fluid samples from 37 ASD cases and 50 controls between a four-year period (1995-1999). Long, et al. (2019). The association between arsenic and ASD

was shy of statistical significance with an adjusted OR per 1 mg/L increase in arsenic of 1.50 (95% CI: 0.92–2.42), but the results did suggest a contribution of prenatal arsenic exposure in relation to ASD. One ecological study (Dickerson, et al. (2016)) examined ambient arsenic levels across census tracts and did not observe an association with ASD prevalence across the census tracts. Ecological studies are great for hypothesis generating but this negative finding does not detract from the positive findings in the studies mentioned above that were much stronger methodologically and more appropriate for inferring causality.

The ability for early life arsenic exposure to cause ASD-like behavior has been supported in experimental research in animals. A 2018 study in rats showed that postnatal low-concentration arsenic exposure impaired learning and social skills and increased anxiety-like behaviors and suggested abnormal frontal cortex neurogenesis as the underlying biological mechanism. Zhou, et al. (2018). In addition, in utero exposure to arsenic in mice caused changes in perseverative/impulsive behavior. Hill, et al. (2015). Animal data has also associated arsenic exposure with alterations in brain cells and neurotransmitters. Tolins, et al. (2014).

The fact that arsenic is a known neurotoxin lends support to the biological plausibility that it can cause ASD. Tolins, et al. (2014). Like lead, arsenic also induces oxidative stress and epigenetic changes that are believed to mediate its relationship with ASD. Not only have arsenic levels been shown to be elevated in children with ASD, but higher arsenic levels have also been associated with many related neurocognitive and developmental deficits, memory, and hyperactivity. Vahter, et al. (2020); Tolins, et al. (2014). For example, a study of schoolchildren in Mexico in an area contaminated with arsenic and lead examined urine arsenic in relation to cognitive performance and showed that arsenic contamination was associated with children's cognitive development, independent of any effect of lead. Rosado, et al. (2007).

Having reviewed the literature and assessed the quality of the studies, I turn to the Hill criteria to consider the burden of evidence to support causality.

Hill Criteria	Evidence
Strength	The Wang, et al. (2019) meta-analysis of blood inorganic arsenic showed a substantial increased level of inorganic arsenic in the blood of autistic cases (mean=1.95±1.49 ug/dL) compared to non-autistic controls (mean=0.37±0.05 ug/dL). This difference was strong in both the absolute difference and statistical significance ($p<0.0001$). Similar results were observed when hair arsenic levels were compared between autistic cases (mean=0.52±0.42 ug/g) and non-autistic controls (mean=0.10±0.05 ug/g), $p<0.0001$.
Consistency	A large number of studies, but not all, have shown a significantly increased risk of ASD among individuals with higher arsenic levels. These observed associations involve diverse study populations, lending strength to the consistency of the observations. The literature has been consistent.
Specificity	Does not apply – the neurotoxic effects of arsenic extend to other neurodevelopmental impairments as well.
Temporality	An association observed between maternal arsenic levels during pregnancy and an increased risk of ASD demonstrate that arsenic levels early in life, prior to an ASD diagnosis, are in fact etiologically relevant. These findings lend support to a temporal relationship consistent with causality.
Biological gradient	Across the literature, the association between arsenic and ASD has been modeled as a continuous linear association rather than as a threshold effect, and no threshold has been determined.
Biological plausibility	The fact that arsenic is a known neurotoxin supports its ability to cause ASD. Like lead, arsenic also induces oxidative stress and epigenetic changes that are believed to mediate its relationship with ASD.
Coherence	The ability for early life arsenic exposure to cause ASD-like behavior has been supported in experimental research in animals.
Experimental Evidence	Intentional exposure of humans to heavy metals in experimental studies is not ethical.

Hill Criteria	Evidence
Analogy	Other neurotoxic metals have also been shown to cause ASD and related neurodevelopmental abnormalities.

A review of the literature, followed by consideration of the Hill criteria, demonstrates, to a reasonable degree of scientific certainty, that early life postnatal arsenic exposure can cause the development ASD. Indeed, the associations observed in the epidemiological literature across multiple studies that examined both blood and hair samples are strong. Biological mechanisms related to neurotoxicity support a causal relationship. The causal role of arsenic is supported by experimental evidence in animal models, and by data on related neurodevelopmental impairments.

C. Mercury and ASD

Mercury exists as multiple types: elemental mercury, inorganic mercury, and organic mercury. The most important organic mercury compound in relation to human exposure is methylmercury, and that is the type of mercury that is relevant to food consumption. It should be noted that another type of organic mercury – ethylmercury, specifically from the preservative thimerosal – has also been examined in many studies in relation to ASD. Ethylmercury does not accumulate and is readily excreted by the body. Ethylmercury is not discussed in this report. This section will focus on methylmercury and total/unspecified mercury as examined in the current literature in relation to ASD.

In total 37 observational epidemiological studies (including cohort, case-control, and cross-sectional) on the relationship between postnatal mercury exposure and the risk of ASD were identified and reviewed. Most of these studies have utilized a case control design, and mercury levels have been measured in blood, hair, and urine. The majority of these studies have shown that autistic children have higher levels of mercury than the non-autistic controls. Out of 13 studies that examined mercury levels in blood, 9 showed a significant positive association, and 4 showed no statistically significant association (in 2 of these mercury levels were non-

significantly higher in cases). Out of 18 studies that examined mercury in hair, 10 studies showed a significant positive association, 6 studies showed no significant association (in 3 of these mercury levels were non-significantly higher in cases), and 2 studies showed an inverse association. Out of 5 studies that evaluated urine mercury concentrations, 2 showed significant positive associations with ASD, and 3 studies showed no statistically significant association (in all 3 of these mercury levels were non-significantly higher in cases). Therefore, overall, the current body of literature is reasonably consistent in its conclusions that the burden of mercury in the bodies of children with ASD is higher than that in the bodies of children without ASD.

The vast majority of these studies had small sample sizes, under 100 participants, which limits the ability to detect significant associations even when they exist. This limitation can be overcome in meta-analysis or pooled analyses in which the data from individual studies are combined to achieve greater statistical power to detect significant associations. In 2020, Sulaiman and colleagues conducted a systematic review and meta-analysis of the data on mercury levels in blood, hair, and urine in relationship to ASD published through June 2019. In this systematic review of 23 studies, the authors concluded that ASD risk was associated with increased levels of mercury in blood, hair, and urine.

The Sulaiman meta-analysis compared 509 cases with a mean mercury concentration of 1.16 (SD 0.33) μg/g to 587 controls with a mean concentration of 0.49 (SD 0.11) μg/g, representing a statistically significant and strong association between hair mercury levels and ASD ($p<0.0001$), consistent with the findings from most of the individual studies. For the studies measuring urine mercury, there were 186 cases with a mean mercury concentration of 1.25 (SD 3.27) μg/g-creatinine compared to 229 controls with a mean concentration of 0.64 (SD 0.81) μg/gcreatinine, again representing a strong and statistically significant positive association with ASD ($p=0.01$). For measures of blood mercury, there were a combined 744 cases with a mean mercury concentration of 7.6 (SD 1.9) μg/L and 665 controls with a mean concentration of 4.8 (SD 1.1) μg/L, which was again highly statistically significant ($p<0.0001$).

An earlier meta-analysis from 2017 by Jafari and colleagues focused on case control

studies and found that mercury levels in whole blood (Hedges =0.43, 95% CI: 0.12, 0.74, P =0.007; 16 studies), red blood cells (Hedges =1.61, 95% CI: 0.83, 2.38, P<0.001; 5 studies), and brain tissue (0.61 ng/g, 95% CI, 0.02, 1.19, P =0.043; 3 studies) but not urine (0.51 mg/g creatinine 95%CI, -0.14, 1.16, p=0.12; 8 studies) were higher in ASD patients compared with controls, with the differences reaching statistical significance. In 23 studies that measured mercury levels in hair, the meta-analysis did not see a difference in means (0.63 mg/g, 95% CI: −0.21, 1.46, P =0.141), but when 3 influential studies were excluded the results suggested that the ASD cases in fact had lower hair mercury levels compared to controls (-0.14 mg/g, 95% CI: −0.28, -0.01, P =0.04). Subgroup analyses attributed the lower hair mercury levels in ASD cases to studies in America. Regarding the associations with hair mercury levels, the authors postulated: "The low levels of mercury in the hair of ASD patients may be due to the retention of mercury inside the cells. A portion of mercury is retained in the cells of central nervous system." Based on this thorough and methodologically rigorous meta-analysis of case control studies the authors concluded: "Results of the current meta-analysis revealed that mercury is a causal factor in the etiology of ASD."

Moreover, the Saghazadeh and Rezaei (2017) meta-analysis included 38 studies that were published through the end of 2016 with mercury measurements conducted in blood (including neonatal blood spots, plasma, serum), red blood cells (erythrocytes), hair, urine, nail, and teeth but only showed data from hair, blood, urine, and erythrocyte measures of mercury. The authors did not find differences in urinary mercury levels between patients with ASD and control subjects. Erythrocyte mercury concentrations were higher in cases with a summary effect size of 1.562 (Z = 2.68, p = 0.007). For hair measurements of mercury, they evaluated 26 studies (1092 patients with ASD, 973 control subjects) and found no difference in hair mercury concentrations between patients and control subjects (effect size of 0.224; Z = 0.44, p =0.661). However, subgroup analyses indicated that ASD patients in developing but not in developed lands have higher hair concentrations of mercury in comparison with control subjects.

Furthermore, a comprehensive review by Kern and colleagues (2016) evaluated 91

studies assessing the relationship between mercury exposure and ASD. The authors concluded that "the preponderance of the evidence indicates that mercury exposure is *causal* and/or contributory in ASD." (emphasis added).

A 2011 study in India, conducted by Priya and Geetha, showed that the mercury levels in nails was significantly higher in 45 ASD cases compared to 50 healthy controls.

Although hair mercury levels are understood to reflect long-term methylmercury exposure, which is the exposure of greatest interest in this context, data from other biomarkers such as urine, blood, nails must also be considered in totality for a meaningful assessment of causation, as noted by the authors of Jafari, et al. (2017).

It is important to note that the 2020 meta-analysis by Sulaiman and colleagues did not include several observational epidemiological studies on mercury in relation to ASD. The overwhelming majority of these studies also showed that mercury levels were significantly associated with ASD, only strengthening the conclusion about a strong and consistent relationship between mercury exposure and ASD. In 2018 Li et al. compared blood mercury levels in 180 ASD cases and 184 non-autistic controls (ages 3-8) and showed that the cases had substantially higher mercury levels (median 37.84 vs 8.38μg/L). Significantly higher hair mercury levels in ASD cases compared to controls was also observed by Al-Ayadhi et al. in 2005 and in the all-male case control study by Fido and Al-Saad in 2005. A 2014 case control study in Egypt (Yassa, et al. 2014) with 45 ASD cases and 45 matched controls observed substantially higher mercury levels among ASD cases in both hair (5.21±0.08 vs 0.11±0.05 ug/gr) and blood (4.02±0.54 vs 0.00±0.02 ug/dl). A small study in China with only 34 ASD cases and 34 controls (age 3-5) also showed that the median blood mercury levels were more than 3-fold higher in the cases than the controls (3.83 vs 1.09 μg/L). Qin, et al.)2018). Another small case control study from 2017 in an older child population (mean age 7) showed that the mean mercury in red blood cells in the 35 ASD cases was 35% higher than the 30 controls. El-Ansary, et al. (2017). The fact that all of these studies showed significant differences in mercury levels despite the very modest sample sizes is noteworthy because only large differences are

observable in studies with smaller samples. As explained above, statistical significance in small studies speaks to the strength of the observed associations given that it is hard to observe statistical significance with smaller study sizes. In contrast, in 2017 Skalny and colleagues compared blood and hair levels between a small sample of ASD cases and controls and observed no significant differences, with cases having non-significantly lower mercury levels. And a very small 2015 study by Macedoni-Luksic et al. compared 52 ASD cases with 22 children who had other neurological disorders, and observed no difference in blood mercury levels, which supports the proposition that mercury is a predictor of many neurological impairments in children. In the latter study the cases had non-significantly higher mercury levels.

Although mercury in tooth enamel has also been investigated in only a couple of studies, they are highly relevant in this context because such studies can measure exposure during the perinatal period. In 2007, Adams et al. compared the levels of mercury in baby teeth of 15 autistic children and 11 typically developing children and reported that the autistic children had mercury levels that were significantly higher (2.1-fold higher than the controls). The authors did note that the cases also reported greater use of oral antibiotics as infants which may have impaired their ability to excrete mercury. In contrast, another study that compared mercury levels across different regions of baby teeth in 22 autistic cases and 22 typically developing controls, observed no significant difference in mercury levels in both the regions identified as representing prenatal exposure and the regions identified as representing postnatal exposure. Abdullah, et al. (2012). However, the authors of Abdullah noted the potential for measurement imprecision of metals in the tooth enamel.

Studies have also examined ambient levels of mercury and have shown positive associations with ASD risk. The value of these studies is that they are free from any potential bias of reverse causality as ASD never impacts the ambient levels of mercury. Dickerson, et al. (2016) studied 2558 census tracts across 5 states and found that children living in census tracts in the top quartile for ambient mercury had a 14% increased ASD prevalence compared to census tracts in the bottom quartile for ambient mercury, a difference that was statistically significant.

Further, their ecological findings suggested that mercury exposure was more detrimental when combined with other ambient metals, as the authors concluded that there were synergistic effects between mercury exposure with elevated levels of ambient lead and arsenic. Importantly, these findings accounted for differences in neighborhood race, urbanicity, and socioeconomic status. Consistent with these findings, in 2011, Blanchard, et al. conducted a study in Bexar County, Texas and Santa Clara County, California and observed that the relative risk of ASD was higher in the geographic areas with higher levels of ambient mercury. In another study, Windham, et al. (2006) linked the California ASD surveillance system to estimated heavy metal air pollutant concentrations compiled by the U.S. Environmental Protection Agency. This study included 284 autistic children and 657 controls born in 1994 in the San Francisco Bay area. Children born in census tracts in the top two quartiles for ambient heavy metals had a significantly higher risk of ASD compared to children born in the bottom 2 quartiles for ambient heavy metals, and the two heavy metals that were most strongly driving this increased risk were ambient levels of cadmium and mercury. Specifically, children born in the top quartile for ambient mercury levels had a 92% increased risk of ASD compared to children born in the bottom two quartiles (95% CI 1.36-2.71), adjusting for maternal age, education and child race. These studies further indicate that the observed associations between mercury and ASD in the case control studies are likely not explained by reverse causality.

The causal association between mercury exposure and ASD is convincingly supported by multiple large prospective cohort studies as well. In 2017 Ryu and colleagues conducted a prospective study that examined blood mercury levels in 458 children in utero (maternal blood) during early and late pregnancy, cord blood, and at age 2 and 3, and quantified the associations with mild-moderate autistic behaviors at age 5 using the social responsiveness scale (SRS), a reliable and validated ASD screening tool. A notable strength of this study was the wide range of factors that they adjusted for in their models including maternal education, income, maternal age, maternal tobacco use, parity, pre-pregnancy BMI, birth weight, sex, and even maternal fish intake during pregnancy. Linear dose-response associations were observed between mercury

levels and ASD behaviors in this study. A doubling of blood mercury levels at late pregnancy, in cord blood, at 2 years of age, and at 3 years of age was associated with an increase in the SRS T-scores by 1.84-, 2.24-, 2.12-, and 2.80-fold, respectively. In addition, a doubling of blood mercury levels at late pregnancy and in cord blood was associated with an increase in the risk of the ASD phenotype including mild to moderate features (defined as SRS T-scores ≥ 60) by 31% and 28%, respectively). This study is particularly noteworthy because it is the only prospective longitudinal study on the association between mercury exposure at multiple time points from early pregnancy to early childhood in relation to ASD behavior. The study examined mercury exposure in early life prior to ASD diagnosis, which supports the understanding that mercury exposure increases ASD risk rather than the other way around (i.e., it refutes the possibility of reverse causality). As such, the study provides important insight into the temporality of the relationship between mercury exposure and ASD as well as supporting a dose-response relationship. However, studies on the association with prenatal mercury exposure have not been consistent, and this may be partly explained by the counterbalancing protective effect of essential fatty acids from fish consumption that varies between studies. One study was conducted within a high fish consuming population (Seychelles Child Development Study) which showed that prenatal methylmercury exposure was associated with DNA methylation (gene expression) at genetic sites believed to impact neurodevelopment among children aged 7, a finding that again supports a causal effect of early life methylmercury exposure on childhood neurodevelopment. Ulloa, et al. (2021).

Geier, et al. (2009) also conducted a prospective study in which they examined prenatal exposure to maternal dental amalgams (50% mercury) in relation to symptom severity in 100 autistic children. They reported 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, again, adds to the weight of evidence linking mercury exposure to the development of ASD.

Early life methylmercury exposure has also been prospectively associated with related

neuropsychological deficits, including visuospatial processing and memory. Grandjean, et al. (2014). This supports a causal association.

Fish consumption is one important predictor of methylmercury exposure, which must be considered when evaluating the available data. Fish not only contains toxic methylmercury, but also neuroprotective essential fatty acids. Therefore, it is important to note that the neurological and developmental detrimental effects of methylmercury may be diluted or counterbalanced in epidemiological studies when it is highly correlated with the nutritionally beneficial properties of fish rich in essential fatty acids. A 2010 population-based case-control study by Hertz-Picciotto, et al. compared the blood mercury levels between 332 autistic cases and 166 typically developing controls, adjusting for age, sex, maternal education, maternal birthplace, fish consumption, nasal sprays, and amalgams. In this study fish consumption was the primary predictor of blood mercury levels, and adjusting for dietary, medical, pharmaceutical, and dental sources of mercury, there was no difference in blood mercury between cases and controls. Statistical adjustment for maternal diet during pregnancy has resulted in stronger effects of methylmercury exposure. Budtz-Jorgensen, et al. (2007); Strain, et al. (2008). Budtz-Jorgensen, et al, (2007) clearly explained: "The adverse effects of methylmercury exposure from fish and seafood are likely to be underestimated by unadjusted results from observational studies, and the extent of this bias will be study dependent." It is important to note that most studies did not take into account the neuroprotective effects of fish consumption when estimating the impact of mercury on ASD risk, which may account for some of the inconsistent associations observed for early life exposure to methylmercury in relation to ASD risk.

Though experimental data in animals is limited, the available data support a range of neurotoxic and developmental effects due to mercury exposure. Research in mice has shown that low-level prenatal exposure to methylmercury analogous to typical human exposure results in chronic motor and memory impairment (Montgomery, et al. (2008)), cognitive dysfunction, and altered motivation-driven behaviors. Onishchenko, et al. (2007). Experimental data in mice also show that perinatal methylmercury exposure results in depression as well as changes to DNA

methylation (i.e., gene expression). Ceccatelli, et al. (2013). Data from rats suggests that the neurobehavioral effects of methylmercury exposure may be due to the effects of early postnatal methylmercury exposure on the dopaminergic system. Dreiem, et al. (2009). Overall, the weight of the evidence from rodent studies has demonstrated neuropathological damage and neurobehavioral changes from brain mercury levels at birth. Castoldi, et al. (2008).

Mercury is a known potent neurotoxin and developmental toxin. It is widely known that mercury exposure damages the nervous system and can result in cognitive and neurological impairments. In 2011, Garrecht & Austin reviewed the literature on the plausibility of a role for mercury in the etiology of ASD and concluded that "[f]rom a cellular perspective, it would appear that the existing scientific literature supports the biological plausibility of a [mercury]-based ASD pathogenesis. [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[.]" Garrecht & Austin (2011). The neurotoxicity of organic mercury has been demonstrated to exhibit a dose-response effect. In a review of the neurotoxicity of organic mercury, Pletz and colleagues wrote: "The effect of interest here is developmental neurotoxicity. Methylmercury exposure to the developing brain compromises neuronal proliferation, migration and as a result neuronal differentiation, synaptogenesis, tightly regulated apoptosis, and other processes vital to the formation and functioning of the nervous system. The time window which encompasses the vulnerability of the brain to disturbances of all these processes is ample." Pletz, et al. (2016). Mercury crosses the blood brain barrier and methylmercury, in particular, enters the brain easily. Methylmercury is believed to impact ASD susceptibility by damaging brain cells and impairing the function of astrocytes (glial brain cells that provide nutrients to the brain, control the blood brain barrier, tissue repair after injury, moderate neurotransmission and many other key processes). Mercury exposure also stimulates the immune system and results in immunotoxicity, the release of inflammatory cytokines, and therefore leads to neuroinflammation. Garrecht & Austin (2011).

Having reviewed the literature and assessed the quality of the studies, I turn to the Hill criteria to consider the burden of evidence to support causality.

Hill Criteria	**Evidence**
Strength	The association between mercury and ASD is strong. A recent meta analysis (Sulaiman, et al. (2020) compared 509 cases with a mean mercury concentration of 1.16 (SD 0.33) μg/g to 587 controls with a mean concentration of 0.49 (SD 0.11) μg/g, representing a statistically significant and strong association between hair mercury levels and ASD ($p<0.0001$). For the studies measuring urine mercury, there were 186 cases with a mean mercury concentration of 1.25 (SD 3.27) μg/g-creatinine compared to 229 controls with a mean concentration of 0.64 (SD 0.81) μg/gcreatinine, again representing a strong and statistically significant positive association with ASD ($p=0.01$). For measures of blood mercury, there were a combined 744 cases with a mean mercury concentration of 7.6 (SD 1.9) μg/L and 665 controls with a mean concentration of 4.8 (SD 1.1) μg/L, which was again highly statistically significant ($p<0.0001$). The strength of the association between mercury exposure and ASD risk was also notable in prospective data reported by Ryu, et al. (2017): A doubling of blood mercury levels at late pregnancy, in cord blood, at 2 years of age, and at 3 years of age was associated with an increase in scores on an ASD screening tool by 1.84-, 2.24-, 2.12-, and 2.80-fold, respectively. In addition, a doubling of blood mercury levels at late pregnancy and in cord blood was associated with an increase in the risk of the ASD phenotype including mild to moderate features by 31% and 28%, respectively.
Consistency	Overall, the current body of literature is reasonably consistent in its conclusions that the burden of mercury in the bodies of children with ASD is higher than that in the bodies of children without ASD, and the results of prospective cohort studies and studies of pre-natal mercury exposure confirm an increased risk of ASD following mercury exposure.
Specificity	Does not apply – mercury exposure causes a wide range of neurological and developmental impairments.

Hill Criteria	Evidence
Temporality	Prospective data confirmed an association between mercury exposure and ASD risk, lending support to a temporal relationship consistent with causality. Further, the likelihood of reverse causality is implausible.
Biological gradient	Linear dose-response associations have been observed between mercury levels and autistic behaviors in a prospective cohort, supporting a biological gradient.
Biological plausibility	The existing scientific literature supports the biological plausibility of a mercury-based ASD pathogenesis.
Coherence	Though the availability of experimental data in animals is limited, the existing data supports a range of neurotoxic and neurodevelopmental effects due to mercury exposure, supporting coherence across the literature.
Experimental Evidence	Intentional exposure of humans to heavy metals in experimental studies is not ethical.
Analogy	Other neurotoxic metals have also been shown to cause ASD and related neurodevelopmental abnormalities.

In conclusion, after reviewing the peer-reviewed scientific literature on the relationship between mercury (specifically, methylmercury) and ASD, followed by consideration of the Bradford Hill criteria, I conclude to a reasonable degree of scientific certainty, that early life postnatal mercury exposure can cause the development of ASD. The current body of medical literature consistently shows that a body burden of mercury is causally associated with childhood ASD. The data have suggested linear associations without an apparent threshold effect, across diverse study populations, and demonstrate that mercury exposures prior to diagnosis are relevant. The evidence that mercury body burden can cause ASD is supported by experimental studies in animals and translational research, which support underlying biological mechanisms.

D. Conclusions Regarding Heavy Metals and ASD

In conclusion, after reviewing the scientific literature on the relationships between lead,

arsenic, and mercury (specifically, methylmercury) and ASD, followed by consideration of the Bradford Hill criteria, I conclude to a reasonable degree of scientific certainty, that early life postnatal exposure to lead, arsenic, and mercury can cause the development of ASD.

It is clear that not all children who are exposed to neurotoxic metals will exhibit significant neurodevelopmental impairment. Some children may have altered abilities to metabolize, detoxify, distribute, and/or excrete metals. Other environmental toxins, prenatal and perinatal complications, and genetic factors likely interact with heavy metals to help determine susceptibility. The same is true for the relationship between smoking and lung cancer for example, or alcohol and liver disease, or blood pressure and stroke. The complex interactions that help determine susceptibility do not mean that these risk factors are not in fact causal – rather, the nature of their causal effects are complex. In the absence of more refined understanding of who is particularly susceptible to the effects of neurotoxic heavy metals, avoidance and reduction on the population-wide level is imperative.

E. Lead and ADHD

A very large number of studies have examined the question of whether a higher body burden of lead in infancy/childhood predicts ADHD, and the overwhelming majority of those studies showed that lead was measured at higher levels in children with ADHD than in children without ADHD. The consistency of findings across studies was clear. Lead levels were most commonly measured in blood, but also measured in urine in a few studies.

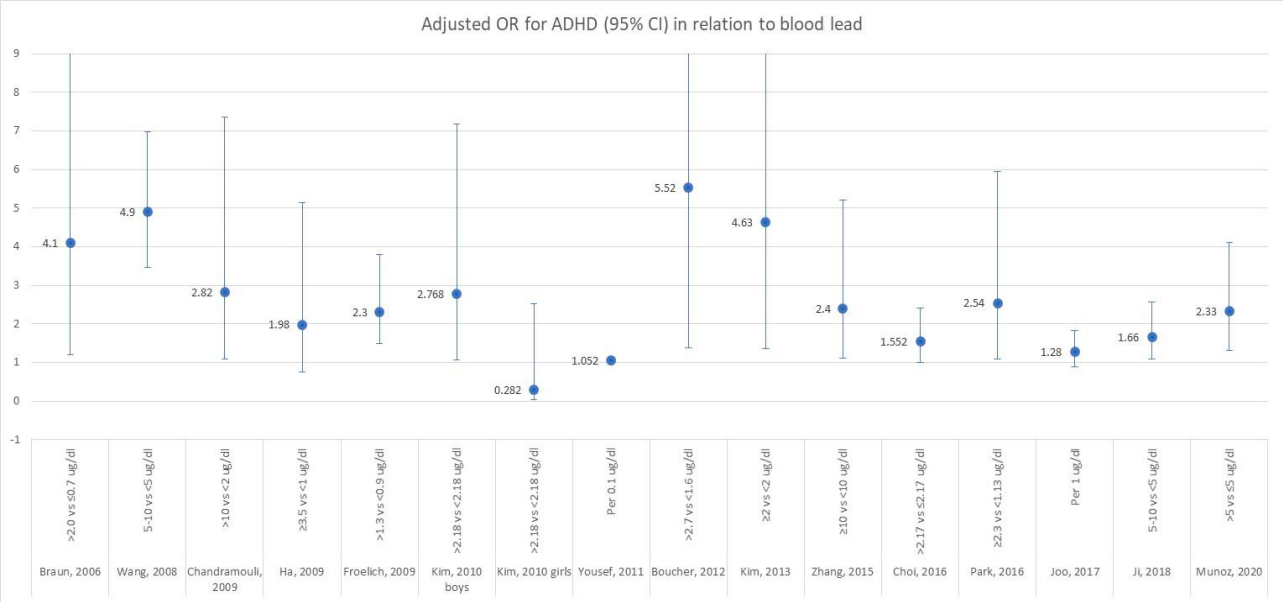
Out of 26 studies that examined blood lead levels in relation to ADHD, 24 showed that blood lead levels were significantly associated with ADHD. The other 2 studies showed no statistically significant association (in both of these studies lead was non-significantly inversely associated with ADHD), and no studies showed that lead levels were associated with a decreased risk of ADHD. In the 2 studies that evaluated urine lead excretion levels, both showed an association between urinary lead excretion and increased ADHD risk. In the large body of observational data, lead was associated with ADHD risk in diverse study populations with varying levels of lead burden in the overall study population. A large body of observational

studies has shown that lead is associated with clinically diagnosed ADHD as well as the underlying symptoms of inattention, hyperactivity, and impulsivity. Lee, et al. (2018). In fact, in 2009 Froehlich et, al, estimated that 25.4% (95% CI: 13.9%–32.5%) of ADHD cases among 8 to 15-year-old children might be attributable to elevated lead exposure (top tertile) based on data from 2588 children in the well-regarded United States National Health and Nutritional Examination Survey.

One older study published in 1996 examined children's hair lead levels in relation to teacher-rated attention-deficit behaviors among 277 first grade students. Tuthill, et al. (1996). The advantage to this design is that hair lead levels are more reflective of long-term cumulative exposure levels, rather than recent acute exposure. The authors reported a clear dose-response relationship between hair lead levels and teacher ratings of attention-deficit behaviors that persisted even after adjusting for age, ethnicity, sex, and socioeconomic status. Further, an even stronger association was observed between hair lead levels and physician-diagnosed ADHD.

Figure 1 below displays a forest plot of the results of 16 published analyses on blood lead levels in relation to ADHD risk. I have created this figure to display the results of all studies that reported odds ratios and 95% confidence intervals. The comparison cut points are also shown, and it is clear that they varied across studies. When multiple models were constructed in studies, I included the most fully adjusted model. As shown, the odds ratio was above 1 (the null) in all but one comparison, showing that children with ADHD had higher levels of blood lead in all but one comparison (the analysis restricted to the girls in Kim, et al. (2010) study sample).

Figure 1



As shown, the 95% confidence bounds excluded 1 (the null) in all but 2 of the studies showing increased blood lead in children with ADHD, indicating that these associations were statistically significant at $p<0.05$. Not only were these results highly consistent showing that ADHD is associated with higher blood lead levels, but the graph also displays the substantial strength of the observed associations across studies. In fact, in the majority (10) of the studies the odds ratios surpassed a value of 2.0, indicating that the odds of ADHD were more than double for children above the given blood lead cutpoint. The cutpoint comparisons for each study are shown on the bottom of the graph and what is noteworthy here is the fact that, overall, these comparisons were not considered extreme blood lead levels. In fact, in 9 of the studies the high cutpoint level included values that today are considered normal or non-pathological by pediatricians. In other words, we are seeing over a doubling of risk of ADHD with higher blood lead levels even when those "high" blood lead levels are still within the range considered normal/non-pathological by pediatricians today. Therefore, a very large portion of our pediatric population are exposed to blood lead levels that are highly associated with an increased risk of ADHD without any guidance to identify and intervene.

It is abundantly clear that blood lead levels are substantially associated with ADHD risk

across diverse study populations in many regions. Most of these studies had very modest sample sizes, and yet still had sufficient statistical power to detect significant associations due to the strength of those associations. Some, but not all, studies adjusted for a wide range of potentially confounding factors, and the results remained significant. The most noteworthy limitation is the fact that most of these studies were not prospective, and the blood lead levels were measured after ADHD had been diagnosed, and not during very early life, the presumed etiologically relevant period. Because of this retrospective design, the concern arises about whether lead levels are increased due to features of ADHD, i.e., reverse causality.

One noteworthy study that utilized a prospective design was conducted by Ji, et al. (2018). Their study included 1479 mother-infant pairs (299 ADHD, 1180 neurotypical) in the Boston Birth Cohort. The child's first blood lead measurement and physician-diagnosed ADHD were obtained from electronic medical records, which are notable strengths as they avoided potential recall bias and reverse causality. They found that 8.9% of the children in the cohort had elevated lead levels defined as 5-10μg/dL in early childhood, which was associated with a 66% increased risk of ADHD (OR=1.66, 95%CI:1.08, 2.56). This strong association in a prospective design provides important evidence about the temporality between lead exposure and ADHD and refutes the possibility that the association between blood lead levels and ADHD risk is explained by reverse causality. In addition, the authors examined possible modifying factors and identified the following variables as effect modifiers: maternal lipid levels, maternal stress, and child sex (among boys the association was significantly stronger (OR: 2.49, 95% CI:1.46, 4.26)).

In 2019 Donzelli, et al. published a systematic review of the association between lead and ADHD and concluded that even low levels of lead raise the risk for ADHD. Their review included cohort, case-control, and cross-sectional observational epidemiological studies. Their review included a systematic analysis of the methodological quality, or the level of evidence attributed to each included study based on a grading scale derived from the principles of evidence-based medicine. They noted that most studies that did not observe an association between lead and ADHD were of poor methodological quality, at high risk of bias, and that the

methodologically strong studies were more consistent in their findings for a significant association between lead and ADHD.

Key potential confounding variables that have been addressed in many, but not all of the studies, have included socioeconomic status, prenatal nutrition, maternal smoking, parental intelligence and education, and low birth weight, and even after accounting for these key potential confounders an association between lead and ADHD has persisted. Goodlad, et al. (2013); Donzelli, et al. (2019).

Evidence in support of the prospective temporal relationship between lead exposure and ADHD risk also comes from data that examined prenatal lead exposure, though data on the relationship between prenatal lead exposure and ADHD have been limited and inconsistent. Data from the Duisburg Birth Cohort Study showed that blood lead levels collected during the 32nd week of pregnancy were significantly associated with ADHD-related behavior in the offspring at age 8-9. Neugebauer, et al. (2015).

Although there is no known safe exposure level for lead, the relationship between lead exposure and ADHD has also been shown to be dose-dependent, and persistent after adjusting for a wide range of covariates. For example, a 2017 study by Geier, et al. utilized the publicly available 2003–2004 National Health and Nutritional Examination Survey (NHANES) dataset, which included 2109 people aged 10-19. A significant dose-response relationship between increasing blood Pb levels and the risk of a reported ADD was confirmed (per ug/dL, odds ratio (OR) = 1.237, $p = 0.0227$), and this remained consistent after adjusting for potential confounding variables such as gender, race, and socioeconomic status.

As detailed above, lead is a well-recognized neurotoxin, and it accumulates in bones and blood, therefore extending the exposure duration and period of impact. The potential neurotoxicological pathways by which lead exposure is believed to impact ADHD are complex. Lead damages multiple key brain regions understood to play a role in ADHD, including the hippocampus, prefrontal cortex, basal ganglia, and the cerebellum. Goodlad, et al. (2013). Damage to the hippocampus has been shown to occur through interaction with the NMDA

receptor, a subgroup of glutamate receptors. Individuals with ADHD have been shown to have reduced volume and activity of the prefrontal cortex and the cerebellum. Karri, et al. (2016); Finkelstein, et al. (1998). As mentioned above, lead readily crosses the blood brain barrier and interferes with central neurotransmitter systems that are believed to play a role in the etiology of ADHD, including the glutaminergic, cholinergic, and especially the dopaminergic systems. Goodlad, et al. (2013); Cory-Slechta, et al. (1995). Stimulant medications prescribed for ADHD treatment are dopamine agonists. Cholinergic systems are important for working memory, sustained attention, and impulsivity. Lastly, experimental rodent data provides key insight into the epigenetic mechanism also underlying the influence of lead on ADHD risk, as data from rats suggested that lead exposure causes hyperactivity in a dose-dependent manner and that histone acetylation plays essential roles in the pathogenesis of this effect. Luo, et al. (2014).

A causal effect of lead in relation to ADHD is consistent with its effects on other related outcomes. Lead has also been strongly related to other neurodevelopmental deficits including conduct problems, antisocial behavior, and intelligence in observational studies in humans, and experimental studies in animals have also shown lead to cause impaired cognitive function. Goodlad, et al. (2013).

There are not many studies that have examined the mixture effects of neurotoxic metals on neurodevelopment, but that is an emerging and important line of research. Sanders, et al. (2015). Lead is the heavy metal most commonly assessed in combination with other heavy metals in the existing limited literature. One study suggested a synergistic effect of prenatal lead and mercury exposure in relation to impulsivity among children aged 9-13. Boucher, et al. (2012). There is also growing evidence indicating that manganese may exacerbate the neurotoxic effects of lead in young children. Sanders, et al. (2015).

Having reviewed the literature and assessed the quality of the studies, I turn to the Hill criteria to consider the burden of evidence to support causality.

Criteria	Evidence
Strength	The association is very strong. Figure 1 above displays the substantial strength of the observed associations between lead exposure and ADHD across studies. In fact, in the majority of the studies the odds ratios surpassed a value of 2.0, indicating that the odds of ADHD were more than double for children above the given blood lead cutpoint.
Consistency	A very large number of studies have examined the question of whether a higher body burden of lead predicts ADHD, and the overwhelming majority of those studies showed that lead was measured at higher levels in children with ADHD than in children without ADHD. The consistency of findings across studies was clear. Out of 26 studies that examined blood lead levels in relation to ADHD, 24 showed that blood lead levels were significantly associated with ADHD. Moreover, this consistent observation is further supported by a prospective cohort study (Ji, et al. (2018), which demonstrates that lead exposure prior to diagnosis is etiologically relevant.
Specificity	Does not apply – lead exposure causes a wide range of neurological and developmental impairments, including ADHD.
Temporality	Prospective data have confirmed an association between lead exposure and ADHD, lending support to a temporal relationship consistent with causality.
Biological gradient	A dose-response relationship between lead exposure and ADHD has been shown, lending support to a causal inference.
Biological plausibility	There is strong biological plausibility. There are multiple underlying biological mechanisms that support a causal relationship between lead exposure and ADHD. Lead damages multiple key brain regions understood to play a role in ADHD, including the hippocampus, prefrontal cortex, basal ganglia, and the cerebellum.
Coherence	There is general coherence in the data. Experimental data in animals has also supported a causal role for lead exposure in ADHD risk. For example, data from rats suggested that lead exposure causes hyperactivity in a dose-dependent manner.

Criteria	Evidence
Experimental Evidence	Intentional exposure of humans to heavy metals in experimental studies is not ethical.
Analogy	Other neurotoxic metals have also been shown to cause ADHD and related neurodevelopmental abnormalities.

After reviewing the peer-reviewed scientific literature on the relationship between lead and ADHD, and consideration of the Bradford Hill criteria, I conclude to a reasonable degree of scientific certainty that early life postnatal lead expo sure can cause the development of ADHD. There is substantial overlap between ASD and ADHD in relation to clinical features and behaviors, risk factors, and underlying neurological mechanisms. A large percentage of children with ASD are also diagnosed with ADHD. Therefore, the conclusion that lead exposure can cause the development of ADHD is consistent with it also being a causative agent of ASD.

Dated: November 12, 2021

Hannah Gardener, Sc.D.

Dr. Gardener Reference List

#	Author(s)	Year	Title of Article
1.	Abdullah, et al.	2012	Heavy Metal in Children's Tooth Enamel- Related to Autism and Disruptive Behaviors
2.	Adams, et al	2006	Analyses of Toxic Metals and Essential Minerals in the Hair of Arizona Children
3.	Adams, et al.	2017	Significant Association of Urinary Toxic Metals and Autism-Related Symptoms -A Nonlinear Statistical Analysis with Cross Validation
4.	Adams, et al.	2012	Toxicological Status of Children with Autism vs. Neurotypical
5.	Alabdali, et al.	2014	A key role for an impaired detoxification mechanism in the etiology
6.	Al-Ayadhi	2005	Heavy metals and trace elements in hair samples of autistic children in central Saudi Arabia
7.	Al-Farsi, et al.	2013	Levels of Heavy Metals and Essential Minerals in Hair Samples of Children with Autism
8.	Arora, et al.	2017	Fetal and Postnatal Metal Dysregulation in Autism
9.	Banerjee, et al.	2007	Environmental risk factors for attention-deficit hyperactivity disorder
10.	Bao, et al.	2009	Behavioural development of school-aged children who live around
11.	Bellinger	2013	Inorganic Arsenic Exposure and Children's Neurodevelopment A Review of the Evidence
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#	Author(s)	Year	Title of Article
348.	EPA	2021	Health Effects of Exposure to Mercury

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HIGHER EDUCATION

Doctor of Science	Epidemiology Minor: Biostatistics Harvard School of Public Health, Boston, MA Date Conferred: November, 2007 GPA: 3.98/4.0
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EXPERIENCE

Academic:

August, 2021-present	Assistant Professor, Department of Neurology, University of Miami Miller School of Medicine
June, 2016-July, 2021	Associate Scientist, Department of Neurology, University of Miami Miller School of Medicine
September, 2009-June, 2016	Assistant Scientist, Department of Neurology, University of Miami Miller School of Medicine
April, 2009-September, 2009	Research Assistant Professor, Department of Pediatrics, University of Miami Miller School of Medicine (Date of appointment: April 6, 2009)
September, 2007-April, 2009	Post-doctoral Associate, Department of Neurology, University of Miami Miller School of Medicine
July, 2002-September, 2004	Senior Research Assistant, Department of Society, Human Development, and Heath, Harvard School of Public Health

Non-Academic:

October, 2015-Present	Medical Advisory Panel, The Clean Label Project, Denver, CO
October, 2016-Present	Consulting Epidemiologist, The Alzheimer's Prevention Clinic, Cornell Medical School
January, 2015-Present	Consulting Statistician, Intersocietal Accreditation Commission
February, 2001-July, 2002	Associate Analyst, Public Health and Criminal Justice Abt Associates, Cambridge, MA

RESEARCH AREAS OF EXPERTISE

Nutritional epidemiology
Neurological epidemiology
Environmental health
Environmental toxicants
Stroke etiology
Dementia etiology
Subclinical vascular disease markers
Vascular risk factors
Acute stroke care
Health disparities
Social determinants of health

Editorial Board Member:

Stroke
Journal of Alzheimer's Disease

PUBLICATIONS

Juried or Refereed Journal Articles:

1. **Gardener H**, Levin B, DeRosa J, Rundek T, Wright CB, Elkind MSV, Sacco RL. Social Connectivity is Related to Mild Cognitive Impairment and Dementia. *J Alzheimers Dis*. 2021. doi: 10.3233/JAD-210519.

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Medicine. 2005;60(10): 2191-2204.

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***Shared first authorship**

Invited Book Chapters:

Gardener H, Lyall K. Pre-, peri- and neonatal factors in autism etiology. In The Comprehensive Guide to Autism.

Gardener H, Wright CB. Mediterranean diet and subclinical vascular disease. In The Mediterranean Diet: An Evidence-Based Approach to Disease Prevention.

Invited Expert Testimony:

Testimony in support of Rhode Island House Bill 5082, a bill to ban the sale of upholstered bedding and furniture that contains more than 100 parts per million of any organohalogen flame retardant. Rhode Island Senate and House of Representatives. March/April, 2017.

Testimony in support of Massachusetts Senate Bill 1191, an act relative to the disclosure of toxic chemicals in children's products. Massachusetts Joint Committee on Public Health. December, 2017.

Selected Invited Speeches:

"Cardiovascular Risk Factors in Relation to Brain and Heart Health" 6th ICCR Congress on Chronic Societal Cardiometabolic Diseases, Quebec, Canada. May, 2017.

"The Mediterranean Diet: Q.E.D for Stroke Prevention?" American Heart Association International Stroke Conference, San Diego, CA. February, 2014.

"Diet and Risk of Vascular Events: The Northern Manhattan Study" University of Miami Department of Endocrinology, Miami, FL. March, 2012.

"Prenatal, Perinatal, and Neonatal Risk Factors for Autism" University of Miami Department of Pediatrics, Miami, FL. September, 2008.

Selected Refereed Abstracts:

Gardener H, Sacco RL, Rundek T, McLaughlin C, Cheung YK, Elkind MSV. Race, Ethnic, and Sex Disparities in Stroke Incidence in the Northern Manhattan Study**.** International Stroke Conference, Los Angeles, CA, February, 2020.

Gardener H, Rundek T, Lichtman J, Leifheit E, Wang K, Romano J, Sacco RL, for the FL-PR CReSD Investigators and Collaborators. Post-stroke quality of care measures in relation to long-term mortality and hospital readmissions in the Florida Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CReSD) Study**.** International Stroke Conference, Honolulu, HI, February, 2019.

Gardener H, Rundek T, Marquez C, Elkind MSV, Sacco RL. Alcohol Consumption in Relation to Inflammation Biomarkers in the Northern Manhattan Study. Nutrition, Boston, MA, June, 2018.

Gardener H, Bowen J, Callan SP. Heavy Metal Contamination in a Large Sample of United States Infant Formulas and Baby Foods. Nutrition, Boston, MA, June, 2018.

Gardener H, Leifheit EC, Lichtman J, Wang K, Wang Y, Gutierrez CM, Ciliberti-Vargas MA, Dong C, Robichaux M, Romano JG, Sacco RL, Rundek T, for the FL-PR CReSD Investigators and Collaborators. Race-Ethnic Disparities in 30-Day Readmission after Ischemic Stroke Among Medicare Beneficiaries in the Florida Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CReSD) Study. International Stroke Conference, Los Angeles, CA, January, 2018.

Simonetto M, **Gardener H**, Caunca MR, Dong C, Elkind MSV, Sacco RL, Rundek T. Vertebral Artery Flow velocities and Cognition Performance in The Northern Manhattan Study. European Society of Neurosonology and Cerebral Hemodynamics Meeting, Berlin, Germany, May, 2017.

Simonetto M, **Gardener H**, Wang K, Gutierrez CM, Ciliberti-Vargas MA, Dong C, Foster D, Waddy SP, Romano JG, Rundek T, Sacco RL. Race/Ethnicity Disparities in In-Hospital Mortality and Disability at Discharge after Acute Ischemic Stroke. Data from the Florida Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CReSD) Study – the NINDS Stroke Prevention Intervention Research Program. American Academy of Neurology Annual Meeting, Boston, MA, April, 2017.

Gardener H, Dong C, Rundek T, McLaughlin C, Cheung K, Elkind MSV, Sacco RL, Wright CB. Diet Clusters in Relation to Cognitive Performance and Decline in the Northern Manhattan Study. American Academy of Neurology Annual Meeting, Boston, MA, April, 2017.

Gardener H, Wang K, Dong C, Ciliberti M, Gutierrez C, Gandia A, Antevy P, Hodges W, Sand C, Romano J, Rundek T, Sacco RL. Race/ethnic Disparities in the Time from Stroke Symptom Onset to Hospital Arrival among Stroke Patients Arriving by EMS in the Florida-Puerto Rico Stroke Registry. American Academy of Neurology Annual Meeting, Boston, MA, April, 2017.

Gardener H, Leifheit-Limson EC, Lichtman J, Wang Y, Wang K, Gutierrez CM, Ciliberti-Vargas MA, Dong C, Robichaux M, Romano JG, Rundek T, Sacco RL, for the FL-PR CReSD Investigators and Collaborators. Race/Ethnic Disparities in Short and Long Term Mortality Among Medicare Beneficiaries in Florida and Puerto Rico: Data from the Florida Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CReSD) Study – the NINDS Stroke Prevention Intervention Research Program. International Stroke Conference, Houston, TX, February, 2017.

Tiozzo E, **Gardener H,** Hudson BI, Dong C, Della-Morte D, Crisby M, Goldberg EB, Elkind MSV, Cheung YK, Wright CB, Sacco RL, Desvarieux M, Rundek T. Subfractions of High-Density Lipoprotein Cholesterol and Carotid Intima-Media Thickness. American Heart Association Epidemiology and Lifestyle Meeting, Phoenix, AZ, March, 2016.

Caunca M, **Gardener H**, Gervasi-Franklin P, Cheung YK, Elkind MSV, Sacco RL, Rundek T, Wright CB. Carotid Intima-Media Thickness and Cognition: The Northern Manhattan Study. International Stroke Conference, Los Angeles, CA, February, 2016.

Ramos A, **Gardener H**, Rundek T, Elkind MSV, Boden-Albala B, Dong C, Sacco RL, Wright

CB. Sleep Disturbances are Associated with Cognitive Decline in the Elderly: Results of the Multi-ethnic Northern Manhattan Study (NOMAS). Association of Professional Sleep Societies Meeting, Denver CO, June, 2015.

Willey JZ, **Gardener H**, Cespedes S, Elkind MSV, Sacco RL, Wright CB. Leisure Time Physical Activity and Cognitive Decline in the Northern Manhattan Study. American Heart Association Epidemiology and Prevention and Lifestyle and Cardiometabolic Health Meeting, Baltimore, MD, March, 2015.

Asdaghi N, Wank K, **Gardener H,** Dong C, Cilibert-Vargas MA, Rose DZ, Santiago FL, Romano JG, Burgin WS, Carrasquillo O, Garcia-Rivera EJ, Koch S, Meschia JF, Nelson JA, Nobo U, Robichauz M, Waters MF, Zevallos JC, Sacco RL, Rundek T. Lower Thrombolysis Rates in Women with Acute Ischemic Stroke in the Florida-Puerto Rico Collaboration to Reduce Stroke Disparities Study - The NINDS Stroke Prevention Intervention Research Program. International Stroke Conference, Nashville, TN, February, 2015.

Yang D, Iyer S, **Gardener H**, Della-Morte D, Crisby M, Wright CB, Sacco RL, Rundek T. Current Cigarette Smoking Is Associated With Echodensity of Carotid Plaque in the Northern Manhattan Study. International Stroke Conference, Nashville, TN, February, 2015.

Sacco RL, **Gardener H,** Wang K, Dong C, Ciliberti-Vargas MA, Romano JG, Burgin WS, Carrasquillo O, Garcia-Rivera EJ, Koch S, Meschia JF, Nelson JA, Nobo U, Robichaux M, Rose DZ, Santiago FL, Waters MF, Zevallos JC, Rundek T, for the FL-PR CReSD Investigators and Collaborators. Race-Ethnic Stroke Disparities in the Florida-Puerto Rico Collaboration to Reduce Stroke Disparities Study - The NINDS Stroke Prevention Intervention Research Program. International Stroke Conference, Nashville TN, February, 2015.

Blanton SH, Beecham AH, **Gardener H**, Wang L, Dong C, Cabral D, Sacco RL, Rundek T, Wright C. An extreme phenotype approach to identify genes in Caribbean Hispanics for carotid plaque, a preclinical marker of atherosclerosis. American Society of Human Genetics Meeting. San Diego, CA, October, 2014.

Wright C, **Gardener H**, Zambrano M, Del Brutto V, Del Brutto O. Comparing Cognitive Screening Tools in a Rural Ecuadorian Population: The Atahualpa Project. American Academy of Neurology 66th Annual Meeting, Philadelphia, PA, April, 2014.

Oboudiyat C, **Gardener H**, Marquez C, Elkind M, Sacco R, DeCarli C, Wright C. Comparing Semi-quantitative and Volumetric Measurements of MRI White Matter Hyperintensities: The Northern Manhattan Study. American Academy of Neurology 66th Annual Meeting, Philadelphia, PA, April, 2014.

Ramos A, **Gardener H**, Elkind M, Cheung K, Santiago M, Sacco R, Rundek T. Sleep duration is associated with subclinical carotid plaque burden and echodensity. The American Institute of Ultrasound in Medicine 2014 Annual Convention, Las Vegas, NV, April, 2014.

Wright CB, **Gardener H**, Dong C, Marquez C, DeRosa JT, Cheung K, Sacco RL, Stern Y, Elkind MS. Infectious Burden and Cognitive Performance: the Northern Manhattan Study. American Heart Association International Stroke Conference, San Diego, CA, February, 2014.

Romano JG, Smith EE, Liang L, **Gardener H**, Camp S, Shuey L, Campo-Bustillo I, Khatri P,

Bhatt DL, Fonarow GC, Sacco RL, Schwamm LH. Thrombolytic Therapy in Patients With Mild Stroke: An Observational Study. American Heart Association International Stroke Conference, San Diego, CA, February, 2014.

Blanton SH, **Gardener H**, Elkind MSV, Sacco RL, Rundek T, Wright C. Carotid IMT and cognitive domains in a tri-ethnic population. International Conference on Heart & Brain, Paris, France, February, 2014.

Khatri M, Moon YP, Scarmeas N, Gu Y, Mora-McLaughlin C, **Gardener H**, Wright C, Sacco RL, Nickolas TL, Elkind MSV. The Impact of a Mediterranean Style Diet on Kidney Function. American Society of Nephrology 2013 Annual Meeting, Atlanta, GA, November, 2013.

Monteith T, **Gardener H**, Dong C, Santiago M, Elkind MSV, Rundek T, Sacco RL, Wright CB. . Migraine, white matter hyperintensities (WMH), and subclinical brain infarction (SBI) in a race/ethnically diverse older cohort: The Northern Manhattan Study. International Headache Conference, Boston, MA, June, 2013.

Della-Morte D, **Gardener H**, Hale EA, Dong C, Elkind MSV, Sacco RL, Rundek T. Association between carotid intima-media thickness and plaque phenotypes: The Northern Manhattan Study. European Stroke Conference, London, England, May, 2013.

Tiozzo E, **Gardener H**, Dong C, Weiss D, Della-Morte D, Elkind MS, Gervasi-Franklin P, Wright CB, Sacco RL. Rundek T. High-density lipoprotein cholesterol subfractions and carotid IMT: The Northern Manhattan Stroke Study (NOMAS). European Stroke Conference, London, England, May, 2013.

Hudson BI, **Gardener H**, Liu-Mares W, Dong C, Cespedes S, Elkind MSV, Wright CB, Sacco RL, Rundek T. Association of soluble RAGE levels with carotid atherosclerosis: The Northern Manhattan Study. American Heart Association Atherosclerosis, Thrombosis, and Vascular Biology Conference, Lake Buena Vista, FL, May, 2013.

Tiozzo E, **Gardener H**, Hudson BI, Dong C, Weiss D, Della-Morte D, Elkind MS, Disla N, Wright CB, Sacco RL, Rundek T. Association between high-density lipoprotein cholesterol subfractions and carotid intima-media thickness: The Northern Manhattan Stroke Study (NOMAS). American Heart Association Atherosclerosis, Thrombosis, and Vascular Biology Conference, Lake Buena Vista, FL, May, 2013.

Monteith T, **Gardener H**, Dong C, Santiago M, Elkind MSV, Rundek T, Sacco RL, Wright CB. . Migraine, white matter hyperintensities (WMH), and subclinical brain infarction (SBI) in a race/ethnically diverse older cohort: The Northern Manhattan Study. American Academy of Neurology, San Diego, CA, March, 2013.

Kuo F, Della-Morte D, **Gardener H**, Cabral D, Elkind MSV, Sacco RL, Rundek T. Association between carotid stiffness and carotid plaque: The Northern Manhattan Study. International Stroke Conference, Honolulu, HI, February, 2013.

Nabizadeh N, **Gardener H**, Disla N, Alperin N, Elkind M, Sacco R, DeCarli C, Wright C. Age and sex differences in total and regional brain volumes: The Northern Manhattan Study. American Academy of Neurology, New Orleans, LA, April, 2012.

Wang L, Beecham A, Dong C, **Gardener H**, Blanton S, Rundek T, Sacco R. Fine mapping study

revealed novel candidate genes for carotid intima-media thickness in Dominicans. International Stroke Conference, New Orleans, LA, February, 2012.

Katsnelson M, Rundek T, Sacco R, **Gardener H**, Malik S, Southerland AM, Gamble D, Barrett KM, Ossi R, Arsava E, Rexrode K, Biffi A, Helenius J, Huq M, Labovitz D, Weissman D, Sheikh H, Rhodes D, Saraf N, Brenner D, Peddareddygari L, McArdle P, Rosand J, Woo D, Smoller S, Arnett D, Grewal R, Worrall B, Meschia J, Brown RD, Ay H, Kittner S. Stroke subtypes in Hispanic patients in the NINDS Stroke Genetics Network (SiGN): A comparison of two classification systems. International Stroke Conference, New Orleans, LA, February, 2012.

Gutierrez J, **Gardener H**, Bagci A, Marquez C, Rundek T, Elkind MSV, Alperin N, Sacco RL, Wright CB. A population-based study of arterial diameters in dolichoectasia: the Northern Manhattan Study. International Stroke Conference, New Orleans, LA, February, 2012.

Kuo F, **Gardener H**, Dong C, Cabral D, Della-Morte D, Santiago M, Elkind MSV Sacco RL, Blanton SH, Rundek T. Traditional cardiovascular risk factors explain only small proportion of the variation in carotid plaque. International Stroke Conference, New Orleans, LA, February, 2012.

Hudson BI, Liu-Mares W, Dong C, **Gardener H**, Elkind MS, Wright CB, Sacco RL, Rundek T. Association of soluble RAGE levels with carotid atherosclerotic plaque characteristics by high-resolution ultrasound. 35th Annual Meeting of the American Society of Neuroimaging, Miami, FL, January, 2012.

Wallace DM, Shafazand S, Ramos A, **Gardener H**, Carvalho DZ, Lorenzo D, Wohlgemuth WK. Actigraphic Characterization of Insomnia Complaints in Operation Enduring Freedom/Operation Iraqi Freedom Veterans. 25th Annual Meeting of the Associated Professional Societies of Sleep, Minneapolis, MN, June, 2011.

Wallace DM, Shafazand S, Ramos AR, **Gardener H**, Lorenzo D, Carvalho D, Wohlgemuth W. Insomnia Characterization in Operation Enduring Freedom/Operation Iraqi Freedom Veterans with Traumatic Brain Injury and Post-traumatic Stress Disorders. American Academy of Neurology Meeting, Honolulu, HI, April, 2011.

Nearing K, **Gardener H**, Bagci A, Alperin N, Elkind MSV, Sacco RL, Wright CB. Large Dilated Perivascular Spaces in a Stroke-free Community-based Sample: The Northern Manhattan Study. American Academy of Neurology Meeting, Honolulu, HI, April, 2011.

Gardener H, Rundek T, Wright C, Disla N, Elkind MSV, Sacco RL. Dietary Sodium Intake is a Risk Factor for Incident Ischemic Stroke: The Northern Manhattan Study (NOMAS). International Stroke Conference, Los Angeles, CA, February, 2011.

Gardener H, Rundek T, Wright C, Vieira J, Elkind MSV, Sacco RL. Soda Consumption and Risk of Vascular Events in the Northern Manhattan Study. International Stroke Conference, Los Angeles, CA, February, 2011.

Gutierrez J, **Gardener H**, Bagci A, Rundek T, Elkind M, Alperin N, Sacco R, Wright W. Dolichoectasia and Other Intracranial Vessel Characteristics in the Northern Manhattan Study. International Stroke Conference, Los Angeles, CA, February, 2011.

Markert M**,** Cabral D, **Gardener H**, Roberts EL, Dong C, Elkind MSV, Sacco RL, Rundek TR.

Ethnic Differences in Carotid Artery Diameter and Stiffness: The Northern Manhattan Study, National Meeting of the American Neurological Association, San Francisco, CA, October, 2010.

Anderson LM, Mensah G, Moran A, Connor M, Sacco R, **Gardener H**, Truelsen T, Feigin V. A Systematic Review of Published Literature on Stroke Epidemiology in Sub-Saharan Africa for the Global Burden of Diseases, Injuries, and Risk Factors Study. World Congress of Cardiology, Beijing, China, June, 2010.

Anderson LM, Mensah G, Ezzati M, Moran A, Connor M, Sacco R, **Gardener H**, Truelsen T, Feigin V. Stroke in the Global Burned of Disease Study (1995-2005): Current Methodological Approach and Challenges in Finding Reliable and Representative Data. World Congress of Cardiology, Beijing, China, June, 2010.

Gardener H, Scarmeas N, Gu Y, Disla N, Elkind MSV, Sacco RL, Boden-Abala B, Wright C. Mediterranean Diet and Vascular Events. American Neurological Association Meeting, Baltimore, October, 2009.

Della-Morte D, Beecham A, McClendon MS, **Gardener H**, Blanton SH, Sacco RL, Rundek T. Association between Polymorphisms in Coagulation System Genes and Carotid Plaque. 13th Congress of the European Federation of Neurological Societies, Florence, Italy, September, 2009.

Yanuck DM, Beecham A, **Gardener H**, Slifer S, Blanton SH, Wang L, Sacco RL, Rundek T. Gender-specific Associations between Lipid Related Candidate Genes and Carotid Plaque. University of Miami Women's Health Research Day, Miami, May, 2009.

Yanuck, DM, Beecham A, **Gardener H**, Slifer S, Wang L, Blanton S, Sacco RL, Juo SH, Rundek T. Single Nucleotide Polymorphisms that Influence Lipid Metabolism and Carotid Plaque. American Academy of Neurology Meeting, Seattle, April, 2009.

Marcus J, **Gardener H**, Yoshita M, Guzman J, Elkind MSV, Sacco R, DeCarli C, Wright C. Diastolic and not Systolic Blood Pressure is Associated with Subclinical Cerebrovascular Damage: The Northern Manhattan Study. American Academy of Neurology Meeting, Seattle, April, 2009.

Gardener H, Denaro F, Slifer S, Wang L, Blanton S, Sacco RL, Juo SH, Rundek T. Candidate Genes and Carotid Plaque in Hispanics from Northern Manhattan. International Stroke Conference, San Diego, February, 2009.

Sacco RL, Blanton S, Slifer S, Glover K, **Gardener H**, Wang L, Juo H, Sabala E, Rundek T. Linkage of Carotid Intima-Media Thickness (IMT) to Chromosomes 7p and 14q in Family Study of Stroke Risk and Carotid Atherosclerosis. International Stroke Conference, San Diego, February, 2009.

Rundek T, **Gardener H**, Slifer S, Glover K, Cabral D, Denaro F, Della Morte D, Sabala E, Koch S, Blanton S, Sacco R. Genetic Contribution to Carotid Artery Wall Structure and Function: The Northern Manhattan Study. World Stroke Conference, Vienna, Austria, September, 2008.

Gardener H, Cabral D, Denaro F, Elkind MSV, Sacco RL, Rundek T. Lipids and Carotid Plaque in the Northern Manhattan Study. European Stroke Conference, Nice, France, May, 2008.

Yavegal D, **Gardener H**, Newsom S, Drazin D, Rundek T. Medication Use and Prevention of

Ipsilateral Stroke with ICA Occlusion. European Stroke Conference, Nice, France, May, 2008.

Gardener H, Munger KL, Chitnis T, Michels KB, Spiegelman D, Alberto A. Prenatal and Perinatal Factors and Risk of Multiple Sclerosis. American Academy of Neurology Meeting, Chicago, IL, April, 2008.

Gardener H, Gao X, Chen H, Schwarzschild M, Spiegelman D, Alberto A. Prenatal and Early Life Factors and Risk of Parkinson's Disease. American Academy of Neurology Meeting, Chicago, IL, April, 2008.

Gardener H, Cabral D, Denaro F, Elkind MSV, Sacco RL, Rundek T. Lipids and Carotid Plaque in the Northern Manhattan Study. University of Miami Cardiovascular Research Symposium, Miami, March, 2008.

Gardener H, Sacco RL, Juo SH, Rundek T. Segment-specific Genetic Effects on Carotid Intima-media Thickness (IMT): The Northern Manhattan Study. University of Miami Cardiovascular Research Symposium, Miami, March, 2008.

PROFESSIONAL

Professional Affiliations:
American Academy of Neurology - Member 2008
Society of Epidemiologic Research – Member 2007-2008

Honors and Awards:

Certificate of Distinction in recognition of outstanding accomplishments and contributions in teaching: Harvard School of Public Health, Department of Epidemiology, 2006-2007

National Research Service Award grant from the Training Program in Psychiatric Epidemiology and Biostatistics (T32 MH17119): 2004-2006

Presidential Scholar: Department of Psychological and Brain Sciences, Dartmouth College, 1998-2000

First Place Benner Award for Excellence in Research: Dartmouth College, 2000

Phi Beta Kappa: Dartmouth College, 2000

Psi Chi National Psychology Honor Society, Golden Key National Honor Society: Dartmouth College, 2000

Rockefeller Public Service Grant, Richter Memorial Thesis Grant, Senior Scholars Thesis Grant: Dartmouth College, 1998-2000

Reviewer (ad hoc):
Nature Reviews
JAMA
Pediatrics
Journal of Epidemiology and Community Health
Annals of Neurology

Cerebrovascular Diseases
European Journal of Neurology
Neurology
Journal of Internal Medicine
Archives of Internal Medicine
Stroke
Circulation
Paediatric and Perinatal Epidemiology
Parkinsonism and Related Disorders
Journal of Neurology and Neurophysiology
BMC Cardiovascular Disorders
Medical Science Monitor
Canadian Medical Association Journal
Stroke Research and Treatment
Journal of Autism and Developmental Disorders
Annals of Medicine
PLoS ONE
British Journal of Nutrition
Journal of Stroke and Cerebrovascular Diseases
Stroke and Vascular Neurology
The Journal of Nutrition
Molecular Autism
Diabetes, Obesity, and Metabolism
International Journal of Epidemiology
Journal of Alzheimer's Disease
Environmental Research
Chemosphere
Toxicology Reports

TEACHING

2005-2006	Teaching Assistant, Department of Epidemiology, Harvard School of Public Health: Principles of Epidemiology Introduction to Epidemiology Elements of Epidemiologic Research Study Design in Epidemiologic Research Analysis of Case-Control and Cohort Studies
2021 Guest Lectures	"Study Design in Epidemiology" for a Neuroscience pathway course for medical students at the University of Miami Medical School "Overview of Epidemiology Concepts" for the NIH T35 sponsored summer school of research for medical students at the University of Miami Medical School