SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES

NC, a minor, Plaintiff, v. HAIN CELESTIAL GROUP, INC; BEECH-NUT NUTRITION COMPANY; NURTURE, INC.; PLUM, PBC, dba PLUM ORGANICS; GERBER PRODUCTS COMPANY; WALMART, INC.; SPROUT FOODS, INC.; RALPHS GROCERY COMPANY; AND DOES 1 THROUGH 100, INCLUSIVE, Defendants.	Case No.: 21STCV22822 ORDER DENYING DEFENDANTS' MOTION IN LIMINE TO EXCLUDE PLAINTIFF'S EXPERT TESTIMONY ON GENERAL CAUSATION Hearing Dates: January 31, February 1-4 (Plaintiff's experts); March 14 (Defendants' expert); April 4, 2022 (closing arguments) Dept.: 7

This is a complex litigation matter requiring exceptional judicial case management in accordance with California Rules of Court 3.400 et seq. The minor plaintiff in this action has been diagnosed with autism-spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). He alleges that his consumption of heavy metals (lead, arsenic, and/or mercury) contained in baby foods manufactured by the defendants caused his disorders. Defendants deny that their food products contain harmful levels of heavy metals or caused Plaintiff to suffer any harm. From Defendants point of view, consumption of baby food could not have caused Plaintiff's

ASD because ASD is a genetic disorder that develops prior to birth or in the weeks immediately following birth.

To prevail at his jury trial, Plaintiff must present expert testimony establishing general and specific causation. Under *Sargon Enterprises, Inc. v. University of Southern California* (2012) 55 Cal.4th 747, 771-772 (*Sargon*), the court has a "substantial gatekeeping responsibility" to ensure that the expert causation opinions presented to the jury are not "based on a leap of logic or conjecture." At the Court's suggestion and before the parties embarked on the expensive process of discovery, the parties agreed to seek an early ruling on the question whether Plaintiff's experts' opinions that heavy metals are capable of causing ASD and/or ADHD are admissible under *Sargon*. To that end, Plaintiff retained four experts who presented written opinions, answered questions in deposition and testified in Evidence Code section 402 hearings:[1] Drs. Beate Ritz and Hannah Gardener, both epidemiologists; Dr. Michael Aschner, a neurotoxicologist; and Dr. Kevin Shapiro, a pediatric neurologist. Defendants likewise retained an expert epidemiologist, Dr. Eric Fombonne, who submitted a report, submitted to deposition and testified in a section 402 hearing.

Defendants now move, in limine, to exclude Plaintiff's expert witness testimony based on four analytical gaps identified by their expert, Dr. Fombonne. Based on the briefing, argument and evidence, the Court concludes that Plaintiff's expert opinions that lead, arsenic and/or mercury are capable of being a substantial factor causing ASD disorder and ADHD are not inadmissible under *Sargon*.

I. Allegations

Now seven years old, Plaintiff NC ate baby food contaminated with lead, mercury, and arsenic (hereafter, "heavy metals"), causing him to develop ASD — diagnosed in 2016, when he was age two years, nine months — and ADHD, diagnosed in 2020, when he was six. (First

[1] Evidence Code section 402, subdivision (b) permits the court to "hear and determine the question of the admissibility of evidence out of the presence of the jury…."

Amended Complaint (Sept. 7, 2021) ¶¶ 1, 55-78.)[2] On various theories of strict liability and negligence, he brings eight claims against Defendants as the manufacturers, distributors, and retailers of the baby food. (*Id.* at ¶¶ 82-206.)

II. Standards

A. Legal Standard: Admissibility of Expert Testimony

If "the complexity of the causation issue is beyond common experience, expert testimony is required to establish causation." (*Webster v. Claremont Yoga* (2018) 26 Cal.App.5th 284, 290.) In this case, the issues of general causation — whether heavy metals can contribute to ASD and ADHD, and specific causation — whether heavy metals were a "substantial factor" in causing Plaintiff's ASD and ADHD — are issues beyond common experience. (See *Johnson & Johnson Talcum Power Cases* (2019) 37 Cal.App.5th 292, 302 (*Johnson & Johnson*).) Expert testimony is required.[3] There are two aspects to proof of causation of harm. Plaintiffs must establish "general causation" by presenting expert scientific opinion that the allegedly toxic substances are capable of causing the harm that the plaintiff suffered. Plaintiffs must also prove "specific causation" by presenting expert testimony that, to reasonable degree of medical certainty, the plaintiff's harm was caused by his or her exposure. *Cottle v. Superior Court* (1992) 3 Cal.App.4th 1367, 1385; *Hendrickson v. ConocoPhillips Co*. (2009) 605 F. Supp. 2d 1142, 1155.

A court has an obligation to "keep unfounded [expert] opinions from the jury." (*People v. Azcona* (2020) 58 Cal.App.5th 504, 513.) "[U]nder Evidence Code sections 801, subdivision (b), and 802, the trial court acts as a gatekeeper to exclude expert opinion testimony that is (1) based

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[2] Plaintiff also alleges the baby food exposed him to cadmium, but his experts' opinions do not address this metal. (FAC, ¶ 1.)

[3] This Order only addresses Plaintiff's experts on general causation, that is, the issue of whether heavy metals can cause ASD and ADHD. As the term implies, general causation is mostly abstracted from specific causation and the specific allegations of this case. This Order does not consider, for example, the dosages of heavy metals to which Plaintiff was allegedly exposed, the time frame when he was allegedly exposed, or whether heavy metals were a substantial factor in causing his disorders.

on matter of a type on which an expert may not reasonably rely, (2) based on reasons unsupported by the material on which the expert relies, or (3) speculative." (*Sargon, supra,* 55 Cal.4th at pp. 771-772, page number omitted.) "This means that a court may inquire into, not only the type of material on which an expert relies, but also whether that material actually supports the expert's reasoning. 'A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.'" (*Id.* at p. 771.)

However, a court excludes expert opinion cautiously, keeping from the jury only "clearly invalid and unreliable" opinion that "fails to meet the minimum qualifications for admission." (*Sargon, supra,* 55 Cal.4th at p. 772; *Davis v. Honeywell Internat. Inc.* (2016) 245 Cal.App.4th 477, 492 (*Davis*).) A court does not "choose[] between competing expert opinions … weigh an opinion's probative value … [or] resolve scientific controversies." (*Sargon,* at p. 772.) It instead "conducts a 'circumscribed inquiry' to 'determine whether, as a matter of logic, the studies and other information cited by experts adequately support the conclusion that the expert's general theory or technique is valid' — ensuring, in short, "that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." (*Ibid*.) "If the opinion is based on materials on which the expert may reasonably rely in forming the opinion, and flows in a reasoned chain of logic from those materials rather than from speculation or conjecture, the opinion may pass, even though the trial court or other experts disagree with its conclusion or the methods and materials used to reach it." (*Davis*, at p. 429 [citing *Sargon,* at pp. 771-772].)

B. Scientific Standard: Inferring Causation from Epidemiological Data

Epidemiology is the study of the "incidence, distribution, and etiology" of human disease. (Green et al., Reference Manual on Scientific Evidence (3d ed.) Reference Guide on Epidemiology, p. 551 ("Reference Manual").)[4] Based on the assumption that disease is not

[4] California courts cite the Reference Manual on Scientific Evidence to evaluate scientific evidence. (See *Duran v. U.S. Bank National Assn.* (2014) 59 Cal.4th 1, 38; *Johnson & Johnson, supra,* 37 Cal.App.5th 292 at p. 303, fn. 4.)

distributed randomly in a population, an epidemiological study "identifies agents that are associated with an increased risk of disease in groups of individuals, quantifies the amount of excess disease that is associated with an agent, and provides a profile of the type of individual who is likely to contract a disease after being exposed to an agent." (*Id.* at pp. 551-552.) Just because an agent and a disease are associated, however, does not necessarily mean the agent causes the disease. (*Ibid.*) To assess whether an association is causal, a scientist must understand the strengths and weaknesses of a study's design and implementation and judge how the study findings fit with other scientific knowledge. (*Id.* at p. 553.) "[E]pidemiology cannot prove causation; rather causation is a judgment for epidemiologists and others interpreting the epidemiologic data." (*Id.* at p. 598.)

The two main types of human epidemiologic studies are experimental and observational. An experimental study divides test subjects into one of two groups, exposes one group to an agent, and observes the results compared to the other, unexposed group. (Reference Manual, p. 555.) Because experimental human studies allowing exposure to potentially toxic agents are unethical, epidemiologists typically rely on observational studies. Researchers observe a group that was exposed to an agent — a group of cigarette smokers, for example — and compare them to a group that was not exposed to the agent. (*Id.* at pp. 555-556.) Observational studies can be of several different designs, but the two main designs are a) cohort studies and b) case-control studies. (*Id.* at p. 556.) If a study observes a disease is associated with an agent, researchers first consider alternative explanations for the association, particularly a) the possibility it was observed by chance or b) it resulted from bias in the study's methodology, or c) it was observed not because the agent caused the disease, but because both the disease and the agent were jointly caused by a third confounding factor. (*Id.* at pp. 572, 598.)

After considering alternative explanations for the agent-disease association, epidemiologists assess whether the association is causal using the nine Bradford Hill factors:

(1) Temporal relationship: Exposure to an agent must occur before a disease develops — "[w]ithout exposure before the disease, causation cannot exist."

(2) Strength of the association: Relative risk, "one of the cornerstones for causal inferences," measures how often a disease is observed in people exposed to an agent relative to how often the disease is observed in people not exposed to the agent.

(3) Dose-response relationship: A dose-response relationship exists if the greater the exposure to an agent, the greater the risk of disease. Higher exposures generally, but not always, increase the incidence or severity of a disease. A dose-response relationship is therefore "strong, but not essential" evidence of a causal relationship.

(4) Replication of the findings: As in many areas of science, a causal relationship is more likely if a study's findings can be replicated, especially in different conditions or populations. "Rarely, if ever, does a single study persuasively demonstrate a cause-effect relationship."

(5) Biological plausibility (coherence with existing knowledge): Given what is known about the biological "mechanisms by which the disease develops," can the agent plausibly cause the disease? If it is biologically plausible that an agent causes a disease, then it "lends credence to an inference of causality."

(6) Consideration of alternative explanations: As discussed above, a researcher should consider whether an observed association resulted from chance, bias, or confounding.

(7) Cessation of exposure: If an agent causes a disease, then risk of the disease should decrease when exposure to the agent stops. Often data is not available showing the effects of ending an exposure, but if the data is available and it shows a reduction in the incidence of disease, then it "strongly" supports a causal relationship.

(8) Specificity of the association: "An association exhibits specificity if the exposure is associated only with a single disease or type of disease." "[E]vidence of specificity may strengthen the case for causation, [but] lack of specificity does not necessarily undermine it where there is a good biological explanation for its absence."

(9) Consistency with other knowledge: For example, data showed that as cigarette sales in the United States increased, so did men's rate of death from lung cancer. This other knowledge was consistent with a causal relationship between smoking and lung cancer.

(Reference Manual, pp. 597-607.) These factors are not a rigid formula. "One or more factors may be absent even when a true causal relationship exists. Similarly, the existence of some factors does not ensure that a causal relationship exists. Drawing causal inferences after finding an association and considering these factors requires judgment and searching analysis, based on biology, of why a factor or factors may be absent despite a causal relationship, and vice versa." (*Id.* at p. 600, footnote omitted.)

Both sides in this case and courts agree: a Bradford Hill analysis is an accepted epidemiological method to infer causation from data that shows an association between an exposure and a disease. Defendants contend, however, that Plaintiff's experts' Bradford Hill analysis was flawed under *Sargon*.

III. The Experts

Two of Plaintiff's four experts, Drs. Ritz and Gardener, are epidemiologists who conducted a Bradford Hill analysis. The other two experts are Dr. Aschner, a neurotoxicologist, and Dr. Shapiro, a pediatric neurologist, both of whom opine on one Bradford Hill factor, biological plausibility. Defendants proffered their own expert, Dr. Eric Fombonne, who identified four "analytical gaps" in Plaintiff's experts' methodology.

This section summarizes the experts' credentials (which are not at issue on this motion), opinions, and methodology.

A. General Causation Experts

1. Dr. Ritz, Epidemiologist

Dr. Beate Ritz is Professor of Epidemiology at the UCLA Fielding School of Public Health and holds co-appointments in the Environmental Health Sciences and Neurology at the UCLA School of Medicine. (Esfandiary Decl., ¶ 23, Exh. 22, p. 3 ("Ritz Report").) She holds an M.D. (1984) and a doctoral degree in Medical Sociology (1986) from the University of Hamburg, and a doctoral degree in Epidemiology (1995) from UCLA. (*Ibid.*) She primarily researches the health effects of occupational and environmental exposures, focusing on the effects of pesticides and air pollution on chronic diseases including neurodevelopmental disorders and diseases. (*Ibid.*)

She opines that exposure to mercury, arsenic, and lead during sensitive developmental periods in early childhood can cause ASD, and lead exposure can cause ASD at relatively low concentrations; and exposure to lead during sensitive developmental periods in early childhood can cause ADHD, even at low levels of exposure. (Ritz Report, pp. 4-5.)[5] Her opinion is based on peer-reviewed studies on the relationship between exposure to heavy metals and ASD, and lead and ADHD. To reach her opinion, she applied the Bradford Hill factors to the studies' findings. (*Id.* at pp. 12-15, 22-49.)

2. Dr. Gardener, Epidemiologist

Dr. Hannah Gardener has been an epidemiologist at the University of Miami Miller School of Medicine for over 14 years. (Esfandiary Decl., Exh. 20, p. 3 ("Gardener Report").) She holds a Doctorate in Epidemiology and a minor in Biostatistics (2007) from the Harvard School of Public Health. (*Ibid.*) Her research focuses on diet and other environmental causes of neurological diseases; she has published over 100 peer-reviewed manuscripts. (*Ibid.*) She has studied heavy metals in consumer products since 2015, and is currently studying heavy metals in prenatal vitamins, CBD, and pet food. (*Ibid.*) Her areas of expertise include risk factors for neurological outcomes, environmental health, and epidemiological methods. (*Id.* at pp. 3-4.) She currently co-teaches a course on epidemiological methods and biostatistics. (*Ibid.*)

[5] All of Plaintiff's experts state their opinions "to a reasonable degree of scientific certainty," but since this statement is a legal conclusion, the Court omits it from the summary.

She opines that lead, arsenic, and methylmercury accumulation in the body can cause the development of ASD, and lead accumulation in the body can also cause the development of ADHD. (Gardener Report, 4-5.) Like Dr. Ritz, she based her opinion on peer-reviewed studies, and reached her opinion by applying the Bradford Hill factors to the studies' findings. (*Ibid.*)

B. Biological Plausibility Experts

1. Dr. Aschner, Neurotoxicologist

Dr. Michael Aschner holds multiple titles at the Albert Einstein College of Medicine in The Bronx, New York, including Professor of Molecular Pharmacology, Professor of Neuroscience, Professor of Pediatrics, Investigator at the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center, and Member of the Nathan Shock Center of Excellence in the Basic Biology of Aging. (Esfandiary Decl., Exh. 5, p. 4 ("Aschner Report").) He holds a Ph.D. in Anatomy and Neurobiology (1985) from the University of Rochester, School of Medicine and Dentistry in Rochester, New York, where he researched the potential neurotoxic effects of methylmercury. (*Ibid*.) Among his many credentials, he is a European Registered Toxicologist, a Fellow of the American Academy for the Advancement of Science, Chair of the External Advisory Board of the National Center for Toxicological Research (a center of the United States FDA), and past president of both the International Neurotoxicology Association and the International Society for Trace Element Research in Humans. (*Id.* at p. 5-7.) He has authored over 800 peer-reviewed articles, 100 book chapters, and hundreds of abstracts, and estimates his work has been cited nearly 49,000 times. (*Id.* at pp. 7-8.) As a neurotoxicologist, he specializes in assessing the adverse effect of pharmaceuticals, non-therapeutic chemicals, and other potential toxins on humans, with an emphasis on neurological outcomes, and his research interest is the interaction between genetic and environmental triggers of brain diseases. (*Id.* at p. 5.) He has experience interpreting epidemiological studies and modeling in vivo and in vitro blood-brain barrier and mechanisms of neurodegeneration. (*Ibid.*)

He opines there are "well-established" mechanisms by which lead, arsenic, and mercury can pass through the blood-brain barrier and cause "significant and permanent" disruption to the brain's neuropathways. (Aschner Report, p. 9.) He further opines that lead, arsenic, and mercury exposure can cause ASD in children, and lead exposure can cause ADHD in children, via "biologically plausible" mechanisms. (*Ibid.*) Lastly, exposure to mixtures of lead, arsenic, and mercury "will lead to the additive and synergistic effects of the[] metals, given that they share common toxicological modes-of-action." (*Ibid.*) His conclusions are "supported by a wealth of epidemiological data" and the metals' toxicological profiles. (*Ibid.*)

Dr. Aschner did not conduct a Bradford Hill analysis, as he is not an epidemiologist. (Aschner Report, p. 12.) Instead, based on his 35-plus years of professional experience studying heavy-metal neurotoxicity, he reviewed the scientific literature on risk of contracting a disease at any given dose and considered whether the toxicological evidence supports finding biological plausibility. (*Id.* at p. 12-13.)

2. Dr. Shapiro, Pediatric Neurologist

Dr. Kevin Shapiro is Medical Director and Clinical Executive for Research and Therapeutic Technologies at Cortica Healthcare, an organization that provides "comprehensive assessment and therapeutic services for children with autism and other neurodevelopmental disorders." (Esfandiary Decl., Exh. 1, p. 3 ("Shapiro Report").) He is also on the neurology staff at Children's Hospital Los Angeles and is an affiliate staff member at Rady Children's Hospital in San Diego. (*Ibid.*) He holds an M.D. from Harvard Medical School (2008) and a Ph.D. in psychology from Harvard University (2008). (*Ibid.*) He divides his work at Cortica Healthcare between clinical care — evaluating, treating, and following-up with children who have neurodevelopmental conditions including ASD and ADHD — and research into the "efficacy of novel treatment paradigms" for symptoms of ASD and ADHD. (*Id.* at p. 4.)

While ASD has a genetic component, he opines that genetic factors alone cannot explain the varied presentation and severity of ASD behaviors. (Shapiro Report, p. 5.) "Epigenetic mechanisms, environmental risk factors, and gene-environment interactions also contribute to the

emergence of [ASD] symptoms." (*Ibid.*) Known environmental risk factors for ASD include "exogenous agents that affect brain function" by altering cellular signaling and neurotransmitter release and by increasing oxidative stress and inflammation, all of which can occur following exposure to heavy metals in utero or within the first two years of life. (*Ibid.*) The mechanisms by which heavy metals affect neuronal function and development in vivo and in vitro overlap "to a significant degree" with the biological pathways that are implicated in ASD pathogenesis. (*Id.* at p. 6.)

He reached his opinions "using the methods, procedures, and techniques typically used by experts" in his field, relying on his ten-plus years of clinical experience diagnosing and treating ASD, his clinical research into the biological pathogenesis of ASD, and his clinical and research experience on how neurological injuries might produce core ASD symptoms. (Shapiro Report, p. 6.) He also reviewed the "extensive" literature on ASD — its etiology, biological mechanisms, and risk factors — focusing on whether the neurological effect of exposure to lead, mercury, and arsenic is clinically relevant to the pathogenesis of ASD. (*Ibid.*)

C. Defendants' Expert

Dr. Eric Fombonne is a Professor in the Department of Psychology and the Director of the Autism Research Institute on Development and Disability and the Child Development and Rehabilitation Center at Oregon Health and Safety University. (Mojibi Decl., ¶ 6, Exh. 5, p. 3 ("Fombonne Report").) As a researcher, he has conducted epidemiological surveys; as a clinician, diagnosed and treated children with ASD and ADHD; and as a teacher, lectured and trained clinicians on the treatment, diagnosis, and causes of ASD, and trained researchers on how to conduct epidemiological studies on autism. (*Id.* at pp. 3-6.) He belongs to several professional associations, including the International Society for Autism Research and the Scientific Committee of the Association for Research on Autism and Infantile Psychosis; has published over 350 peer-reviewed articles; and regularly reviews research articles on autism for publication. (*Ibid.*)

He testified Plaintiffs' experts' opinions contain the following four "analytical gaps" or leaps of logic. They:

(1) speculated that the temporality factor was satisfied by studies that could "not establish[]" temporality;

(2) relied on scores from questionnaires as outcomes, rather than formal ASD diagnoses,

(3) reached their conclusions "in the face of a body of evidence that finds no consistent association between heavy metal exposure and ASD," and

(4) failed to consider "what is known about ASD."

As Dr. Fombonne put it, "Plaintiff's expert[s] did not follow a methodology [that] is rigorous enough and would be accepted in admitting the standards of the epidemiological community." (Defendants' Closing Arguments, *Sargon* Hearing (Apr. 4, 2022) Slide No. 5 [citing Mar. 14, 2022 Hearing Transcript at p. 15].)

IV. Analysis

The first part of the Court's analysis addresses the four analytical gaps identified by Defendants' expert and the second part addresses arguments presented in Defendants' moving papers.

A. Dr. Fombonne's "Analytical Gaps"

The Court first considers the four "analytical gaps" Dr. Fombonne identified in Plaintiffs' experts' methodology: (1) speculative conclusions resting on studies that lack temporality, (2) improper reliance on behavioral questionnaires, (3) lack of consistent association, and (4) failure to account for what is known about ASD.

1. Temporality

According to Dr. Fombonne, few of the peer-reviewed studies underlying Dr. Ritz's and Gardener's opinions are "capable of establishing temporality," the Bradford Hill factor that considers whether the exposure preceded the disease. (Reference Manual, p. 601.) "Although temporal relationship is often listed as one of the many factors in assessing whether an inference

of causation is justified, this aspect of a temporal relationship is a necessary factor: Without exposure before the disease, causation cannot exist." (*Ibid.*)

Drs. Ritz and Gardener relied on several studies that measured the amounts of heavy metals present in human "biomarkers" such as blood, urine, hair, and nails. The problem, according to Dr. Fombonne, is that most of these studies relied on exposures that occurred too late in time. Because, in his opinion, ASD is a genetic disorder that develops before birth or in the first few months after birth, the relevant period of exposure is pre-natal. To illustrate his point, Fombonne cites, with approval, the Doherty et al. (2020) study measuring concentrations of metals in maternal and infant toenails. (Mojibi Decl., Exh. 17, p. 2.) The researchers in that study collected maternal toenails at 27 weeks of gestation and 4 weeks postpartum, and collected infant toenails at 6 weeks after birth.[6] According to the study's authors, maternal toenail metal concentrations "reflect exposures approximately 6-12 months before toenail collection," whereas infant toenails grow faster — though they admitted the literature on this issue is "sparse," infant toenails "collected at 6 weeks after birth likely represent exposures that occurred in late pregnancy and early neonatal life." (*Ibid.*) The measured effect was a child behavioral assessment called the Social Responsiveness Scale, 2nd edition, completed by the mothers when their children were three years old. (*Ibid.*) The Doherty study researchers therefore measured metal exposure before they measured the potential effect, which in Dr. Fombonne's opinion means the Doherty study "is capable of establishing" temporality, that is, capable of establishing the exposure preceded the disease. (Defendants' Direct Examination of Dr. Fombonne Slides (Mar. 14, 2022) Slide No. 19.)

On the other hand, Dr. Fombonne criticized the Filon et al. (2020) study which collected hair samples from two groups of children aged 2 to 8 years, one "case" group of children who had been diagnosed with ASD and a second "control" group of neurotypical children, that is, children who had not been diagnosed with a neurological disorder. (Esfandiary Decl., Exh. 36, p. 2.) The researchers then compared the metal concentrations in the two groups' hair samples finding a statistically significant association between lead and ASD. The problem, from Dr. Fombonne's

[6] These are median values. (p. 2.)

point of view, is that the researchers collected the biomarkers after the outcome (the diagnosis of ASD) without analyzing or addressing how long ago the exposures to lead actually occurred or could have occurred given the growth and replacement cycle of human hair. This procedure not only violated the cause-and-effect temporality requirement, it introduced the possibility of reverse causation, i.e., that the ASD may have caused the children's exposure to lead, and not vice versa. As an illustration, Dr. Fombonne gave suggested an explanation for the potential reverse causation: children afflicted with ASD can suffer PICA, a pathological craving for things that are not food, including things that contain lead.

Plaintiffs argue that their expert testimony has not "leaps of logic" and is not inadmissible under *Sargon* because Drs. Ritz and Gardener logically explained their analysis of the temporality factor. Dr. Ritz wrote that temporality is a "necessary element for inferring causality," and Dr. Gardener gave "careful consideration to the possibilities of reverse causality." (Ritz Report, p. 13; Gardener Report, p. 12.) Both acknowledged that establishing temporality can be a problem in case-control and cross-sectional studies. A "primary weakness" of these studies is "the timing of the assessment of exposure to heavy metals," wrote Dr. Gardener. (Gardener Report, p. 14.) Ideally "we would assess heavy metal exposure in very early life when there were no clear signs of ASD/ADHD" and then "follow children up until the time of diagnosis with repeated heavy metal assessments," but these studies, if they could be conducted accurately, would be "extremely expensive[,] time-consuming[,] and would require very large samples due to the rarity" of ASD and ADHD. (*Id.* at pp. 14-15.) She explained, however, that the "important" issues of temporality and reverse-causation can be addressed by considering prospective human data and experimental animal data (exposing an animal and then observing the outcome). (Gardener Report, p. 15.) If the prospective data is consistent with the retrospective and cross-sectional study data, then reverse causation is an "unlikely explanation" for the observed associations. (*Ibid.*) Some of the biomarkers, in her opinion, can show long-term heavy metal exposure, contrary to Dr. Fombonne's opinion that biomarkers can only show exposures in the few months preceding measurement. (*Ibid.*) And to her, PICA did "not appear" to explain the causal association between lead exposure and ASD or ADHD, citing one study that "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." (*Id.* at p. 15-16.)

Dr. Ritz also recognized the importance of temporality in reducing or eliminating the "potential of reverse causation i.e., it might be possible that the disease caused the exposure and not vice versa … [the] disease [may have] caused certain behaviors or psychological states that increased exposure levels among the cases" when the samples were collected. (Ritz Report, p. 12.) Echoing Dr. Gardener, she wrote that prospective data from studies of prenatal and early-life exposures can "refute the likelihood of reverse causation." (Ritz Report, p. 12.) For lead and ASD, for example, she cited, as capable of establishing temporality, the Kim et al. (2016), Arora et al. (2017), and Abdullah et al. (2012) studies, which assessed exposures early in a child's infancy by measuring lead levels in shed baby teeth; the Long et al. (2019) study, which measured lead levels in stored amniotic fluid; the Doherty (2020) study, which measured lead in maternal and infant toenails; and the Skogheim et. al. (2021) study, which measured lead in maternal blood at gestation week 17. (*Id.* at p. 23, 24, 26, 30.)

The Court concludes that even on Dr. Fombonne's terms, Drs. Ritz's and Gardener's opinions on temporality are sufficiently logical and non-speculative to pass through the *Sargon* gate. As illustrated below, Dr. Fombonne grouped the various studies by whether they can satisfy temporality or not — that is, whether the study documented evidence of heavy-metal exposure that occurred prior to any diagnosis of ASD or the observation of ASD-proxy behaviors. Plaintiff's experts' agreed with Fombonne's grouping of studies that satisfied temporality, pointing out that some of them observed a positive association between heavy metals and ASD or ASD-proxy behaviors; some returned mixed results; others found a null association; and some a negative association. Based on these studies, Dr. Ritz and Dr. Gardener's opinions are logical. And the extent to which causation can be inferred from these studies, in the Court's view, falls within the range of acceptable scientific disagreement.

As mentioned, Dr. Fombonne's temporality argument is largely an issue of study design. Prospective cohort studies, he explained, "verif[y]" temporality "by their very design." (Fombonne Report, ¶ 153.) Case-control or cross-sectional studies, however, generally assess

exposure when participants are included in the study, that is, "when participants were already diagnosed with autism…." (*Ibid.*)[7] He therefore divides case-control studies into two categories. First are studies that measure past exposure and "allow the temporality criterion to be met." (*Id.* at ¶ 154.) Examples are studies that measured metal concentrations in deciduous teeth, cord blood or archived blood spots, or amniotic fluid samples — all of which can be used to "estimate (past) exposure levels." (*Ibid.*) The second category of case-control studies evaluate exposures retroactively using, for example, "food frequency questionnaires" that "evaluate material diet during pregnancy" to "reconstruct metal exposure…." (*Ibid.*) Both categories of case-control studies, in Dr. Fombonne's opinion, can satisfy temporality "since exposure has necessarily *preceded* the disorder." (*Ibid.*) He calls them "Informative case-control studies." (*Ibid.*)

On the other hand, case-control studies that assess exposure "contemporaneously with study recruitment do not meet the temporality criterion" and are "inapt to evaluate causality." (Fombonne Report, ¶ 156.) These studies measured the concentrations of heavy metals in certain human biomarkers such as hair, blood, and urine, to approximate past exposures to the metals. But Dr. Fombonne rejects this method as "futile" because biomarkers only reflect exposures in the near-past — urine and blood, for example, reflect metal exposures in only the past few hours or days; hair, at most the past few months. (*Ibid.*) If researchers sampled the blood of a five-year-old child with ASD, the heavy metal concentrations would only reflect exposures in the past few months at most, likely after the child was diagnosed. (*Ibid.*) In his opinion, these studies are "uninformative case-control studies." (*Ibid.*)

Dr. Fombonne grouped by type the studies that support Drs. Ritz and Gardener's opinions: (a) cohort studies and informative case-control studies that can, in his opinion, establish temporality; (b) uninformative case-control and cross-section studies, which, in his opinion, cannot; and lastly (c) cross-sectional and ecological studies and meta-analyses and systemic

[7] For lead, arsenic, and mercury, both parties referenced charts that arrange the cited studies by their results. The five groups are: (1) statistically significant association; (2) positive but not statistically significant association; (3) null association; (4) negative but not statistically significant association; and (5) a negative and statistically significant association. (Plaintiff's Exhibits 139, 142, 143; Slide 14.)

reviews. For each of the three heavy metals, the following tables list only (a) the studies that Dr. Fombonne opines can satisfy temporality; their design, biomarkers measured, and findings; and excerpts from his comments about their methodology and findings. For comparison, the bottom of each table recounts Dr. Ritz's and Dr. Gardener's opinions on temporality.

LEAD & ASD:
Studies that, according to Dr. Fombonne, can satisfy temporality

Study (Fombonne Report citation)	**Design**[8]	**Biomarker** (time of measurement)	**Findings**[9] (Dr. Fombonne's description)	**Dr. Fombonne's Comments on Methodology and/or Findings**
Abdullah (2012) ¶¶ 197-200	Case-control	Primary teeth, shed ages 6-12	Null ("no difference")	[Quoting study authors:] "No significant differences … [findings] do not support an association…"
Adams (2007) ¶ 201	Case-control	Baby teeth	Positive, not SS	"Substantial methodological shortcomings … results [therefore] not relevant for evaluating prenatal or early post-natal exposures."
Alampi (2021) ¶¶ 193-196	Cohort	Maternal blood and urine, 1st trimester	Mixed: null, positive at higher SRS scores, but not SS)	"Suggestive findings about more appropriate methods to model the relationship between [heavy metal] concentrations and child outcomes … findings for lead … inconsistent…"
Arora (2017) ¶¶ 202-205	Case-control	Teeth; fetal and early postnatal	Positive, SS ("[L]ead levels generally higher … significant differences…")	"Severe limitations…"
Doherty (2020) ¶¶ 180-183	Cohort	3x mother and infant toenails (27th gestation; 4th week postpartum; 6th week life)	Null ("no significant main effect")	"[S]tudy is of generally high quality." Results are "negative."

[8] All cited cohort studies are prospective.

[9] Findings are taken from Plaintiff's Sargon Hearing Exhibits Nos. 139, 142, and 143, which both sides referenced, including Dr. Fombonne. (Defendants' Direct Examination of Dr. Fombonne Slides (Mar. 14, 2022) Slides Nos. 10-18.) For studies that were not included on Plaintiff's Exhibits (see *id.* at Slides Nos. 12, 15, 18), the Findings are based on how the studies' authors described their results. Descriptions of findings (in parentheses) are Dr. Fombonne's.

Frye (2020) ¶¶ 206-209	Case-control	Tooth matrix	Mixed: Null, positive but not SS ("correlations … not significant"	"[V]ery low quality … results should be disregarded altogether."
Kim (2016) ¶¶ 189-191	Cohort	Child's blood, 3x (ages 7-8, 9-10, 11-12)	Positive, SS	"Significant methodological weaknesses … basic design failure to address central question of links between lead exposure and [ASD]" … exposures measured after ASD development window… findings thus "noncontributory"
Long (2019) ¶¶ 210-212	Case-control	Amniotic fluid (conserved samples)	Mixed: positive, not SS; null	"No evidence for an increased risk of ASD in relation to mid-pregnancy exposures to lead…"
Skogheim (2021) ¶¶ 184-188	Cohort	Maternal blood, 17th week gestation	Mixed: positive, non-linear ("V-shaped relationship … protective effect for lead levels in the middle of the distribution…"	"This study has several strengths."
Dr. Ritz on temporality: "That disease occurred after exposure and that there is an expected delay between the cause and effect has also been reported, i.e., exposures were assessed and recorded for early infancy in baby teeth [Arora?] and the Korean child cohort study [Kim (2016)] and the Norwegian MoBa cohort [Skogheim (2021)]." (Ritz Report, p. 30.)				
Dr. Gardener on temporality: "In the nested case control study (MoBa) [Skogheim (2021)] and the cohort study (New Hampshire) [Doherty (2020)] disease occurred after exposure i.e. there is a delay between the cause and effect supporting causal inference." (Gardener Report, p. 35.)				

MERCURY & ASD:
Studies that, according to Dr. Fombonne, can satisfy temporality

Study (Fombonne Report citation)	**Design**	**Biomarker** (time of measurement)	**Findings** (Dr. Fombonne's description)	**Dr. Fombonne's Comments on Methodology and/or Findings**
Abdullah (2012) ¶¶ 323-325	Case-control	Baby teeth (shed ages 6-12)	Negative, not SS ("no difference")	[Quoting study authors:] "No significant differences … [findings] do not support an association…"
Adams (2007) ¶ 326	Case-control	Baby teeth	Positive, SS ("Mercury levels … were significantly raised in children with autism…")	"[R]esults of this study are unreliable."

Alampi (2021) ¶¶ 320-322	Cohort	Maternal blood and urine (1st trimester)	Mixed: inverted-U distribution, not SS ("unremarkable … no association with elevated SRS scores…"	"[S]tudy had limitations that make it not contributory."
Faroe Islands Study – Grandjean (1997, 1999, 2014) ¶¶ 292-294	Cohort	Cord blood, maternal hair (prenatal); child hair, 2x (1, 7 years); child blood (7 years)	Positive, SS (1999 findings); Positive (2014)	Cohort was "intensively scrutinized, tested and clinically examined. The absence of reporting of autism diagnoses or of increases in such a diagnosis is of interest. Furthermore, it should be noted that an epidemiological survey of autism in the population of the Faroe Islands was performed in 2002 in the local population of children aged 8 to 17. There was no evidence that the prevalence of autism was higher in this mercury exposed population compared to other populations (Ellefsen et al., 2007)."
Geier (2009) ¶¶ 371-373	Cross-sectional	Number of maternal dental amalgams, self-reported and unverified	Positive, SS	"The authors found a significant association between risk of autism and having 6 or more dental amalgams opposed to having 5 of fewer … [but] [t]his study is flawed in key aspects" and "cannot be relied upon for any information."
Golding (2018) ¶¶ 311-315	Cohort	Maternal blood (gestation weeks 9-13); proxy measurement (questionnaire and dental records during pregnancy)	Null	Some strengths (successful recruitment, measurement early in pregnancy, cofounder adjustment); some limitations (no later measurements, few formal diagnoses). Findings "provide no support for an association between mercury exposure and autism."
Long (2019) ¶¶ 331-333	Case-control	Amniotic fluid (conserved samples)	Null (mercury not detected in samples)	"No evidence for an increased risk of ASD in relation to mid-pregnancy exposures to mercury…"
McKean (2015) ¶¶ 327-330	Case-control	Complex modeling of newborn blood spots combined with food-frequency questionnaires	Null: "After adjusting for potential confounding, we found no association between cumulative MeHg exposure and the risk of autism … or developmental delay"	"This is a well-designed and executed study that provides no support for the hypothesis of an association between mercury exposure and autism risk."
Ryu (2017) ¶¶ 316-319	Cohort	Maternal blood, 2x	Positive, SS	"[S]ignificant increase in SRS scores for every doubling of the total mercury blood

		(early gestation, late pregnancy); child blood, 2x (birth, ages 2-3)		level … [and] a significant increase … in the probability of scoring high on the SRS" … study's "longitudinal prospective design" is a strength, though it also has "several limitations … [and] does not provide evidence of an association between mercury exposure and autism."
Skogheim (2021) ¶¶ 307-310	Cohort	Maternal blood, 17th week gestation	Null ("no significant association")	"This study has several strengths."
van Wijngaarden (2013) ¶¶ 295-300)	Cohort	Maternal hair (at child's birth)	Null: "No consistent association…"	"No significant association … strengths of this study lie in its prospective design, its population-based sampling, and its large sample size."
Yau (2014) ¶¶ 301-209	Case-control nested in cohort	Maternal serum (mid pregnancy); neonatal blood (1-2 days post-birth)	Mixed (positive, SS; null when adjusted)	"[W]ell-designed" … identifies several confounders "that ought to be controlled for in all investigations" … findings show autism risk is not raised by "exposure levels that slightly exceed [EPA's] recommended thresholds for mercury"
Dr. Ritz on temporality: "This criterion is met by the Korean child cohort study [Kim (2016)] and also the Faroese study [Grandjean (1997, 1999, 2014)] but the later assessed general psychomotor development." (Ritz Report, p. 42.)				
Dr. Gardener on 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." (Gardener Report, p. 45.)				

ARSENIC & ASD:
Studies that, according to Dr. Fombonne, can satisfy temporality

Study (Fombonne Report citation)	**Design**	**Biomarker** (time of measurement)	**Findings** (Dr. Fombonne's description)	**Dr. Fombonne's Comments on Methodology and/or Findings**
Alampi (2021) ¶¶ 407-409	Cohort	Maternal blood and urine (1st trimester)	Mixed: somewhat linear relationship, from negative to positive, not SS	"[S]tudy had limitations that make it not contributory."
Doherty (2020) ¶¶ 399-402	Cohort	3x mother and infant toenails (27th week gestation; 4th week postpartum; 6th week life)	Positive, SS	"[S]tudy is of generally high quality" … Positive associations observed, but were "attenuated" after "imputation of missing covariate data…" "[N]o support for an

				increase in the risk of autism following arsenic exposure…."
Long (2019) ¶¶ 410-412	Case-control	Amniotic fluid (conserved samples)	Positive, not SS	"No evidence for an increased risk of ASD in relation to mid-pregnancy exposures" to arsenic
Skogheim (2021) ¶¶ 403-406	Cohort	Maternal blood (gestation week 17)	Mixed: positive, SS in 2nd quartile	"This study has several strengths … [but] provides no evidence that arsenic exposure increases the risk of ASD."
Dr. Ritz on temporality: "In the nested case control study (MoBa) [Skogheim (2021)] and the cohort study (New Hampshire) [Doherty (2020)] disease occurred after exposure i.e. there is a delay between the cause and effect supporting causal inference." (Ritz Report, p. 35.)				
Dr. Gardener on 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." (Gardener Report, p. 34.)				

These tables illustrate a few points. First, the room for professional judgment and scientific disagreement increases from left to right. On the left are hard facts: the year a study was published (column one), its design (column two), and the biomarker it measured (column three). Study results (column four), too, are published as data, but here some professional judgment creeps in: data can be presented in different ways, and statistical assessments of the data require judgment. Two measurements of statistical significance are the p-value — the probability of observing an association as least as large as the association actually observed, assuming there is, in fact, no association between the toxin and the disease — and the confidence interval, a range of results that would be observed x% of the time if the study was repeated multiple times drawing samples from the same population. (Reference Manual, pp. 574-583.) Some courts have established baselines for these measures by referring to baselines conventionally used in science,[10] and excluded testimony based on studies that do not meet the baseline. However, among epidemiologists and biostatisticians, "[t]here is some controversy … about the appropriate role of significance testing."

Commented [A1]: Should we cite a case as an example here?

[10] Conventional p-values are <0.05, meaning there is less than a 5% chance of observing the same association assuming there is, in fact, no true association, and a 95% confidence interval, meaning a range of values that encompasses the results that would be expected 95% of time in samples repeatedly drawn from the same population. (Reference Manual, pp. 577-578.)

(*Id.* at pp. 578-579.) Some scientists reject as inadequate studies whose p-value is not less than a chosen level while others criticize this approach. (*Ibid.*)[11]

The rightmost columns afford the most room for professional judgment and, by extension, disagreement. For example, based on limitations in the design of some studies, Dr. Fombonne discounted them as "not contributory" or "unreliable" even though the studies observed a positive association. From the Court's point of view, the extent to which a study is "unreliable" is a matter properly reserved for cross-examination at trial. As noted in the Reference Manual, "[i]t is important to emphasize that all studies have 'flaws' in the sense of limitations that add uncertainty about the property interpretations of the results." (Reference Manual, p. 553; *Cooper v. Takeda Pharmaceuticals America, Inc.* (2015) 239 Cal.App.4th 555, 589 (*Cooper*).) "Some flaws are inevitable given the limits of technology, resources, the ability and willingness of persons to participate in a study, and ethical constraints. In evaluating epidemiologic evidence, the key questions, then, are the extent to which a study's limitations compromise its findings and permit inferences about causation." (Reference Manual, p. 553.)

Second and most importantly, even if Plaintiffs' experts relied only on the studies Dr. Fombonne identifies as satisfying temporality, their conclusions on the temporality factor would not be "clearly invalid and unreliable" under *Sargon*. (*Sargon, supra,* 55 Cal.4th at p. 772.) By way of contrast, an expert's opinion is "unreliable" when it gives "significant weight" to the strength-of-association factor based on data revealing a risk factor "somewhere around 1.2" on a scale calculating no association as 1.0. (*In re Viagra (Sildenafil Citrate) and Cialis (Tadalafil) Products Liability Litigation* (N.D. Cal. 2020) 424 F.Supp.3d 781, 796 (*Viagra*).) "Although a risk factor in that range would not necessarily preclude a conclusion that causation exists, it is

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[11] Bradford Hill was himself skeptical of statistical baselines as necessary conditions for causation. "No formal tests of significance can answer" the question of causation; "[s]uch tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis." (Bradford Hill Article, p. 299.) "[T]oo often I suspect we waste a deal of time, we grasp the shadow and lose the substance, we weaken our capacity to interpret data and to take reasonable decisions whatever the value of P. And far too often we deduce 'no difference' from 'no significant' difference." (*Id.* pp. 299-300.)

undeniably not a strong association" — given that no association is calculated as a risk factor of 1.0. (*Ibid.*) It was particularly unreliable where the expert was also "unwilling to identify what she perceived the strength of association to be, instead testifying that she found it in the 'totality' of the evidence." (*Ibid.*)

The Court cannot conclude that Drs. Ritz's and Gardener's opinions on temporality are clearly unreliable. The three studies Dr. Fombonne identified as "capable of satisfying temporality" returned mixed results overall. Where the researchers found a positive, even statistically significant association using a study with a compromised design, Dr. Fombonne gave the studies little or no weight. Where researchers using better-designed studies found a null association, Dr. Fombonne gave them more weight.

Where the experts diverge is the weight they give to these studies. In Dr. Fombonne's opinion, the studies that both satisfy temporality and observed a positive association provide weak evidence of causation. However, under California law, the strength or weakness of a study's design is a matter of professional judgment outside the trial court's purview. If the validity of studies, their strengths and weaknesses, are subject to "considerable scientific interpretation and debate," a court abuses its discretion by "stepping in and resolving the debate over the validity of the studies." (*Cooper, supra,* 239 Cal.App.4th at p. 589.) Nor can a court disregard "piecemeal … individual studies" because it finds their methodology, "fully explained to the scientific community in peer-reviewed journals, to be misleading" — "it is essential that … the body of studies be considered as a whole." (*Id.* at pp. 590, 593.) Flaws in study methodology should instead be "explored in detail through cross-examination and with the defense expert witnesses" and affect "the weight[,] not the admissibility" of an expert's opinions. (*Id.* at p. 593, page number omitted.)

As a final point, there is a distinction between studies that, one the one hand and in Dr. Fombonne's opinion, cannot as a matter of design establish temporality and, on the other hand, studies that conclusively prove temporality is not met — such as a study that measures an exposure in diagnosed subjects who definitively were not exposed before their diagnosis. Dr. Fombonne's opinion is logical — temporality is not established by a study that measures an exposure at the

same time as or long after a disease is diagnosed. Such a study does not, however, prove that the exposure came after diagnosis of the disease. Dr. Fombonne's argument ultimately goes to the weight of Dr. Ritz and Dr. Gardener's opinions rather than admissibility under *Sargon*.

2. Questionnaire Scores

Dr. Fombonne criticizes Plaintiff's experts' reliance on studies that, as a proxy for diagnosed ASD, compared metal concentrations to scores on behavioral assessments such as the Social Responsiveness Scale, 2nd edition (SRS-2), the Behavior Assessment System for Children, 2nd edition (BASC-2), and the Autism Spectrum Screening Questionnaire (ASSQ). He testified that an SRS score is not a reliable substitute for an ASD diagnosis because the SRS questionnaire has a 90% error rate in identifying "true" ASD, meaning 90% of the children who screen positive for ASD on the SRS do not actually have ASD, or at least do not meet the standard for a clinical ASD diagnosis. (Defendants' Direct Examination of Dr. Fombonne Slides (Mar. 14, 2022) Slide No. 26.)

To support Dr. Fombonne's argument, Defendants point out that Dr. Ritz agreed with Dr. Fombonne that ASD is a neurodevelopmental disorder characterized by impairments in language development, social interaction, communication, behaviors, and reaction to environmental changes, the severity of which can be "quite variable making the autism phenotype look clinically distinct." (Ritz Report, pp. 15-16.) Defendants similarly criticize Dr. Ritz's reliance on the Doherty et al. (2020) study, which found a statistically significant association between the levels of arsenic in infant toenails and scores on the BASC-2 Behavioral Symptoms Index, one of four BASC-2 composite scores, rather than a diagnosis of ASD. (Mojibi Decl., Exh. 17, pp. 2-3, 6.) Defendants point out that even though none of the three other composite scores or the SRS-2 total score showed a statistically significant association with a 95% confidence interval, Plaintiff included Doherty (2020) as evidence of a positive, statistically significant association between arsenic exposure and ASD. (*Id.* at p. 6; Defendants' Direct Examination of Dr. Fombonne Slides (Mar. 14, 2022) Slide No. 16.)

Plaintiff responds that ASD is a spectrum of disorders and that the presence of disorders, registered on a questionnaire, can at least approximate diagnosed ASD. As Dr. Shapiro testified, ASD is a "complex constellation of symptoms" diagnosed "based on the presence of certain behavioral symptoms." (Shapiro Depo., 177:15-25, 212:17-19.) "[F]rom a clinical perspective, particularly it's the symptoms that are interesting and not the label." (*Id.* at 177:23-25.)

Although Dr. Ritz's use of questionnaire scores as a proxy for ASD relies on an inference, the Court finds it is not "too great an analytical gap" to allow Plaintiffs to present Drs. Ritz's and Gardener's opinions to the jury. (*Sargon, supra,* 55 Cal.4th at p. 771 [citing *General Electric Co. v. Joiner* (1997) 522 U.S. 136, 146 (*Joiner*)].) With all of the experts agreeing ASD is a spectrum of behavioral disorders, it is not unreasonable to measure the presence and severity of ASD's characteristic behavioral disorders to approximate diagnosed ASD. Where on the spectrum the presence and severity of various behaviors become diagnosable as ASD is a matter of degree, and reasonable clinicians can disagree about where on the spectrum an ASD diagnosis is appropriate. The Court according finds that Dr. Fombonne's opinion the SRS poorly approximates an ASD diagnosis goes to the weight of Plaintiff's experts' testimony, not its admissibility.

Moreover, it would be one thing if Drs. Ritz and Gardener based their opinions solely on studies they had conducted or if, in using behavioral questionnaires as a proxy for an ASD diagnosis, they were alone in the epidemiological field. But Drs. Ritz and Gardener base their opinions not only on their own research, but on peer-reviewed studies by other epidemiologists and researchers who accepted these proxies as a measurement of ASD. The Kim et al. (2015) study's authors, citing other scientific authorities, wrote, for example, that the SRS "evaluates autistic behaviors as a continuum, rather than 'all or none,' and gives an index of deficiency in reciprocal social interactions." (Mojibi Decl., Exh. 20, p. 195.) It "is a widely used instrument to screen ASD in the public health setting, among children and adolescents aged between 4 and 18 years (Constantino and Gruber, 2007)," the Ryu et al. (2017) study's authors wrote, "comparable to other assessing instruments such as the Autism Diagnostic Interview (ADI-R), the Autism Diagnostic Observation Scale (ADOS), and the Social Communication Questionnaire (SCQ) in terms of validity and reliability (Bölte et al., 2008; Charman et al., 2007; Murray et al., 2001)."

(Mojibi Decl., Exh. 19, p. 253.) In short, other epidemiologists have assumed that autistic behaviors approximate diagnosed ASD. The Court therefore declines to exclude the testimony of Drs. Ritz and Gardener under *Sargon*, even though other professionals such as Dr. Fombonne reject the same assumption. (*Davis, supra,* 245 Cal.App.4th at p. 492; *Sargon, supra,* 55 Cal.4th at p. 772 [citing *Kumho Tire Co. v. Carmichael* (1999) 526 U.S. 137, 152].)[12]

Defendants cite an instructive case from Maryland's highest court. In that case, Dr. Hall-Carrington testified to general and specific causation — that lead exposure can generally cause "attention problems[] or ADHD" and specifically caused the plaintiff's ADHD. (*Rochkind v. Stevenson* (2017) 454 Md. 277, 283 (*Rochkind*).) The court had not yet "decide[d] the extent to which epidemiological studies can support expert testimony on causation," so it looked to *Joiner, supra,* 522 U.S. at p. 136, the second case in the Supreme Court's *Daubert* trilogy. (*Id.* at p. 289.) *Joiner* "held that the studies could not support the expert testimony because none of them had found a causal link between PCB's and cancer," and although one study found higher-than-expected lung cancer deaths among former employees of an electric plant, the study could not support an expert's causation opinion because the study's authors "were unwilling to say that PCB exposure had caused cancer among the workers they examined…." (*Ibid.* [citing *Joiner,* at p. 145].)

Following *Joiner,* the Maryland court excluded Dr. Hall-Carrington's testimony, which was based on an Integrated Science Assessment by Environmental Protection Agency (EPA-ISA) study noting that "'multiple, high-quality epidemiologic studies' have revealed 'a causal relationship between [lead] exposure and attention decrements, impulsivity, and hyperactivity in children.'" (*Rochkind, supra,* 454 Md. at p. 288.) According to the court, the expert "did not provide a sufficient factual foundation," because she failed to explain "why she thought the EPA-ISA supported her conclusion that lead exposure can cause ADHD [and] [t]he studies described in the EPA-ISA finding a causal relationship between lead exposure and attention deficits and

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[12] The potential unreliability of the SRS-2 as a proxy for ASD is mitigated by the other behavioral scores the studies used. And as the Kim et al. (2015) study's authors note, a measurement of behaviors on a numerical scale is more sensitive to potential associations than a binary yes-ASD-diagnosis versus no-ASD-diagnosis.

hyperactivity do not go that far." (*Id.* at p. 290.) The Maryland court also concluded "the jump from attention deficits and hyperactivity to a clinical ADHD diagnosis may seem reasonable, but we have explained that 'just because a conclusion is reasonable does not mean that a court must permit an expert to make it.'" (*Id.* at p. 291 [citing *Ross v. Housing Authority of Baltimore City* (2013) 430 Md. 648, 664].)

There are two problems with the *Rochkind* court's reasoning, at least for proof of general causation under California law. First, epidemiological studies generally do not make conclusions on causation; they report findings as data. Other experts then review the studies and the data, apply the Bradford Hill criteria (among other methods), and make a judgment on causation. "[E]pidemiology cannot prove causation; rather causation is a judgment for epidemiologists and other interpreting the epidemiologic data." (Reference Manual, p. 598.) The Maryland court did not seem to understand the distinction between studies documenting statistical associations between a causal agent and an effect and expert testimony applying the Bradford Hill factors to opine that the associations were "causal". The court said that "[w]ithout epidemiological studies — or other reliable evidence — demonstrating a *causal link* between lead exposure and ADHD . . . Dr. Hall-Carrington's testimony 'amounted to no more than mere speculation and conjecture.'" (*Rochkind, supra,* 454 Md. at p. 294; emphasis added.) This statement overlooks the fact that the expert's testimony on causation *was* the "other … evidence … [of] a causal link." (*Ibid.*)

Second, citing Maryland precedent, the court excluded the expert's opinion because it involved an inferential "jump" — the use of "attention deficits" as a proxy for diagnosed ADHD — even though, to the court, the inference "seem[ed] reasonable." (*Rochkind, supra,* 454 Md. at p. 291.) California law allows such inferences: "If the opinion is based on materials on which the expert may reasonably rely in forming the opinion, and flows in a reasoned chain of logic from those materials rather than from speculation or conjecture, the opinion may pass, even though the trial court or other experts disagree with its conclusion or the methods and materials used to reach it." (*Davis, supra,* 245 Cal.App.4th at p. 492.)

3. No Consistent Association

Combining gaps (1) and (2), Dr. Fombonne testified there is no consistent positive association between heavy metals and ASD among the studies that satisfy the temporality factor and assess a clinical ASD diagnosis as the outcome, rather than a behavioral assessment. (Slide 30.) The Court finds that this argument goes to the weight of Plaintiffs' expert testimony, not its admissibility. Bradford Hill called his nine points "viewpoints." (Bradford Hill Article, p. 299.) Dr. Fombonne applied the "viewpoints" more like criteria — he excluded studies from his analysis that, in his opinion, did not a) satisfy temporality or b) measure formally diagnosed ASD, and then considered only the studies that remained.

The fact that Plaintiff experts did not follow the same procedure in in their Bradford Hill analysis does not render their opinions impermissibly illogical. Drs. Ritz and Gardener separately applied each Bradford Hill "viewpoint" to the entire body of underlying studies, regardless of whether any particular study failed to satisfy other factors. Neither approach is "clearly invalid and unreliable" even though they might result in different conclusions. (*Sargon, supra,* 55 Cal.4th at p. 772; *Davis, supra,* 245 Cal.App.4th at p. 492.) "If the opinion is based on materials on which the expert may reasonably rely in forming the opinion, and flows in a reasoned chain of logic from those materials rather than from speculation or conjecture, the opinion may pass, even though the trial court or other experts disagree with its conclusion or the methods and materials used to reach it." (*Davis*, at p. 429 [citing *Sargon,* at pp. 771-772].)

4. Failure to Account for What Is Known About ASD

Dr. Fombonne's final challenge to Plaintiff's experts' methodology is the failure to consider the role of genetics as a cause of ASD. They did not rely on any articles, according to Dr. Fombonne, examining whether "genetics combined with an exposure to lead, arsenic, or mercury cause autism." (Defendants' Direct Examination of Dr. Fombonne Slides (Mar. 14, 2022) Slide No. 38.) As Defendants' counsel aptly summarized Dr. Fombonne's argument, "if you're going to try to figure out whether there's a causal relationship between an exposure and an outcome and you're looking at two groups of kids, one who have autism and one who don't, you want to

know if there's genetic differences. And there's no such study." (Sargon Closing Arguments Transcript (Apr. 4, 2022) 57:23-25, 58:1-4.)

Like the null hypothesis, Dr. Fombonne's is a hypothesis that, when assumed to be true, can expose weaknesses in a study's design and the probability its findings were by accident, by chance. Two common errors in a study's design and execution are confounding and bias. "Confounding occurs when another causal factor (the confounder) confuses the relationship between the agent of interest and the outcome of interest." (Reference Manual, p. 24.) Genes, in this case, are a potential confounding variable: they might both cause ASD and inhibit the body's ability to shed heavy metals, thereby confounding an observed association between ASD and bodily heavy-metal concentrations.

A gene-related example of bias would be a case-control study on the effects of smoking (exposure) and heart disease (outcome) that solicits volunteer subjects for study. (Reference Manual, p. 583-584.) If subjects volunteer because they smoke and have a family history of heart disease, the study will suffer from selection bias. Its observed association would be "biased upward because of the additional disease among the exposed smokers caused by genetics." (*Id.* at p. 584.) "[C]ases and controls in case-control studies should be selected independently of their exposure status, so the exposed and unexposed participants in cohort studies should be selected independently of their exposure status." (*Ibid.*) Similarly, "the exposed and unexposed participants in cohort studies should be selected independently of their disease risk. For example, if women with hysterectomies are overrepresented among exposed women in a cohort study of cervical cancer, this could overstate the association between the exposure and the disease." (*Ibid.*)

Dr. Fombonne highlighted potential biases in Plaintiff's cited studies. In the case-control studies, the "cases" — children with ASD or ASD-like behaviors — may have been genetically predisposed to ASD. If so, any observed association between their disorders and heavy-metal concentrations is explained either by chance or confounding. The studied cohorts may also over-represent children who are genetically predisposed to ASD. If so, the observed results would overstate any association between heavy metals and ASD.

For *Sargon* purposes, however, Dr. Fombonne's points about possible confounding and bias do require the court to find that Plaintiff's experts' methodology is impermissibly illogical. It is certainly possible that at least some of the studied individuals' ASD or ASD-behaviors were caused not by their exposures to heavy metals, but by genetic factors. Yet "[i]t is important to emphasize that all studies have 'flaws' in the sense of limitations that add uncertainty about the property interpretations of the results." (Reference Manual, p. 553.) The studies' authors acknowledged that genetic factors play a role in ASD etiology. (Mojibi Decl., Exh. 25, p. 2 [Long et al. (2019)] footnotes omitted.) Plaintiff's expert Dr. Shapiro testified that there are "genetic syndromes that are highly associated with the emergence of [ASD] symptoms." (Shapiro Depo., 117:6-11.)

Moreover, Dr. Fombonne's genetic hypothesis and Plaintiff's experts' hypothesis that environmental factors are capable of causing ASD are not mutually exclusive. Both could logically contribute to (be a substantial factor causing) the ASD behaviors. As Dr. Shapiro testified, "Fragile X" is a "well-recognized genetic [factor] associate[ed] with autism," but "not nearly a hundred percent of kids with Fragile X go on to have the diagnosis of autism. The figure is something like 30 to 50 percent. So even if …. in a child [diagnosed] with autism, Fragile X is a reason for the autism or a contributor, it can't be the only contributor. There must be other things that have contributed to that particular constellation of behavioral symptoms in th[e] child." (Shapiro Depo., 117:6-25 [citing Dr. Fombonne's Report], 118:1-2.) "Genetics is an important risk factor for ASD, but it cannot explain ASD entirely [citation]," wrote the authors of the Alampi et al. (2021) study. (Mojibi Decl., Exh. 16, p. 1803 [Alampi et al. (2021)].) "A growing body of research shows that environmental factors, especially those that affect the developing fetus, play an important role in ASD [citation]." (*Ibid.*) "We must … keep in mind that diseases may have

more than one cause," wrote Bradford Hill. (Bradford Hill Article, p. 297.) "Indeed[,] I believe that multi-causation is generally more likely than single causation…." (*Ibid.*) [13]

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Dr. Fombonne's four points together form a cohesive hypothesis: of the studies that both establish temporality and measured clinically-diagnosed ASD, the results are mixed, and none of them considered that ASD is primarily caused by genes. His hypothesis is, however, ultimately an opinion on general causation that competes with the opinions proffered by Plaintiff's experts. It is not the Court's role to resolve scientific controversies. Dr. Fombonne's critiques go to the weight of Plaintiff's evidence, not its admissibility. (*Cooper, supra,* 239 Cal.App.4th at p. 592.)

B. Points Raised in Defendants' Moving Papers

In their moving papers, Defendants raise several arguments regarding each of Plaintiff's experts, (1) Dr. Ritz, (2) Dr. Gardener, (3) Dr. Aschner, and (4) Dr. Shapiro, based on their respective deposition testimony.

1. Dr. Ritz

Defendants argue Dr. Ritz's testimony should be excluded because she (a) "repeatedly disagreed" with the conclusions of the studies on which she relied; (b) "disregarded or attempted to rewrite basic epidemiological concepts" so she could conform the studies to her "preferred

[13] Dr. Fombonne makes a corollary argument that Drs. Ritz and Gardener only considered studies that analyzed ADHD comorbid with ASD, rather than analyzing heavy metals and ADHD alone. In his opinion, ADHD manifests differently by itself than it does when comorbid with ASD. (Defendants' Direct Examination of Dr. Fombonne Slides (Mar. 14, 2022) Slide No. 46.) His argument is essentially that the experts did not consider studies that isolated ADHD's causal factor, instead linking it to ASD. But as he testified, ADHD is "substantially" more prevalent in people with ASD than in people without ASD, and though he opines this fact is also explained by genetics, it also makes Plaintiff's use of studies that measured ASD and ADHD together not illogical. (*Ibid.*) In other words, if heavy metals are associated ASD, and ADHD is associated with ASD, then it is not illogical to opine heavy metals are associated with and can contribute to both disorders. Whether this "reasoned chain of logic" is ultimately unpersuasive against Dr. Fombonne's genetics argument is not at issue here. (*Davis, supra,* 245 Cal.App.4th at p. 492.)

outcome"; and (c) applied her "unreliable methodology" to reach a "pre-determined conclusion on causation, all under the guise of a Bradford Hill analysis." (Motion Brief, 34:17-23.)

a. Basis for Opinion

Defendants argue Dr. Ritz's deposition testimony shows she is at odds with the studies that support her opinion. "She repeatedly rejected the study authors' explanations of the relevant literature, disagreed with their cautionary statements about the limitations of their own studies, and dismissed every author's reference to the need for further research before reaching conclusions on causation." (Motion Brief, 35:10-12.)

Defendants first cite her responses to questions about statements in the studies' introductions. The Skogheim et al. (2021) study, for example, says, "Altogether, there is still limited knowledge on prenatal exposure to metal or variations of maternal levels of essential elements and clinician-based ASD and ADHD diagnoses in childhood. In addition, there are inconsistencies regarding study designs and findings." (Mojibi Decl., Exh. 22, p. 2.)[14] When asked if she agreed with this statement, Dr. Ritz said it was "not [her] opinion. That's what these authors say. And I can tell you that I write this in my introduction so that reviewers will consider my paper novel. That's an old trick … they are stating what they have to state to get their paper published, and one of the statements that you do in the end of your introductory paragraph is say, oh, this is novel because there's not enough knowledge, we are — we are here to fill this gap, because otherwise this is not new and journals don't publish something just because you're for the tenth time showing that something actually exists." (Ritz Depo., 138:25, 139:1-18.)

[14] Other examples of statements from study introductions: "[D]ue to lack of consistency among the various study findings, the effects of iAs [inorganic arsenic] and Pb [lead] on ASD have not been established" (Mojibi Decl., Exh. 34, p. 1905 [Wang et al. (2019)]); "Studies of toxic metals and nutritional elements in ASD have yielded mixed results" (Mojibi Decl., Exh. 26, p. 2 [Arora et al. (2017)]); and "[P]revious studies evaluating the association between lead exposure and ASD have reported inconclusive results, with evidence for positive [citations], null [citations], and negative associations [citations]" (Mojibi Decl., Exh. 20, p. 194 [Kim et al. (2016)].).

Dr. Ritz's statements do not put her at odds with the studies' authors. She explained that researchers often introduce their studies with a "general statement" that does not necessarily reflect a "systemic review or evaluation" of previous studies, but instead "paraphras[es] what's out there in the literature" while "emphasizing something that is still unexplained in order to make it novel, and in order to make the audience and the editors interested in publishing your results." (Ritz Depo., 197:9-19.) An author's statement in a study introduction, in other words, is not necessarily a definitive statement supported by systemic review of the literature.

Defendants next cite Dr. Ritz's testimony about limitations the study authors placed on their findings. The authors of the Arora et al. (2017) study, for example, wrote that it "has multiple strengths, such as the inclusion of an informative twin sample recruited from population-based cohorts, a rigorous diagnostic assessment, and the use of direct fetal biomarkers," whereas limitations were "a relatively small non-random sample, although the sample size was adequate to uncover significant associations after stringent statistical adjustments, and our twin sample represented a significant subsample (11.3%) of the total population of twins discordant for ASD in Sweden in the examined age range." (Mojibi Decl., Exh. 26, p. 8.) Dr. Ritz logically explained, however, that she disagreed with the statement that the Arora sample was "non-random" because "[t]wins are never a random sample — never" and the author thus "misuse[d] the term 'nonrandom.'" (Ritz Depo., 208:17-25, 209:1-25, 210:1-3.) Defendants also cite her response to a question about one limitation stated by the authors of the Kim et al. (2016) study — "Is that a limitation of the study?" "I don't see it as a limitation, no." — but omit her extensive answer that "all of these are limitations because they are introducing measurement error. I totally agree with the authors … [t]he more error you — you introduce into a study, the less signal you get. It's a signal to noise ratio. You raise the noise, you don't see the signal, you drown it out. And that's, of course, a limitation. We wish that wouldn't be the case." (*Id.* at 223:11-16, 243:7-25, 244:1-5.)

Lastly, Defendants argue Dr. Ritz dismissed the authors' cautionary statements about the need for more research. The authors of the Arora et al. (2017) study, for example, wrote that "caution should be exercised when generalizing our findings, and additional studies are needed in

different populations, particularly larger non-twin ASD samples to corroborate our findings, and differentiate genetic and non-genetic contributions in understanding the relation between metals and ASD." (Mojibi Decl., Exh. 26, p. 8.) Dr. Ritz "dismissed out of hand" this statement, Defendants argue, as "merely reflect[ing] the authors' ulterior financial motives," citing her testimony that "You always ask for more research … And guess what, Manish [Arora] wanted more money for more studies and this is one of the arguments you make." (Motion Brief, 36:19-28; Ritz Depo., 222:13-18.) But her complete testimony is more nuanced. "Well, that's what we always teach our students to say, right? You never conclude anything from just one study. You always ask for more research, and you ask for more studies and nontwins. And guess what, Manish wanted more money for more studies and this is one of the arguments you make." (Ritz Depo., 222:13-18.) Her statement is logical.

In sum, Dr. Ritz has reasonable critiques of statements by the authors of the studies that support her opinion. But this does not demonstrate that her opinion is "unsupported by the material on which [she] relies…." (*Sargon, supra,* 55 Cal.4th at pp. 771-772.)

b. Mythological Deviation from Epidemiological Principles

Defendants argue Dr. Ritz deviated from or distorted "bedrock epidemiological principles." (Motion Brief, 37:14-15.)

First, they asked if "as a general matter" she agreed that an advantage of a cohort study is the "temporal relationship between exposure and disease can be established more readily than in [a] case-control study." (Ritz Depo., 46:21-25.) The statement, she replied, is "too general" because "there are nested case-control studies within cohorts that do exactly the same thing." (*Id.* at 46:10-12, 47:9.)[15] Disagreeing with Dr. Fombonne, she further explained that certain biomarkers "store" toxins so the exposure can be tracked "quite far back" in time:

> It can go quite far back because lead is stored in the bone and there's a constant replacement of lead in the blood from the bone. So if a child, for example, was very highly exposed in

[15] For example, Dr. Ritz cited in her Report a case-control study nested with the Historic Birth Cohort at Statens Serum Institute in Denmark. (Ritz Report, 23-24.)

> its first life year through drinking leaded — from leaded pipes water, then that gets stored in the child's bone and it constantly replaces what you see in the blood. It never has to be exposed again, it can tell you about this first year of life.

(*Id.* at 38:14-23.) She also said a study can examine blood samples collected at birth "so there is sampling from an earlier time period." (*Id.* at 37:14-21.)

Defendants also argue Dr. Ritz "brushed aside" the requirement that an epidemiologist, before she can apply the Bradford Hill factors, must have evidence of an association between an agent and a disease. They asked her, "Didn't Dr. Bradford-Hill, in his article where he announced the Bradford-Hill criteria, say that you first have to have an unconfounded association before you apply the Bradford-Hill factors?" "If he had said that," she replied, "we couldn't apply his factors ever." (Ritz Depo., 86:20-25, 87:1.) Arguing that her answer is wrong and outside the scientific mainstream, Defendants cite a portion of Bradford Hill's 1965 article. "[W]e have this situation. Our observations reveal an association between two variables, *perfectly clear-cut and beyond what we would care to attribute to the play of chance*. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?" (Mojibi Decl., Exh. 15, p. 295, emphasis added ["Bradford Hill Article"].)

Yet Bradford Hill never said that causation can only be inferred from a "perfectly clear-cut" positive association. The statement Defendants cite appears early in his article where it appears he referred to a "perfectly clear-cut" association as an idealized, hypothetical "situation" to expound his factors. (Bradford Hill Article, p. 295 ["we have this situation…"].) He went on to write, "We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so. Relatively few persons harbouring the meningococcus fall sick of meningococcal meningitis. Relatively few persons occupationally exposed to rat's urine contract Weil's disease." (*Id.* at p. 296.) He was also skeptical of rigid statistical tests — "[T]oo far often we deduce 'no difference' from 'no significant difference'." (*Id.* at p. 300.) Therefore, the observed association, "perfectly clear-cut" or not, should be considered not as an isolated prerequisite to a Bradford Hill analysis, but as part of the analysis itself. "First upon my list [of

factors] I would put the *strength* of the association"; second, "the *consistency* of the observed association"; and third, the "*specificity* of the association." (*Id.* at pp. 295-297.)

Dr. Ritz agreed. "Bradford Hill is there because you are evaluating studies according to validity criteria, and confounding is one of the validity criteria you're assessing. You're not stating beforehand that there is no problem with validity and then you assess it, [instead] you're actually doing the assessment." (Ritz Depo., 326:16-22.) She reasonably said to require a "pure, unconfounded" association was as "tautologic[al]" because the observed association — its statistical strength, potential confounding variables, and so forth — are considered as part of the Bradford Hill analysis. Ultimately, while the Bradford Hill factors are "employed only *after* a study finds an association," there is no requirement the association first be "perfectly clear-cut" or "unconfounded." (Reference Manual, pp. 598-599.)

Defendants also argue Dr. Ritz "reshape[d]" the Bradford Hill analysis, citing her description of the "consistency" factor. (Motion Brief, 39:13-14.) In her analysis, they argue, she considered the "consistency" factor "met" if a study's results were "consistent with what *she* believe[d] the answer should be," but her testimony does not support their argument. (Motion, 39:21-23.) "[C]onsistency," she said, "means given the hypothesis you have and given what you already know[,] is the study consistent with that kind of reading." (Ritz Depo., 273:18-20.) Asked to explain how she "reached a conclusion that the consistency Bradford-Hill factor was met" given "all th[e] null studies that we just discussed," she said "it's not consistency of study results. It's consistency of what you would expect from certain studies and what you wouldn't expect from them, and how you put them into context. So you have different studies that have different criteria — that have different methods of analyzing their results. This Saghazadeh [and Rezaei (2017) study] did a ton of different comparisons, but, you know, overall results are only so much. You also want to look at the individual studies, and you want to consider individual studies, not just — because they pick and choose — these meta-analysts pick and choose which studies to include and which studies to exclude. And when you look at the studies overall, there is a consistent signal." (Ritz Depo., 258:8-25, 259:1-2.) Her description is consistent with the Reference Manual's description of the "consistent with existing knowledge" factor — whether the association

consistent with "other relevant knowledge," such as the association between smoking and lung cancer being consistent with data that shows increased cigarette sales are positively associated with an increase in lung cancer death rates. (Reference Manual, pp. 604-605.)[16]

Dr. Ritz description of her methodological principles does not support a finding that her methods were illogical or impermissibly speculative.

c. Methodology: Bradford-Hill Factors

Lastly, Defendants argue Dr. Ritz's Bradford Hill analysis was "highly subjective" and "results-driven." (Motion Brief, 40:8-9.) Specifically, they argue she could not describe the weight she gave to the specific factors and she formulated them to support her pre-determined opinion.

Defendants first argue that Dr. Ritz could not describe how much weight she gave to any individual Bradford Hill factor in her overall analysis citing, as an example, her reasoning that for arsenic and ASD, the strength of association factor is "partially met" because "the overall meta-analytical (point) effect estimates reported reflecting a weak to moderate size differences and the dose response relation-ship was non-linear at low levels of exposure in the MoBa study." (Ritz Report, p. 35.) She entered on a spreadsheet the weight each meta-analysis she read gave to the underlying studies, though she admits this was not possible to do for some of the meta-analyses she reviewed. (Ritz Depo., 102:6-12.) She also admitted she did not have the spreadsheet and "probably deleted" it. (*Id.* at 103:7-8.) She also failed, as Defendants point out, to list "dose-response" as one of the nine Bradford Hill factors — she lists only eight — though she did discuss dose-response as a statistical and methodological term in her "Methodology" section. (Ritz Report, p. 11, 13-14.) She also did not separately analyze the "strength of association" and "dose-response" factors but combined them under one "strength" factor. (*Id.* at p. 35.)

[16] Bradford Hill called this factor "coherence," but its substance is the same — "the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease…." (Bradford Hill Article, p. 298.)

What matters under *Sargon* is whether the studies supporting Dr. Ritz' opinions "can provide a reasonable basis" for her opinion irrespective of whether Defendants disagree with her conclusion. (*Cooper, supra,* 239 Cal.App.4th at p. 590.) To take Defendants' example, her conclusion the "strength" factor was "partially met" for arsenic and ASD is not an impermissible leap of logic. Dr. Ritz cited several studies that observed at least some positive association between arsenic exposure and ASD. She ascribed "high validity" to the Norwegian case-control study, for example, because the autism diagnoses used for the "case" group were "retrieved from national disease registers" and Norwegians have universal access to health care. (Ritz Report, p. 34 [Skogheim et al. (2021)].) And the study's findings — an "increased risk of ASD and ADHD [are] associated with prenatal arsenic exposure" — were "important," in her view, because the study measured a large sample size and, in Dr. Fombonne's words, satisfied temporality, the arsenic in the study population having "originated mainly from fish and seafood consumption of the participating pregnant women." (Ritz Report, p. 34; Mojibi Decl., Exh. 34, p. 9.) She also considered the Wang (2019) meta-analysis of 14 studies on arsenic exposure, which provided her with "consistent evidence supporting a positive association between early life [inorganic arsenic] exposure and diagnosis of ASD, and a meta-analysis by Saghazadeh and Rezaei (2017) of 15 studies whose results were mixed — "no difference in blood, urine, or hair arsenic concentrations between ASD and control subjects overall" — but "[f]or arsenic measurements of hair, the summary effect of 4 studies from developing countries with a total of 158 cases and 167 controls was marginally statistically significant." (Ritz Report, p. 33.) Based on these studies and others, it was not a leap of logic for Dr. Ritz to conclude the "strength of association" factor is "partially met."

Defendants' argument Dr. Ritz admitted her Bradford Hill analysis was "somewhat arbitrary" omits her complete testimony. Aside from the temporality factor — "we do want temporality" — she refused to rank the factors she considers "most important" because "[e]ach one of them, I have to consider. If I don't have data on one, then, you know, I have to live with that and still make my consideration." (Ritz Depo., 274:6-11.) She applies the factors to "everything I know about these studies, and then I — I mean, it's arbitrary in a way that you have

to say, okay, this study meets this, this, or this. That study meets this, this, and something else." (*Id.* at 275:12-16.) Defendants omit what she went on to say: "It seems arbitrary, *but it's not* [,] because it's a big puzzle piece. And some studies may not help me with consistency and some studies may not help me with specificity or strengths, but each one of them tells a piece of this puzzle that in the end is the Bradford Hill and makes up the picture. [¶] So it's not like I rank them. It is really the integration of the knowledge, the studies, what I know about the subject matter and how it fits together. Whether a picture emerges or doesn't emerge, that tells me that the Bradford-Hill is actually applicable in the way that we described it." (*Id.* at 275:17-25, 276:1-3, italics added.)

Her answer largely tracks the Reference Manual.

> There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines. One or more factors may be absent even when a true causal relationship exists. Similarly, the existence of some factors does not ensure that a causal relationship exists. Drawing causal inferences after finding an association and considering these factors requires judgment and searching analysis, based on biology, of why a factor or factors may be absent despite a causal relationship, and vice versa. Although the drawing of causal inferences is informed by scientific expertise, it is not a determination that is made by using an objective or algorithmic methodology.

It also tracks Bradford Hill's own description of the factors.

> What I do not believe — and this has been suggested — is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. 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 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?

(Reference Manual, p. 600, footnotes omitted; Bradford Hill Article, p. 299.)

Defendants' argument Dr. Ritz defined the Bradford Hill factors to suit her preferred outcome — she allegedly "reconfigure[ed]" the "consistency" factor, for example, to "construe virtually any study outcome as supporting her position" – also omits relevant portions of her testimony. Defendants cite her description of this factor as "consistent with the expectation with

respect to what I think the answer should be." (Motion, 42:9-11 [citing Ritz Depo., 134:5-7].) But her complete answer is more illuminating:

> You say [whether a study's findings are] consistent with the expectation with respect to what I think the answer should be if the study had been done correctly or if the study had been done unbiased or what I know from mechanisms, what I know about this population, what I know about the exposure level, what I know about co-exposures, and what I would expect to be able to see given the size of the cohort, the size of the study. And that is consistency in a scientific way.
>
> It's not consistency check mark one study yes, one study no, one study null. That is simplistic and that's not science.
> …
> That it is consistent with the expectation of what science has to say about the data and what the measures that each of the studies are using are actually telling me as a scientist, and I'm not — you know, otherwise I could do a computer analysis. I could say, okay, computer count one, count two, count three, and then we look on average. That's not how I do my analysis and nobody has recommended that.

(Ritz Depo., 133-10:25, 134:1-25, 135:1-16.) Her complete answer is reasonable: the Bradford Hill consistency factors considers whether a study's findings are consistent with other, relevant scientific knowledge. (Reference Guide, p. 606.)

The Court likewise cannot exclude Dr. Ritz's conclusion on consistency as illogical. The Skogheim et al. (2021) study, for example, found a negative association between mercury and ASD. (Mojibi Decl., Exh. 22.) This finding, Dr. Ritz explained, was "consistent" with other knowledge and her opinion because, as the study's authors wrote, the participants, all Norwegian, were likely exposed to mercury from eating fish and shellfish, and "if mercury is from certain types of fish that also contain other omega-3 fatty acids, then the adverse effect of mercury is counteracted, most likely by these beneficial effects in fish-eating … So this is very consistent with everything we know about mercury and fish." (*Id.* at p. 2; Ritz Depo., 151:15-25, 152:7-8.) As another example, Defendants asked her if a statistically significant negative association between a compound and an outcome suggests the compound has a "protective effect." (Ritz Depo., 116:21-24.) The answer, she explained, depends on the context, but if a study shows a negative association and protective effect between a known neurotoxin and a disease — lead, for

example, and ASD — then she would, given her scientific knowledge, "scratch my head and say, 'What's wrong with my study?' And that's when I search for factors that could have caused this … factors [that] are usually considered bias." (*Id.* at 117:2-16.) Dr. Ritz explains she reached her consistency opinion logically.

Defendants argue Dr. Ritz refused to admit that the dose-response factor would not be met by a hypothetical study that found a negative association between lead and ASD. (Motion, 42-43.) The testimony Defendants cite, however, addressed a single graph, Figure 2, in the Skogheim et al. (2021) study, which ultimately found a positive albeit non-linear association between lead exposure and ASD. (Ritz Depo., 136:4-5 [introducing Skogheim study], 137:8-9 ["Let's look at that study"], 147:7-18, 155:20-22.) The study's authors wrote,

> We identified a non-linear (U-shaped) association with prenatal lead exposure and ASD, while there were no such findings for ADHD diagnosis in children. The non-linear/U-shape observed in this study, indicate that both low-level and higher prenatal exposures to lead are associated with increased risk of ASD in children. Non-linear dose–response relationships have been shown in several studies of lead exposure in childhood and neurodevelopmental outcomes, such as IQ [citation].

(Exh. 22, p. 10 [§ 4.1.4].) From Figure 2 alone, Dr. Ritz did find support for or a rejection of a dose-response relationship between lead and ASD. But Figure 3, which shows a spline regression, was a more sophisticated way, in her opinion, to present the data to show a dose-response relationship, if one existed. (Ritz Depo., 145:9-23, 147:13-18.) She considered both Figures 2 and 3 and Figure 2 had limitations; it showed only data for the 17th week of gestation, for example, and not the 27th week, where lead exposure could have a larger effect. (*Id.* at 144:9-21, 145:20-23, 147:19-21.) Her analysis is not unduly speculative.

As for the temporality factor, Defendants argue Dr. Ritz suggested "an epidemiologist might be able to find causation in the *absence* of clear evidence of temporality, provided that there is no conclusive evidence in either direction." (Motion, 43:7-9.) While she admitted temporality is "the most important" Bradford Hill factor and if the evidence shows temporality is *not* met, then a causal inference cannot generally be inferred, she further explained she evaluated temporality "study by study, piece of evidence by piece of evidence" and even if temporality was not clearly

established because "there's not enough data," causality can still be inferred using other Bradford Hill factors such as consistency with "other data … from animal studies" and biological plausibility ("mechanism"). (Ritz Depo., 88:19-20, 89:3-4, 90:5-10, 24-25, 91:1-4.) Her testimony echoes Bradford Hill's statement that temporality "certainly needs to be remembered" but none of his nine "viewpoints" are "required as a *sine qua non*" of causal inference. (Bradford Hill Article, p. 299.)

Lastly, Defendants argue Dr. Ritz admitted she essentially began her analysis on the assumption that heavy metals can cause ASD and then looked for studies that disproved her assumption. Their argument, however, is based on her testimony discussing the results of individual studies in isolation. They asked her, for example, whether the Doherty et al. (2020) study "support[ed] her opinion," a study that compared lead concentration in maternal and infant toenails to a behavioral assessment of the child at age three. (Ritz Depo., 129:24-25, 130:1-2; Mojibi Decl., Exh. 17, p. 2.) The authors observed "inconsistent associations" between lead levels and behavioral problems, which they concluded was "unexpected" and "not supported by the prior literature" but possibly attributable to "residual confounding by, for example, unmeasured lifestyle factors" or "chance, as we did not correct for multiple testing owing to dependence among outcomes (and potentially exposures) and because this was an exploratory analysis." (Mojibi Decl., Exh. 17, p. 2 pp. 4, 6.)

Though its findings made Doherty a "null study," Dr. Ritz did not exclude it from her analysis. She considered it "carefully … what they measured, how they measured it," and said "[i]t supports my opinion like every other piece of evidence … I do not exclude null studies from what I look at … null studies are [a] piece of the puzzle, and I try to understand why they are null. [¶] I'm not saying they are wrong, they're not wrong, they are what they are. They are data. I do not exclude data and every piece of data that I see informs me. So yes, they did inform my opinion." (Ritz Depo., 129:16-17, 130:9-14, 131:11-19.) Her explanation turns on the word "support" — because one null study does not logically support a causal inference, the Doherty study *by itself* did not "support" her opinion, but it did "support" her opinion as *one of many* studies she read and considered. She also logically explained how it figured into her overall analysis. "It

was a relatively small study for the level of lead … measured in [infants'] toenails. You probably need a much larger study to see differences at these levels." (*Id.* at 130:15-18.)

As additional evidence Dr. Ritz made speculative assumptions, Defendants cite her testimony that the findings of the Skogheim et al. (2021) study were "not enough data to convince [her] otherwise." (Ritz Depo., 143:21-23.) But Dr. Ritz said this in response to a question whether the Skogheim study's findings *alone* were "consistent with [her] opinions," and she answered it did not "convince [her] otherwise" considering the findings of the *many studies* she had read. Defendants' counsel acknowledged this difference: "Well, surely one — one study's not going to convince you of anything, correct, you need more than one study?" "Correct." (*Id.* at p. 143:24-25, 144:1-2.) And she again gave a reasoned explanation of how she interpreted the Skogheim study's results:

> I really don't know what you mean by "support." But I'm looking at this, I'm saying, well, this is 17th week, maybe they're correct. Maybe in the 17th week, there's no effect. Maybe in the 27th week, there's a big effect. They haven't given me data for the 27th week. They haven't given me data for the 7th week after birth or for the seven[th] year after birth. They are just showing 17th week estimates. 17th week estimates are what they are, in this case suggesting a null association, but that doesn't convince me that lead is not a neurotoxicant at the levels that they actually have lead in the blood of these women, which is relatively low.

(Ritz Depo., 144:7-21.) Dr. Ritz's comments on individual studies, in other words, do not demonstrate her preferred outcome drove her Bradford Hill analysis.

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"It bears repeating that applying the Bradford Hill criteria involves a certain amount of subjectivity, and experts will often disagree when doing so." (*In re Roundup Products Liability Litigation* (N.D. Cal. 2018) 390 F.Supp.3d 1102, 1134.) The evidence does not show that Dr. Ritz's opinion is "(1) based on matter of a type on which an expert may not reasonably rely, (2) based on reasons unsupported by the material on which the expert relies, or (3) speculative." (*Sargon, supra,* 55 Cal.4th at p. 771-772, page number omitted.)

2. Dr. Gardener

Defendants argue Dr. Gardener should not be allowed to testify (a) because she did not reliably apply the Bradford Hill factors and because of (b) her previous statements and (c) issues with how she prepared her Report.

a. Methodology: Bradford Hill Analysis

Dr. Gardener described a reliable Bradford Hill analysis. Pressed to name the quantity of positive studies needed to infer causation, she said she would not infer causation from one study alone, but beyond that there was "no [set] number" of positive studies.

> My methodology would be the same if I had 20 studies all showing the exact same thing or 20 studies with only one study showing a statistically significant [association]. I look at the literature in totality. I look at the strengths, the weaknesses, the methodological differences. I look at whether the studies are all the same or whether they're different.
>
> "Different" is great because then what it does is it tests your assumption in all sorts of different scenarios. I look at issues related to validity, accuracy … Accuracy relates to validity, and I look at the literature in totality and determine how likely an association might be biased to the degree that what we're observing would not be the real association. The process is the same no matter how many studies there are and no matter how varied the results are.
>
> You go through all of the different studies and you think about what are their strengths, what are their limitations, what does the totality of the literature show. You think about things like sample size and different study populations and different statistical techniques and you go through the Bradford Hill criteria and then you use your judgment.

(Gardener Depo., 175:13-25, 176:1-8; 181:15-23.)

Defendants argue Dr. Gardener admitted she applied the Bradford Hill factors without evidence of a positive association between heavy metals and ASD. She never said this. She said that "in the world of biostatistics," "everything is associated. There's always an association … an association is equivalent to a relationship." (Gardener Depo., 143:12-22; 145:17-18.) "[A] 1.0 means … the relative risks are the same. That is the association. That is the relationship." (*Id.* at 145:23-25; 146:1.) For a study that observed a relative risk of 1.0, she would still "refer" to the Bradford Hill factors to consider "how valid that 1.0 is, whether it was … biased toward the null

… [a]nd that's where the Hill criteria come into play because one of the Hill criteria is the strength of the association, so that would be, that would represent the strength of the association, would be a relative risk of 1.0." (*Id.* at 146:8-20.) She considered a study's findings, in other words, as part of her Bradford Hill analysis — a logical method, as discussed above regarding Dr. Ritz.

Defendants argue Dr. Gardener "summarily categorize[d]" the associations between lead, arsenic, and mercury and ASD as "strong" without explaining why and "rejected the meaningfulness of statistical significance…." (Motion Brief, 46:18-24.) The evidence does not support this argument. Dr. Gardener explained at length how she evaluates a study's findings. Like Dr. Ritz, she cited a study's design and sample size as affecting "the validity of the estimate as well as the reliability … how big, how wide the confidence bounds are." (Gardener Depo., 198:4-14.) Another "important" factor, in her opinion, is the unit of measurement of the heavy metal — for example, the blood-lead concentration expressed in micrograms of lead per deciliter — and whether it is significant in real-world terms. (*Id.* at 198:20-23.) "Are you talking about a ten-microgram [of lead]-per-deciliter [of blood] increase? Are you talking about greater than ten versus less than two micrograms per deciliter? Are you talking about greater than ten versus less than five? So the contrast is the first thing that you want to keep in mind when evaluating the magnitude because a really small magnitude associated with a .001-microgram-per-deciliter difference could be actually really huge. It's that the unit of measurement is really small, and that's something that we, as epidemiologists, always sort of strive to put into context for our readers, is understanding sort of real-world understanding of the magnitude of effect." (*Id.* at 197:7-25; 198:1-3.) Variations in the effect magnitude were also why she did not simply pool the studies' numerical findings to measure the "strength of association" factor.

> [I]f you were comparing kids with greater than 20 micrograms per deciliter of blood versus kids with less than one, that would be a huge, huge contrast … [but for each of the studies,] each of the comparisons are different. So, for example, if you look at Kim 2013, their contrast was kids with greater than two micrograms per deciliter versus less than two … So the comparison is different for each of [the studies]. If all of them, if each study had compared greater than or equal to two versus less than two, then it would be really easy to create a summary effect.

(Gardener Depo., 167:10-25.)

Defendants' argument that Dr. Gardener did not "apply *any* statistical testing or 'numerical thresholds' to her consideration of the epidemiological evidence" misstates her testimony. She said that epidemiologists do not rate a positive association "strong" simply because it exceeds a certain risk ratio, even though courts sometimes do.[17] (Gardener Depo., 204:1-10.) She explained other factors that epidemiologists use to evaluate risk ratios include the baseline risk and the consequences of the increased risk. "If something increased your risk of a cold by tenfold, that's not as much of a public health problem as if something increased your risk of ALS or childhood cancer tenfold. The disability, the years … lost are very different." (*Id.* at 201:23-25, 202:1-3.) And there is no evidence Dr. Gardener ignored statistical significance.

> I factored [statistical significance] in in terms of like if an association — if I see an effect estimate that's really strong but the confidence bound goes right below one so the P-value is .06, you know, there are methodological reasons why the confidence bounds could be wide, especially if it's a small study or if they over-adjusted or, you know, then I might say, like I'm not so worried about it being a P-value of .06. Like I have enough clinical experience to say, you know, that's not really meaningfully different than if the P-value, than if the confidence bounds went right above one. But I'm an epidemiologist. I am part of this sort of world of medicine where we conventionally use this .05. That is the P-value that we pretty much use in my studies, and so it is certainly something I keep — it's impossible not to sort of keep that in mind, but it's not the full picture. I would never discount an association that didn't reach that threshold. I try to say like why, like look at the confidence interval and say let's think about that confidence interval, why is it so wide, why is it so narrow?

(Gardener Depo., 208:13-25, 209:1-17.)

Defendants next argue Dr. Gardener reformulated the "consistency" factor into a subjective test of whether the study results were "consistent with her preexisting opinions." (Motion Brief, 47:3.) This was not her testimony, however. She declined to set a number or percentage of studies that must have positive findings in order to be "consistent" — there are many other factors that

[17] "[O]nly [epidemiological] studies showing relative risk estimates greater than 2.0 are useful to the jury and may properly be used to 'extrapolate from generic population-based studies to conclusions'" on specific causation, that is, "'what caused a specific person's disease.'" (*Johnson & Johnson, supra,* 37 Cal.App.5th at p. 325 [citing *Cooper, supra,* 239 Cal.App.4th at p. 593].)

affect how a study's findings should be interpreted, and she thus explained that epidemiologists weigh consistency based on their "judgment and expertise." (Gardener Depo., 251:9-18.)

> There is no definition of 'consistency.' In any literature, you won't find perfect consistency. If you look through all my literature, you will see that I once published a study showing no association between maternal smoking during pregnancy and birth weight. We know maternal smoking affects birth weight. My study was sort of particularly methodologically strong using a sibling design. We know that smoking during pregnancy affects it even within families. So when we have known associations, you're never going to see perfect consistency, so there's no perfect number. It's not like 50/50 or 60/40.
> …
> [I]n my training, there is no number, you know, oh, consistent association is 50 percent of observed studies. You have to really think about what consistency you're looking for. Are you looking for always statistically significant, statistical significance in every single study? Are you looking for effect estimates that are similar in magnitude across studies? You have to think about a lot of things when you're thinking about consistency.
> …
> So what I thought about is when studies showed different associations, why? Like, you know, was the magnitude of effect different because the cutpoints are really different because the time periods were really different?
>
> Like these days you wouldn't, you might not look at a contrast of greater than 20 micrograms per deciliter of blood lead because that's so rare right now. When we were all children, that blood lead level was far more common, so you want to think about consistency in relation to why studies might be different. Are the study populations different? Is the frequency of exposure or the types of exposure? It's like you were saying before, most of these studies didn't assess where the lead, arsenic or mercury was coming from. That will vary between populations, and can explain differences that you see in different populations.

(Gardener Depo., 250:10-25, 251:10-20, 251:23-25, 252:1-19.) Defendants asked her, for example, if an "even division" between positive and null studies would "weigh against a causal inference," comparing the number of positive studies to the number of times a coin-flip returns heads versus tails. (*Id.* at 278:5-13, 23-25; 279:1.) But the consistency factor does not simply compare the number of positive studies to the number of null studies — it involves a more nuanced inquiry.

> There's no definition of what percentage would be consistent. You have to think about the strengths and weaknesses of the designs. You have to think about consistency in terms of

> what, whether they are finding an association or not, the strength of the association, whether the association is more in some populations than the other. And you have to think about why the studies are inconsistent, what are the reasons for the inconsistencies. Is it that every study that included both males and females showed something and then all studies that just included males showed something else, and then you could think, all right, the association between your exposure and your outcome would be stronger in females, so things like that. You want to think about whether there are reasons to explain any inconsistencies that you do see.

(*Id.* at 277:10-25; 278:1-4.) The Court is not persuaded that Dr. Gardener reformulated the consistency factor.

Defendants argue she ignored the principle that exposures might be causally associated with an outcome at a high, but not low level of exposure — essentially the "dose-response" Bradford Hill factor. They also argue her analysis was results-driven because she started on the assumption that lead causes ASD and then looked for studies that disproved her assumption. But once again, her testimony was more nuanced. She admitted she could not "off the top of [her] head" recall any specific epidemiological studies that established a dose-response relationship between heavy metals and ASD, and when asked if she believed "any amount of exposure to lead is causally associated with autism," she replied she did not see a level of lead exposure "that is reliably not associated" with lead. (Gardener Depo., 185:19-22, 347:6–348:8.) There is no "amount of lead exposure" at which a "causal association emerges with autism" — "[i]t does not exist. Like if you said what number of cigarettes does an association with lung cancer exist, you would never see that because it doesn't exist … it's not a realistic epidemiological question. It's not like people say, oh, at 20 cigarettes you get lung cancer." (*Id.* at 153:22-25, 154:1-6.) Her answer is logical: there is some level of lead exposure, even an infinitesimal amount, below which no association with ASD is observed, but no study has pinpointed the threshold.

Lastly, Defendants argue Dr. Gardener "buck[ed] the scientific consensus" by "ignor[ing]" the "specificity of association" Bradford Hill factor. (Motion Brief, 48:6-10.) Contrary to Defendants' argument, she did not ignore the factor, but instead gave a logical explanation of how it played into her overall analysis:

> [T]he specificity criteria refers to whether the exposure of interest only impacts the disease of interest which is almost never applicable even in the situation of causality. Like smoking causes lung cancer. The fact that smoking also causes heart disease, oral cancers, head and neck cancers doesn't detract from the fact that smoking causes lung cancer, so it's a criteria that rarely applies to human exposures that are causal … It's part of the Hill criteria … [but] [i]t's really totally irrelevant. If it were the Hannah Gardener criteria, specificity would not be included. That's sort of a widely-held belief among epidemiologists that of all of the criteria especially, it is most often very — I can't even think of an example, actually, where off the top of my head it does apply in a situation where you have a causal association.

(Gardener Depo., 339: 21-25; 340:1-6, 11, 22-5; 341:1-6.) At first glance, her opinion the specificity factor is "almost never applicable" is somewhat at odds with the Reference Manual, which says "[t]he vast majority of agents do not cause a wide variety of effects." (Reference Manual, pp. 605-606.) But the Manual gives the example of asbestos exposure — no evidence shows asbestos causes cancers besides mesothelioma, lung cancer, and perhaps "one or two other cancers" — arguably proving Dr. Gardener's point that *one* agent is rarely associated with only *one* disease. (*Id.* at p. 606.) The Manual also echoes her smoking example but explains "one good reason" why tobacco's health consequences "do not require specificity": tobacco and cigarette smoke are not single agents but consist of "numerous harmful agents." (*Ibid.*) "Thus, whereas evidence of specificity may strengthen the case for causation, lack of specificity does not necessarily undermine it where there is a good biological explanation for its absence." Ultimately, Dr. Gardener's statement on specificity as applied to her opinion in this case, however, is not illogical and does not render unreliable her overall Bradford Hill analysis.

b. Previous Statements

Defendants contend that Dr. Gardener has previously written about how ASD commonly develops during gestation or shortly after birth, but contradicted herself in her deposition, "steering so wildly in the other direction as to assert that full grown adults aged 30 or more can, for the first time, develop the brain abnormalities that give rise to ASD…." (Motion Brief, 49:11-14.) Defendants argue this evidence shows she has not employed the same rigor in this case as she employs in her profession.

In 2014, for example, Dr. Gardener co-wrote a paper entitled "Perinatal and Neonatal Complications in Autism Etiology." (Mojibi Decl., Exh. 44, p. 1.) It begins: "The perinatal time period, which encompasses the 5 months before to the 1 month after birth, is increasingly recognized as key in autism's etiology. Critical phases of brain development occur during fetal development through early postnatal life, and alterations in brain development are thought to be involved in autism." (*Ibid.*) She co-wrote another paper in 2009, "the first quantitative review and meta-analysis of the association between maternal pregnancy complications and pregnancy-related factors and risk of autism," that says, "[a]lthough the distinctive neuropathology [of ASD] remains elusive, studies have shown macroscopic, microscopic and functional brain abnormalities. These brain abnormalities suggest that the aetiologically relevant period may be *in utero* because the pathogenesis may begin during the prenatal period." (Mojibi Decl., Exh. 45, p. 1.)

Dr. Gardener did not contradict her previous writings. The testimony Defendants cite was her response to an irrelevant hypothetical question: "Do you believe that a 30-year-old who is not autistic can be exposed to a chemical or substance or heavy metal and because of that develop autism?" (Gardener Depo., 269:20-23.) Adult ASD was not the subject of either her opinion or the studies upon which she based opinion, nor is adult-ASD causation or diagnosis at issue in this case. She did say that people are often diagnosed with ASD as adults, sometimes aged 30 years or older. (*Id.* at 268:12-16.) She also said "we don't really sort of define when people develop autism," but instead define autism by when people start show behavioral symptoms, which can change over time, appear, disappear, and then reappear. (*Id.* at 269:24-25; 270:1-10.) But she said nothing to contradict her previous writings about the importance of early life in ASD etiology.

Dr. Gardener's previous writings do not show her opinion in this case is unreliable.

c. Issues with Report Preparation

Defendants argue Dr. Gardener could not answer basic questions about the studies she cited in her Report, implying that counsel prepared it for her or she simply copied Dr. Ritz's Report. In her Report, she cited the Kim et al. (2016) study, for example, as a prospective cohort study that observed a "strong" association between lead and ASD behaviors, and the Skogheim et al. (2021)

study that found a "non-linear association between maternal blood arsenic during pregnancy and offspring ASD risk." (Gardener Report, pp. 29, 32.) During her deposition, however, she had "no idea what the Kim study is," the name Skogheim "did not ring a bell," and she had not read her Report again after November 12, over a month before her deposition on December 16. (Gardener Depo., 304:3-7, 309:22-25, 312:10-22.)

Plaintiff protests that Defendants did not afford Dr. Gardener an opportunity during her deposition to read and review the studies when asked about them. Indeed, given the number of studies that form the basis for her opinion, some of the questions asked of her were quite specific — for example, "whether or not any measurement of heavy metals in the blood was taken during infancy or early childhood in the Kim study?" (Gardener Depo., 305:25; 306:1-2.) To answer this question, Dr. Gardener would have needed to recall the Kim study by name and the biomarkers it had measured — a difficult task to perform on the spot. She testified that she had "no recollection of the details" of the Kim study. (*Id.* at 306:3-7.)

On the other hand, she might reasonably have been expected to recognize the names of the studies she cites in her Report and, as Defendants pointed out on the record, an expert witness must generally be "sufficiently familiar with the pending action to submit to a meaningful oral deposition concerning the specific testimony, including an opinion *and its basis*, that the expert is expected to give at trial." (Code Civ. Proc., § 2034.260, subd. (c)(4), italics added.) At this stage, however, the Court's "circumscribed inquiry" is limited to whether Dr. Gardener based her opinion on "matter of a type on which an expert may not reasonably rely" and whether the matter logically supports her opinion. (*Sargon, supra,* 55 Cal.4th at pp. 771-772.) Her failure to recall details of studies during her deposition goes to the weight of her opinion, not its admissibility.

3. Dr. Aschner

Defendants argue Dr. Aschner, the toxicologist, should not be allowed to testify for four reasons: (a) he is not qualified to review epidemiological data, (b) the data does not show an association between heavy metals and ASD; (c) his opinion is speculative, and (d) he improperly equates ASD-like symptoms with clincal ASD.

a. Qualifications

Defendants argue Dr. Aschner's deposition revealed he "lacks a basic understanding of epidemiological principles and the rules for using epidemiology" and "ma[de] no pretense of conducting a Bradford Hill analysis or otherwise engaging in a reproducible method for assessing causation." (Motion Brief, 51:14-15, 26-27.)

While Dr. Aschner is a toxicologist, not an epidemiologist, the two disciplines lean on each other, "often go[ing] hand in hand with assessments of the risks of chemical exposure, without artificial distinctions being drawn between them." (Reference Manual, pp. 657-658.) His opinion partly relies on epidemiological studies. He began by reviewing the "relevant scientific literature, including animal studies and epidemiological papers," and writes that "discussion of a biological mechanism" by which an exposure causes a disease — the subject of his opinion in this case — must be founded upon "reliable scientific evidence of an association…." (Aschner Report, pp. 10, 12.)

Defendants' argument is based on his deposition testimony. He gave an unclear definition of a case-control study, defining it as "mostly case reports … you look specifically at one individual and potential exposures" and then, moments later, said "a case control is not a case report. They're different because case report refers only to one individual." (Aschner Depo., 94:7-13, 95:3-6.) He also said that when reviewing epidemiological studies, he did "not try to parcel out" the studies by their design, "whether they are case reports, whether they are cross-sectional or whether they are ecological studies. I did not do that because, again, it's not my expertise." (Aschner Depo., 95:7-11.) Assuming he meant he did not consider study design, his statement is a potential concern; a study's design, as discussed, can have a serious impact on its findings and whether the findings can reliably support the "temporality" and "strength of association" Bradford Hill factors, among others. His testimony would also conflict with his Report, where he wrote that he "considered the benefits and limitations of observational epidemiology in general, as well as the strengths and weaknesses of specific epidemiological studies prior to arriving at my conclusions." (Aschner Report, p. 12.) And though Plaintiff argues that Dr. Aschner merely

"supplement[ed]" his "causation opinions" with epidemiological evidence, he both discusses epidemiological studies at length in his Report and expressly bases his opinions on epidemiological studies' findings. (Opposition Brief, 40:23-24.) For lead and ASD, for example, he writes that "[a] large body of epidemiological data demonstrates the causal association between lead exposure and ASD," and then spends several pages discussing these studies. (Aschner Report, pp. 29-33.)

Defendants' argument exposes a broader issue: the scope of Dr. Aschner's opinion is unclear. One opinion in his Report is that "exposure to arsenic, mercury, and lead can cause ASD in children," "supported by a wealth of epidemiological data and the toxicological profile of these heavy metals." (Aschner Report, p. 9.) He testified, however, that his opinion was limited to only one Bradford Hill factor, biological plausibility. "[E]pidemiology is not my expertise. I was asked to look at biological plausibility." (Aschner Depo., 98:18-20.)

A few factors, however, weigh in favor of admitting Dr. Aschner's more-limited opinion on biological plausibility. As an initial matter, it is not clear he meant to say he did not consider study design. In his Report, he recognized and discussed the importance of study design, noting, for example, the Doherty et al. (2020) study had "etiological relevance" as a prospective cohort study that measured arsenic exposure "pre-diagnosis." (Aschner Report, p. 25.) He has also written about epidemiological studies and their findings in peer-reviewed, published articles, suggesting by not "parcel[ing] out" studies he simply meant he did not follow Drs. Ritz and Gardener and categorize by design studies mentioned in his Report. (Esfandiary Decl., Exh 62 ["The Effect of Lead Exposure of Autism Development"]; Exh. 63 ["Environmental influence on neurodevelopmental disorders: Potential association of heavy metal exposure and autism"].)[18]

Most importantly, although the findings of epidemiological studies provide a background for his opinion, its logic is not affected by the studies' designs. Unlike Drs. Ritz and Gardener, he does not interpret or analyze the studies' findings; he instead explains toxicologically *how* an association could plausibly be causal — *how* heavy metals could plausibly affect biological

[18] Plaintiff also notes Dr. Aschner did not solely look at epidemiological studies; for example, he also considered animal studies.

mechanisms and result in ASD — an opinion that, to be logical and reliable, does not require an epidemiologist's knowledge of study design. "'Biological plausibility' … is only a subsidiary consideration in the larger question of general causation." (*Viagra, supra,* 424 F.Supp.3d at p. 791.)

Dr. Aschner's biological plausibility opinion is not barred by *Sargon*. He may not, however, testify as an expert epidemiologist. Dr. Aschner admits he is not an epidemiologist and did not conduct a Bradford Hill analysis. He therefore may not opine that epidemiological studies, analyzed via the Bradford Hill factors, show heavy metals can generally cause ASD and ADHD.

b. No Association

Defendants argue Dr. Aschner should not be allowed to testify because "the human evidence is insufficient" to support an association. (Motion Brief, 52:8-9.) This is Dr. Fombonne's first point and is addressed above.

Defendants' authority is distinguishable. (*In re Bausch & Lomb, Inc. Contact Lens Solution Products Liability Litigation* (D.C. S. Carolina, 2009) 2009 WL 2750462.) The expert in that case based her general-causation opinion on in vitro tests, the results of which she then extrapolated to "real world causation," even though she and the defendant's experts "agree[d] that in-vitro tests are only the first step, and that animal studies followed by human trials are necessary to determine applicability of an hypothesis to humans." (*Id.* at *12.) The in vitro tests "suggest[ed]" it was biologically plausible that contact-lens solution caused eye infections, but plausibility alone was "insufficient to demonstrate causation." (*Ibid.*) "While [the expert's] biological theory may be exactly right, at this point it is merely plausible, not proven, and biological possibility is not proof of causation…." (*Id.* at *12 [citing *In re Accutane Products Liability* (M.D. Fl. 2007) 511 F.Supp.2d 1288, 1296].) The expert's testimony was inadmissible under *Daubert*.

Here, in contrast, Dr. Aschner does not opine that because it is biologically plausible, heavy metals can cause ASD — essentially bootstrapping "heavy metals plausibly cause ASD" into "heavy metals cause ASD." His instead opines that causation is biologically plausible — "a

subsidiary consideration in the larger question of general causation." (*Viagra, supra,* 424 F.Supp.3d at p. 791.)

c. Speculative Opinion

The court excludes speculative expert opinions. (*Sargon, supra,* 55 Cal.4th at p. 771-772.) Plaintiff's general-causation theory is that heavy-metal exposure can cause ASD and ADHD, and Dr. Aschner opines this theory is biologically plausible.

Defendants argue Dr. Aschner's opinion is speculative because the biological mechanisms he describes in his Report "are not specific to ASD or ADHD … or even the human brain or neurological injury." (Opposition Brief, 53:15-16.) They cite his opinion that "arsenic activates p38 mitogen -activated protein kinase (P38 MAPK) … leading to neuronal cell death (Karri et al., 2016)." (Aschner Report, p. 22.) "MAP kinase signaled pathways," he testified, are a "very basic biological function, a signaling pathway … implicated in many [other] diseases" besides ASD — Parkinson's disease, Alzheimer's disease, various forms of cancer, renal, digestive, and cardiovascular diseases — akin to "oxidative stress," another mechanism he identified as a plausible ASD causal mechanism, which similarly "happens at all ages and … many things cause it." (Aschner Depo., 242:7-10, 274:6-25, 275:1-15, 276:4-6.) Defendants argue these are "catch-all mechanisms that effectively prove everything and nothing." (Opposition Brief, 53:27-28.)

Defendants' argument that Dr. Aschner does not identify a biological mechanism "unique to ASD" is misplaced. (Aschner Depo., 243:24-25, 244:1-2 ["oxidative stress … It's not specific to anything unique to ASD?"].) The Bradford Hill "plausibility" factor is not whether heavy metals can biologically cause ASD and ASD only — it is whether a causal relationship is plausible based upon "existing knowledge about the mechanisms by which the disease develops." (Reference Manual, p. 604.) Merely because Dr. Aschner identifies biological mechanisms that plausibly cause other diseases — that heavy metals have many biological effects ("[t]here's a lot of other mechanisms that are affected by arsenic," for example) — does not mean his opinion as to heavy metals and ASD is illogical or speculative. (Aschner Depo., 248:2-4.)

d. Symptoms

Defendants' final argument is essentially Dr. Fombonne's fourth point — Dr. Aschner considered whether heavy metals can biologically cause certain symptoms, but these symptoms are not logically equivalent to an ASD or ADHD diagnosis. As noted above, the Court is not persuade by that argument.

4. Dr. Kevin Shapiro

Defendants argue Dr. Shapiro's opinion is speculative because he offers only "an inventory of theories by which heavy metals *could* interfere with certain biological mechanisms that *may* be involved in the development of symptoms that overlap with some ASD symptoms." (Motion Brief, 56:1-4.) But they misstate his opinion, which he summarized as: "Heavy metals are toxic to the brain and have a measurable and demonstrable impact on neurodevelopment …. [a]nd … the mechanisms by which they affect neurodevelopment are similar and in many cases the same as the biological mechanisms that have been implicated in Autism Spectrum Disorders." (Shapiro Depo., 119:7-16.) His opinion, like Dr. Aschner's, is limited to one Bradford Hill factor, biological plausibility, not the broader question of whether heavy metals can contribute to ASD and ADHD.

"Mere possibility alone is insufficient to establish [causation]," Defendants argue, citing *Jones v. Ortho Pharmaceutical Corp.* (1985) 163 Cal.App.3d 396, 402. But *Jones* was the appeal of a motion for nonsuit following trial, and the court held the experts' "conjectural and ambiguous testimony … that the ingestion of the drug may have had some effect on the development or progression of the disease" was insufficient evidence to support the verdict for the plaintiff. (*Ibid.*) "That there is a distinction between a reasonable medical 'probability' and a medical 'possibility' needs little discussion … A possible cause only becomes 'probable' when, in the absence of other reasonable causal explanations, it becomes more likely than not that the injury was a result of its action." (*Id.* at p. 403.) Unlike the *Jones* experts, who opined on both general and specific causation, Dr. Shapiro's opinion is limited a subsidiary issue within general causation — whether heavy metals can plausibly cause ASD, given what is known "about the mechanisms by which the disease develops." (Reference Manual, p. 604.) His opinion is not speculative.

IV. Conclusion

The Court finds that, consistent with the Court's gatekeeping role under *Sargon*, Plaintiff's experts' opinions that heavy metals are capable of being a substantial factor in causing ASD and ADHD are admissible.

Dated: _____ _____

AMY D. HOGUE
JUDGE OF THE SUPERIOR COURT