UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

IN RE: BABY FOOD PRODUCTS LIABILITY LITIGATION	Case No. 24-MD-3101-JSC MDL 3101 Hon. Jacqueline Scott Corley
This document relates to: ALL ACTIONS	**JOINT STATEMENT PURSUANT TO PRETRIAL ORDER NO. 3** Date: June 20, 2024 Time: 11:00 a.m. PT Location: Courtroom 8 19th Floor 450 Golden Gate Ave. San Francisco, CA 94102

Pursuant to Pretrial Order No. 3 (ECF No. 148), the Parties submit this Joint Statement in preparation for the June 20, 2024 Case Management Conference:

I. The Proposed Scope of the General Causation Expert Proceeding

The parties were unable to reach agreement on the proposed scope of the general causation expert proceeding, and therefore submit their respective positions below.

Plaintiffs' Proposal:

> Can Plaintiffs present admissible expert testimony that the ingestion of toxic heavy metals (aluminum, arsenic, cadmium, lead, and/or mercury) in defendants' baby food products can cause neurodevelopmental harm sufficient to result in a diagnosis of ASD and/or ADHD?

Defendants' Proposal:[1]

> Can Plaintiffs present admissible expert testimony under Rule 702 that consumption of any of Defendants' baby food products during infancy and/or

[1] Unless otherwise stated, "Defendants" as used herein refers to defendants that manufacture baby food products—i.e., Beech-Nut Nutrition Company ("Beech-Nut"), Gerber Products Company ("Gerber"), Hain Celestial Group, Inc. ("Hain"), Nurture LLC ("Nurture"), Plum, PBC ("Plum"), and Sprout Foods, Inc. ("Sprout")—and does not include retailers, parent companies, or other entities that may be named as defendants in one or more cases.

early toddlerhood can cause Autism Spectrum Disorder ("ASD"), with or without ADHD?

A. Plaintiffs' Position

Defining the scope of the general causation question is critical because it guides what underlying scientific evidence "fits" the claims at issue. It would seem then, based on the asymmetrical burden carried by Plaintiffs in civil litigation, that this question should be largely determined by Plaintiffs. Ultimately it is Plaintiffs who must decide the theory of causation they will pursue at trial and it is Plaintiffs who bear the burden of proving that theory with admissible expert testimony. Thus, it would make little sense to foist upon Plaintiffs a causation theory they do not intend to pursue simply because Defendants happen to prefer it.

Here, Plaintiffs intend to pursue a theory of causation that is consistent with the California state court litigation and the general discovery that has been conducted to date. Specifically, Plaintiffs intend to prove that ingesting the toxic heavy metals found in Defendants' baby food products can cause neurodevelopmental harm, which, in turn, results in the constellation of symptoms diagnosed as autism spectrum disorder (ASD) and/or attention deficit hyperactivity disorder (ADHD). To prove this theory of causation, Plaintiffs will present highly nuanced expert testimony on various topics, including:

- The symptoms that result in an ASD and/or ADHD diagnosis, and the unique aspects of each "disorder";
- The various neurotoxic effects of aluminum, lead, arsenic, mercury, and/or cadmium, and the known mechanisms by which these toxins damage neurodevelopment and cause other injuries;
- How toxic heavy metals cross the blood brain barrier and cause brain damage;
- How toxic heavy metals interfere with the complex neural connections being made in the brain of an infant and impair neurodevelopment;
- Why an infant's physiology is uniquely susceptible to absorption of toxic heavy metals and transmission of those metals to the brain;
- How exposure to toxic heavy metals at a young age can, in later years, lead to

different physical brain structures and grey matter development;

- How epidemiological studies show that exposure to toxic heavy metals at a young age, based on various known biomarkers (blood, hair, urine, teeth, brain tissue, etc.) increases the risk that a child will be diagnosed with ASD, ADHD, and/or experience the behavioral issues associated with those disorders;
- How genetics in combination with environmental factors work in tandem in leading to the development of ASD and ADHD;
- How toxic heavy metals have been measured and found in Defendants' baby food products and at what levels;
- How the "other ingredients" in Defendants' baby food products do not mitigate the toxic effect of the heavy metals found in the products at issue; and
- How the levels of toxic heavy metals found in Defendants' baby food products can increase the body burden of toxic heavy metals in infants and lead to, for some children, neurodevelopmental harm sufficient to result in an ASD and/or ADHD diagnosis.

The parties met and conferred about what the general causation question should be, and although some agreement was reached, there are three clear differences regarding how this question should be framed: (1) whether the question should include reference to toxic heavy metals, i.e., the injury causing agent at issue; (2) whether the question should reference neurodevelopmental harm, i.e., the alleged injury; and (3) whether the question should include a standalone diagnosis of ADHD. As explained below, Plaintiffs' proposed question tracks Plaintiffs' theory of causation and, thus, should guide the Court's consideration of the admissibility of Plaintiffs' general causation expert opinions.

1. Toxic Heavy Metals Are the Injury Causing Agent At Issue and, Thus, Is at the Core of the Causation Question

The first issue is whether toxic heavy metals should be part of the general causation question. The answer is yes. As the JMPL recognized in its coordination ruling, these cases involve young children who were "***exposed to elevated quantities of toxic heavy metals*** (namely,

arsenic, lead, cadmium, and mercury) from consuming defendants' baby food products and, as a result, suffered brain injury that manifested in diagnoses of autism spectrum disorder (ASD) and/or attention deficit hyperactivity disorder (ADHD)." *In re Baby Food Mktg., Sales Pracs. & Prod. Liab. Litig. (No. II)*, No. MDL 3101, 2024 WL 1597351, at *1 (J.P.M.L. Apr. 11, 2024) (emphasis added). The JPML, in overruling Defendants' objection to forming this MDL, explained:

> All actions share common issues of fact regarding the presence of *heavy metals* in defendants' products, their knowledge of and testing for *heavy metals* in their products, whether the presence of these *heavy metals* could have caused plaintiffs' alleged injuries, and whether defendants adequately warned of the presence of *heavy metals* in their products.

Id. The relationship between the toxic heavy metals in the Defendants' baby food products and the resultant injury caused to the developing brain of an infant stands at the heart of why this MDL was formed and, in turn, general causation.[2]

To be clear, and contrary to Defendants' repeated assertions, this litigation is not an attack on "baby food," nor is it an attack on every product manufactured or sold by these MDL Defendants. Rather, this litigation involves products that contain dangerous levels of heavy metals. Indeed, the evidence will demonstrate that each MDL Defendant sells several baby food products that do *not* contain dangerous levels of heavy metals. Even so, Defendants want the Court to focus on whether "baby food," in general and regardless of heavy metal content, can cause the alleged injuries. That is not Plaintiffs' claim. Plaintiffs do not allege that baby food, generally, causes ASD or ADHD. Baby food is just food. And food uncontaminated with toxic heavy metals is safe. However, some of Defendants' baby food products have alarming levels of heavy metals, levels that science plainly links with neurodevelopmental harm.[3] And, Plaintiffs have some test results demonstrating these dangerous levels from prior discovery, but that data is

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[2] To date, the underlying complaints focus on lead, arsenic, mercury, and, for a few complaints, cadmium. However, as this an MDL and the general causation proceeding should only be done once, Plaintiffs will add aluminum to the Master Complaint in case any plaintiff or future plaintiff intends to also allege brain injury from this well-documented neurotoxic metal.

[3] There are several reasons why the toxic heavy metals are found in some products but not others, to include negligent sourcing, ingredient selection, and contaminated soil.

limited and sporadic. Plaintiffs will provide expert testimony that heavy metals found in some of Defendants' baby food products—foods contaminated with toxic heavy metals—when consumed, can cause damage to the developing brain of an infant. Thus, any consideration of general causation must focus on the ability of toxic heavy metals to cause the alleged brain injuries.

These simple points have been recognized by all courts to consider general causation in this litigation. For example, in California state court, the first court to adjudicate the issue correctly recognized that "general causation…[is] the issue of whether heavy metals can cause ASD and ADHD." *N.C. v. Hain Celestial Group, Inc.*, No. 21STCV22822, 2022 WL 21778549, at *2, n.3 (Cal. Super. Ct. May 24, 2022). Indeed, the court correctly focused the general causation question on the *toxic exposures* at issue: "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." *Id.* at *2. Similarly, the Texas district court that evaluated the admissibility of the plaintiff's experts under the *Daubert* standard recognized that "Hain may not impose a causation burden on the [plaintiffs] that is wholly unrelated to the injury for which they seek to hold Hain responsible—Ethan's *heavy-metal toxicity and resultant brain injuries*." *Palmquist v. Hain Celestial Grp., Inc.*, No. 3:21-CV-90, 2022 WL 18143413, at *2 (S.D. Tex. Dec. 28, 2022)[4] (emphasis added). To be sure, the general causation question proposed by Plaintiffs recognizes that the source of metal exposure stems from consumption of Defendants' baby food products—which will set up the next question, in the context of specific causation, of whether the heavy metal exposure a plaintiff sustained by eating Defendants' products did, more likely than not, play a substantial factor in causing her injuries. This is why Plaintiffs framed the question to focus on exposure to heavy metals "found in defendants' products." This will ensure proper guardrails to a "general causation first" approach and avoid a situation where (should Plaintiffs prevail) Defendants seek a second bite at the apple (like in the *N.C.* case).

[4] The *Palmquist* case, which ultimately resulted in a directed verdict, was recently reversed and vacated by the Firth Circuit, as the trial court lacked subject matter jurisdiction due to an improper removal to federal court. *Palmquist v. Hain Celestial Grp., Inc.*, No. 23-40197, 2024 WL 2720460, at *9 (5th Cir. May 28, 2024).

This is not just semantics. Defining the question without reference to toxic heavy metals transforms the inquiry away from what Plaintiffs intend to prove at trial. Indeed, this is why Defendants do not want the question to reference toxic heavy metals. They want to be able to argue that the overwhelming number of studies demonstrating that exposure to toxic heavy metals in infancy, whether through food, environment, or otherwise, increases the risk of ASD and ADHD are not "relevant" or do not "fit" the question because they are not studies about "baby food." Indeed, this point is underscored below, when Defendants claim that no study shows that baby food consumption causes ASD or ADHD. Of course they do not. No study has ever attempted to examine such a question, because doing such a study would not tell you anything *unless* the study distinguished baby food consumption by some other *underlying exposure*, i.e., toxic heavy metals. All humans consume food, babies or otherwise. Looking at food consumption generally would not reveal a risk. The study would need to quantify underlying exposures, i.e., to toxic heavy metals from food and other potential sources, and determine whether the differential exposures, were associated with the injury. And, it should come as no surprise, that there are hundreds of such studies confirming the association between toxic heavy metal exposure and ASD and/or ADHD using numerous biomarkers measurements.

This "product only" argument was raised, repeatedly, in California state court, and it was rejected. Judge Hogue was clear:

> 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.

NC, 2022 WL 21778549, at *2 n.3. Below, Defendants claim that Judge Riff excluded certain experts in the *NC* case because they did not consider the product as whole—that is misleading. Judge Riff allowed the general causation experts, but indicated that when those opinions were applied in specific causation context, Plaintiffs' experts must account for any potential "beneficial" effects of nutrients in the specific foods the child consumed.

By removing the toxic heavy metal issue from the question, Defendants are attempting to

reframe the inquiry in way that supports their preferred science. But, again, that is not how this process should work. Plaintiffs do not intend to prove that baby food consumption, generally, causes ASD/ADHD—but that consumption of toxic heavy metals in Defendants' baby food products causes neurodevelopmental harm which, for some, may result in an ASD and/or ADHD diagnosis. And, Plaintiffs will further prove that the "other ingredients" in the dangerous baby foods do not mitigate the heavy metal toxicity. If that is what Plaintiffs intend to prove, then that is what this Court should consider in assessing the admissibility of Plaintiffs' expert opinions to that effect—which was the question being addressed in state court. Anything else would, effectively, amount to a strawman; litigating a question or issue that Plaintiffs are not pursuing.

Below, Defendant make a series of spurious arguments. For example, they claim this is a "products liability" case and, thus, the question must be about the products. And, superficially, Plaintiffs agree—it is why Plaintiffs' proposal specifically references the Defendants' products. However, the disagreement is not whether the question should include reference to products; rather, it is about whether it should include reference to the injury causing agent, i.e., toxic heavy metals. And, even under most constrained Defense-friendly reading, excluding reference to the injury causing agent makes little sense. Consider, for example, an asbestos case—it would be silly to frame the question as to whether working with fiberboard causes mesothelioma, without any reference to asbestos. Some fiberboard is safe, and some is not. At issue is whether *asbestos-containing fiber board*, like toxic heavy metal contaminated baby food, can cause the injury.

Below, Defendants claim that this is product-centered inquiry because, in the first California proceeding, Plaintiffs' experts did not address whether the other ingredients in baby food could offset the effects of toxic heavy metals. But, this argument proves Plaintiffs' point. This time around, Plaintiffs' experts will clearly reject the "protective effect of nutrients" as unsubstantiated science that has been rejected by all credible scientific groups—including Defendants' own experts. But, it highlights that the inquiry is not about one Defendants' cinnamon applesauce, but whether a Defendants' products, for a specific Plaintiff, where a substantial factor in causing their injury.

Defendants cite three cases that purport to validate their product-only analysis. The first is

In re Zantac (Ranitidine) Prods. Liab. Litig., 644 F. Supp. 3d 1075, 1108 (S.D. Fla. 2022), where a federal judge excluded various experts related to ranitidine consumption and cancer. There, bound by the Eleventh Circuit's decision in the *Fixodent* cases, the court concluded that the question should focus on whether ranitidine, the drug substance, causes cancer, as opposed the underlying carcinogen, N-Nitrosodimethylamine ("NDMA"). In doing so, the court largely disregarded NMDA epidemiology and focused on ranitidine studies. This is a perfect example of why framing the question matters—and, candidly, why the Zantac MDL got it wrong. Since the MDL ruling, four different courts—in California, Illinois (twice), and Delaware[5]—have disagreed; finding that the question was not simply whether ranitidine causes cancer, but whether the NDMA in ranitidine could cause cancer. The most recent example comes in a thoughtful and detailed order from the Hon. Vivian L. Medinilla, in Delaware Superior Court, where she addressed the Zantac MDL's error in focusing on ranitidine and not the cancer-causing agent, NDMA. *In re Zantac (Ranitidine) Litig.*, No. N22C-09-101 ZAN, 2024 WL 2812168, at *9–10 (Del. Super. Ct. May 31, 2024). Citing Ninth Circuit caselaw and comparing the issue to asbestos, Judge Medinilla noted that the cancer-causing agent at issue was NDMA, not ranitidine—like asbestos in frictionless brake pads—and that, in this case, the "facts here compel the same conclusion … this Court cannot constrain its gatekeeping function solely to the studies related to ranitidine. NDMA's dangers, the science, the studies, and the opinions therein must be given due consideration." *Id.* at *10; *accord In re Ranitidine Cas*es, No. 21CV002172, 2023 WL 2725766, at *9 (Cal. Super. Alameda Cnty. Mar. 23, 2023) (causation question must focus on NDMA).

Defendants also cite two gasoline/benzene cases, to support their claim that the question should only look at products, not the underlying injury-causing chemical: *Burst v. Shell Oil Co.*, Civil Action No. 14-109, 2015 WL3755953, at *10 (E.D. La. Aug. 8, 2014), *aff'd* 650 F. App'x 170 (5th Cir. 2016); *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1156 (E.D. Wash. 2009). However, both cases *strongly support* Plaintiffs' formulation of the question. Those cases

[5] Co-Lead Plaintiffs' Counsel, R. Brent Wisner is also Co-Lead Counsel in the Zantac California JCCP and Delaware proceedings—he was not involved or part of the Zantac MDL.

involved whether the benzene found in gasoline could cause leukemia. In both cases, the courts did not disregard or ignore benzene-specific scientific evidence. *Henricksen*, 605 F. Supp. 2d at 1156 (E.D. Wash. 2009) ("Because gasoline exposure is a source of benzene exposure, evaluations of both gasoline and its toxic component benzene are obviously relevant to the Plaintiffs' case."); *Burst*, 2015 WL 3755953, at *9 ("Because benzene is a known human carcinogen and because all gasoline contains benzene, the Court recognizes that literature pertaining to benzene is generally relevant to the causation question at issue."). Indeed, in *Henricksen*, the court explained that the exposure to benzene in gasoline, like exposures to toxic heavy metals in baby food, were integral to the general causation question: "The general causation question before the court is whether exposure to the benzene-component of gasoline is capable of causing [leukemia]." 605 F. Supp. 2d at 1156. And, in *Burst*, the court echoed Plaintiffs' argument: "This is a toxic torts case where plaintiff alleges that gasoline containing benzene caused her husband's [leukemia]. Accordingly, plaintiff must show general causation—that gasoline containing benzene can cause [leukemia]—and specific causation—that defendants' products caused Mr. Burst's [leukemia]." 2015 WL 3755953, at *1. In both cases cited by Defendants, the injury-causing agent was specifically *included* in the general causation question; just as it should here.

Going down this "baby food product only" rabbit hole, Defendants illustrate the false burdens they seek to impose. Defendants claim that Plaintiffs will need to establish on a "product by product" basis that each product is capable of causing injury. But, such a concept is simply injecting specific causation without any specific plaintiff. Whether the toxic heavy metals in the Defendants baby food products caused any specific plaintiffs' injury will necessarily depend on which products that plaintiff consumed, and whether the toxic heavy metal exposures from those products were a substantial factor in causing the ASD and/or ADHD. *See NC*, 2022 WL 21778549, at *2 n.3. Clearly, to establish liability of any Defendant, for a specific Plaintiff, it will need to be shown that the specific Defendants' negligence was, itself, a cause of the injury. *See, e.g.*, CACI 400 ("That [name of defendant]'s negligence was a substantial factor in causing [name of plaintiff]'s harm."). Below, Defendants argue that Plaintiffs must show that each product was defective and that each defective product caused an injury. But that is an incorrect recitation of

Plaintiffs' burden. Whether sounding in failure to warn or product defect, the law does not require Plaintiff to show that one specific product, itself, caused an injury, but rather that the Defendants' conduct, i.e., failure to warn, design, or negligence, was a substantial factor in causing the injury—and that liability attaches to all the baby food products a specific plaintiff consumed from that Defendant. Put another way, Plaintiffs will prove, in the context of a specific Plaintiff, that the cumulative exposure to toxic heavy metals from consuming a Defendant's specific products was, itself, a substantial factor in causing the injury. But this is a specific causation question, that can only be addressed in the context of the specific foods a Plaintiff consumed by a specific Defendant. To claim, at the general causation phase—untethered to an actual fact pattern—that Plaintiffs must prove that a single baby food product consumed by some hypothetical child for some hypothetical amount of time, by itself, could cause ASD and/or ADHD, completely misses the burden Plaintiffs bear at trial. It's a strawman.

2. Neurodevelopmental Harm that Manifests as ASD/ADHD Diagnosis Is the Alleged Injury in this Litigation

The injury alleged is neurodevelopmental harm, which for some children, rises to the level of being diagnosed as ASD and/or ADHD. Conditions such as ASD and ADHD are defined by the presence of a cluster of behavioral symptoms that are labeled per diagnostic criteria. *See* Ex. 1, ASD and the Environment (NIH, April 2019) ("The term spectrum refers to the wide range of symptoms, skills, and levels of impairment that may challenge those with ASD. Some are mildly impaired by their symptoms, while others are severely disabled."). And, it is generally accepted that the symptoms diagnosed as ASD/ADHD can arise from an interruption of key phases of early brain development. Ex. 2, Sutcliffe, J. (2008) ("The brain continues to develop long after birth…and environmental input play an important role in subsequent development. Synapses (connections between neurons) mature partly as a function of experience-dependent neuronal activity and of the gene expression changes that accompany it."); Ex. 3, Zoghbi (2003) ("ASD result[s] from disruption of postnatal or experience-dependent synaptic plasticity."). Plaintiffs allege that early life toxic heavy metal exposure is one of the ways in which neurodevelopment can be interrupted to—as recognized by the Centers for Disease Control—cause the cluster of

behavioral symptoms that can be diagnosed as ASD and/or ADHD. Ex. 4, Lead Tox Profile at 133 ("The following neurobehavioral effects in children have been associated with PbB…Altered mood and behaviors that may contribute to learning deficits, including *attention deficits, hyperactivity, autistic behaviors*, conduct disorders, and delinquency." (emphasis added)).

Against this background, omitting reference to neurodevelopment harm distorts the nature of Plaintiffs' allegations—namely, as noted by the JPML, that exposure to metals causes "*brain injury* that manifested in diagnoses of autism spectrum disorder (ASD) and/or attention deficit hyperactivity disorder (ADHD)." *In re Baby Food Mktg.*, 2024 WL 1597351, at *1. ASD and ADHD diagnoses reflect a constellation of neurodevelopmental harm, i.e., brain injury. Indeed, there are dozens of studies showing that exposing an infant's brain to toxic heavy metal causes various types of neurodevelopmental harm, some of which manifest as an ASD or ADHD diagnosis. However, sometimes, harm is observed, even if the harm does not rise to the level of a full-fledged diagnosis, i.e., lead exposure linked to autistic behaviors as opposed to a full-fledged diagnosis of autism. In other words, because these diagnoses are found on a *spectrum*, it is important to consider the injuries along that spectrum of neurodevelopmental harm. Hence, the concept should be included in the question presented. To suggest that these cases do not allege neurodevelopmental harm is simply not true. In the anticipated Master Complaint, Plaintiffs will make these allegations clear to avoid any confusion.

3. ADHD, Without ASD, Is a Standalone Injury that Should Be Addressed in the General Causation Context

The last issue centers on whether the question should include a general causation question about ADHD as a standalone injury. Defendants insist that this case is about ASD "with or without ADHD". This misses the mark. While the cases currently coordinated before the Court involve allegations that exposure to metals from consumption of baby foods caused the Plaintiffs to develop ASD, or ASD with ADHD, Plaintiffs' counsel represents hundreds of severe ADHD cases, without any ASD diagnosis. Although they have not yet been filed, this issue should be addressed now, as this Court assesses the admissibility of Plaintiffs' general causation expert opinions. Indeed, the JPML was clear that this MDL was to focus on whether the metals in

Defendants baby food cases caused brain injury that manifested as "diagnoses of autism spectrum disorder (ASD) ***and/or*** attention deficit hyperactivity disorder (ADHD)." *In re Baby Food Mktg.*, 2024 WL 1597351, at *1 (emphasis added). Cases involving just ADHD were always contemplated. Moreover, consideration of standalone ADHD injuries was also done in California state court. It thus makes little sense to carve out from the general causation proceeding general causation of ADHD. This would result in a waste of time and resources re-litigating general causation at a later point focused just on ADHD.

B. Defendants' Position

A threshold legal issue in this MDL, as in all products liability MDLs, is whether Plaintiffs can meet their burden under Fed. R. Evid. 702[6] of proffering reliable and relevant expert opinions on general causation—in this case, on whether any of Defendants' commercial baby food products are capable of causing the specific injury at issue, Autism Spectrum Disorder (with or without accompanying ADHD). If Plaintiffs' theory of causation fails when considered at a general (*i.e.*, population) level, the litigation need go no further; Plaintiffs necessarily cannot demonstrate through reliable evidence that any individual Plaintiff's ASD was caused by any Defendant's product(s). Accordingly, Defendants believe the appropriate question for purposes of an initial general causation proceeding is:

> Can Plaintiffs present admissible expert testimony under Rule 702 that consumption of any of Defendants' baby food products during infancy and/or early toddlerhood can cause Autism Spectrum Disorder ("ASD"), with or without ADHD?

This formulation tracks the one contemplated by the Court at the initial case management conference on May 16, 2024. *See* Hearing Tr. at 16:14-16 ("So generally, at a very high level, the question is can Defendants' product cause Autism Spectrum Disorder, ADHD, in infants, right, that's at the high level[.]"). It also serves several important goals and avoids the problems that would be created

[6] Rule 702 was amended effective December 1, 2023. The amendment provides, among other things, that the proponent of expert testimony must "demonstrate to the court that it is more likely than not" that the requirements of subsections (a)-(d) are met. The Advisory Committee Note to the revised rule observes that many courts had not applied the Rule as originally intended, and thus the Rule was amended to clarify the burden on the proponent of the evidence.

by Plaintiffs' proposed framing of the question, as discussed further below.

First, it appropriately focuses the inquiry on consumption of Defendants' baby food products, which are what Plaintiffs allege caused their injury, and on the specific injury all Plaintiffs allege – ASD, with or without concurrent ADHD. Second, it ensures that expert opinions address the timing of baby food consumption—infancy and early toddlerhood—as Plaintiffs' experts must reliably show that exposures in that specific window of time can cause ASD, not simply precede a diagnosis of ASD, which in the United States is frequently not until after three years of age. Third, it recognizes that "baby food" is not a single product from a single company, but rather a myriad of products from at least seven different Defendant companies, and thus Plaintiffs' expert causation opinions must be particularized as to which specific baby foods or categories of foods sold by which Defendants allegedly can cause ASD.

Defendants envision a process followed by many products liability MDL courts, including those in this district,[7] whereby before the parties engage in full-blown, costly discovery, the Court would oversee a threshold proceeding on general causation, in which both sides would (1) serve Rule 26 expert reports limited to the general causation question, as defined above, (2) depose those experts (if desired), and (3) file Fed. R. Evid. 702 motions to exclude, challenging the reliability of the experts' opinions. After that, the Court would convene a hearing—perhaps in coordination with the judge presiding over the parallel California JCCP proceeding—to hear argument on the motions.

If the Court were to grant Defendants' motions, leaving Plaintiffs with no admissible general causation evidence, the Court would enter summary judgment on all of Plaintiffs' claims, effectively ending the MDL; if the Court were to deny Defendants' motions in such a way that Plaintiffs had admissible general causation testimony, the parties would proceed into discovery on other issues

[7] *See, e.g.*, *In re Viagra/Cialis*, 424 F. Supp. 3d 781, 799 (N.D. Cal. 2020) (Seeborg, C.J.); *In re Viagra/Cialis*, No. 3:16-md-02691, ECF No. 1021 at 2 (N.D. Cal. Apr. 8, 2020); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 3:05-md-01699, ECF No. 1098 at 1-4 (N.D. Cal. Mar. 16, 2007) (Breyer, J.); *In re Incretin Mimetics Prods. Liab. Litig.*, No. 3:13-md-02452, ECF No. 325 at 1 (S.D. Cal. Feb. 18, 2014); *In re Mirena IUD Prod. Liab. Litig.*, 713 F. App'x 11, 14 (2d Cir. 2017); *In re Nexium (Esomeprazole) Prods. Liab. Litig.*, No. 2:12-ml-2404, ECF No. 89 at 7 (C.D. Cal. Mar. 11, 2013); *In re Acetaminophen Prods. Liab. Litig.*, 1:22-md-3043, 2023 WL 8711617 (S.D.N.Y. Dec. 18, 2023).

and selection and workup of bellwether cases. In another recent MDL involving claims that exposure to a product (in that case, acetaminophen/Tylenol) could cause ASD and/or ADHD, Judge Cote in the Southern District of New York followed this same process. *See In re Acetaminophen*, 2023 WL 8711617, at *1–2.

1. The Proper General Causation Question Must Focus on Baby Food Products

Plaintiffs present the question as whether "*ingestion of toxic heavy metals* found in defendants' products" can cause certain injuries. This is a *products* liability MDL; the products at issue, as reflected in the very caption of the litigation, are Defendants' baby food products. "Toxic heavy metals" are not a product, and baby foods are not simply delivery vehicles for feeding metals to children. Indeed, as all parties agree, all humans are exposed to heavy metals as early as in the womb from any number of sources, including air, water, soil, breast milk, and even what their mothers' exposures were before conception. Plaintiffs here make a very specific claim: that they developed ASD because they ate certain of Defendants' baby food products. Those products, individually or in various combinations, consist of multiple ingredients—fruits, vegetables, and grains that are grown on farms, and (for some products) supplements to promote healthy brain development, such as iron, calcium, and vitamins. These foods (carrots, bananas, sweet potatoes, squash, and the like) are not simply "other ingredients," as Plaintiffs suggest above – as if heavy metals rather than food are the primary ingredients. These foods are the products themselves. In order to proffer reliable expert testimony on general causation, Plaintiffs must address the question whether eating any of these baby food *products* during infancy or early toddlerhood, taking account of all the food ingredients, nutrients, and other constituents they may contain, can cause ASD, with or without ADHD.

As Plaintiffs indicate above, their experts will offer opinions that some of these baby food products can cause ASD because the fruits, vegetables, and grains they are made with naturally take up some trace amount of one or more heavy metals during the growing process. But, as Judge Riff found in the first baby food lawsuit to proceed to judgment in California, the plaintiff (represented by the same lead counsel the Court appointed here) was required to produce experts who offer opinions specific to *baby food products*, not heavy metals alone. As Judge Riff noted, Defendants'

baby food products contain a variety of ingredients, including vitamins and antioxidants that both promote healthy brain development and inhibit human absorption of heavy metals.[8] Thus, contrary to Plaintiffs' suggestion, Judge Riff specifically found that plaintiff's experts in that case did not offer admissible opinions because they failed to address the *products*—as opposed to simply any heavy metals that might be present in them—in answering the *general causation* question. *Id.* at 26:9–10 (plaintiff's experts failed to "consider[] the mixture as a mixture for the so-called general causation question"). This failure to consider the products as a whole as a matter of general causation was one reason why Judge Riff excluded the testimony of certain of plaintiff's causation experts and granted Defendants' summary judgment motion. Many federal courts similarly have held that in a toxic tort products liability matter, plaintiffs must present reliable expert testimony that the product as a whole—not just a constituent part of it—can cause the injury alleged. *See, e.g.*, *In re Zantac (Ranitidine) Prods. Liab. Litig.*, 644 F. Supp. 3d 1075, 1108 (S.D. Fla. 2022) ("The Court resolves the parties' dispute by framing the general causation question on the product the Plaintiffs consumed, ranitidine, in lieu of the mechanistic theory by which the Plaintiffs seek to prove their case, NDMA."); *Burst v. Shell Oil Co.*, Civil Action No. 14-109, 2015 WL3755953, at *10 (E.D. La. Aug. 8, 2014), *aff'd* 650 F. App'x 170 (5th Cir. 2016); *Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1156 (E.D. Wash. 2009). In addressing this case law showing that the product itself must be the focus of the general causation question, the very language from the cases that Plaintiffs quote demonstrates that point—for example, in the gasoline cases, the courts repeatedly stated that the general causation inquiry must be centered on *gasoline*. Plaintiffs continue to confuse the inquiry, citing portions of these opinions stating that studies involving the alleged contaminant (in the gasoline cases, benzene) might be relevant in *answering* the general causation

[8] *See* Hr'g Tr. (8/24/23) at 26:4–10, *N.C. v. Hain et al.*, 21STCV22822 (Cal. Super. Ct., Los Angeles Cty.) ("[H]ere the court finds that there is enough information, evidence, of potential inhibition of absorption of some or all of the heavy metals in controversy by virtue of other components of the baby food mixtures to have required someone on the plaintiff's side to have considered the mixture as a mixture for the so-called general causation question"); *id.* at 27:5–14 (describing the failure of plaintiffs' experts to "confront" the "real studies and real regulatory statements to the effects or potential effects of these inhibitory or antagonistic toxicological properties" as a "methodological failure of significant import").

question—but, as the courts plainly held, the question itself must focus on the overall product.[9]

In seeking to center the general causation inquiry on heavy metals, Plaintiffs cite the JPML's order establishing this MDL, but the JPML did not make any determination about the appropriate general causation question for the proceedings, and in any event the very language Plaintiffs quote repeatedly refers to common issues regarding Defendants' "products." The JPML created a baby food products MDL, not a heavy metals MDL.[10]

Plaintiffs also claim they should be the ones to frame the general causation question because they have the burden of proof, and they should be able to answer whatever question they choose. This makes no sense. What Plaintiffs must prove, with competent expert testimony, to satisfy their burden on general causation, is a question of *law* for the Court to decide. That is exactly how Judge Riff treated it in the *NC v. Hain* case, and that is one reason why the plaintiff in that case lost on summary judgment—the plaintiff had no reliable expert testimony (indeed no expert testimony at all) on whether baby food products could cause ASD. Plaintiffs are seeking to frame the general question to *escape* their required burden of proof, not satisfy it.[11]

In addition to the above problems with Plaintiffs including "heavy metals" in the question, Plaintiffs propose to define "heavy metals" to include not only lead, arsenic, and mercury, but also

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[9] In arguing otherwise, Plaintiffs offer the example of asbestos in fiberboard. But asbestos is treated by courts and under state laws as a unique product, where a plaintiff has a different, and more lenient, burden of proof on causation.

[10] Indeed, a heavy metals MDL could never be created because it would be boundless, given all of the sources of metals exposure that exist in the world and that humans are exposed to from well before birth. This point also is highlighted by the fact that Plaintiffs continue to add new "heavy metals" into the mix (such as aluminum), a process that effectively could go on *ad infinitum* and, in each case, if Plaintiffs' approach were followed, require a new causation inquiry.

[11] Plaintiffs quote an order from Judge Hogue, who was the initial judge overseeing the *NC v. Hain* case, concerning the general causation *Sargon* issue she initially addressed. Plaintiffs fail to note that Judge Hogue decided to divide the general causation inquiry into two parts. The first was an initial inquiry that addressed only heavy metals, in which the parties were prohibited from addressing baby food products—that is the order Plaintiffs cite. But Judge Hogue recognized that Plaintiffs would then need to satisfy the second hurdle in the general causation process she set up, and show that Defendants' *baby food products* could cause ASD. As Judge Riff later held, Plaintiffs could not satisfy that burden because their causation experts offered no opinions about those products.

aluminum and cadmium. None of the complaints filed to date in this MDL alleges that aluminum or cadmium in baby foods caused the plaintiff's ASD (or any other injury). Defendants object to the inclusion of metals like cadmium and aluminum that have not been placed at issue in this litigation.

Plaintiffs' fundamental problem in this litigation lies in the fact that there are no epidemiological studies, or any studies of any kind, that have found that consuming baby food products can cause or increase the risk of ASD and/or ADHD. That is indeed a major—and, Defendants believe, ultimately dispositive—problem with Plaintiffs' claims. But Plaintiffs cannot sidestep that reality by reformulating the general causation question. If Plaintiffs' experts can muster only studies about heavy metals, unconnected to baby foods, to support their opinions, they will be free to opine that those studies nonetheless are relevant to the causation question. Whether such opinion, based on extrapolation from heavy metal studies to Defendants' baby food products, is reliable is a classic Rule 702 question, addressed in many products liability MDLs as part of general causation proceedings. *See, e.g., In re Zantac (Ranitidine) Prods. Liab. Litig.*, 644 F. Supp. 3d at 1217-21 (excluding general causation experts under Rule 702 in part because they relied on extrapolations from studies involving the alleged toxic agent in a medication). Nothing about Defendants' framing of the question precludes Plaintiffs from making whatever arguments they want to offer about the scientific literature relating to heavy metals, including all the arguments about the complete absence of any studies on baby food products that they raise above. And if, as Plaintiffs suggest above, their experts intend to opine that the abundant vitamins, minerals, and nutrients contained in baby food products, which all agree are essential for healthy brain development, "do not mitigate the toxic effect of the heavy metals found in the products at issue," so be it; at least that is an opinion about the products, which Defendants will challenge, and the Court will be able to evaluate, under Rule 702.

2. The Proper General Causation Question Also Must Take Into Account the Differences in the Many Baby Food Products at Issue

Plaintiffs' proposed question (using the collective phrase "defendants' baby food products") seeks to avoid product-by-product proof of general causation, even though the law requires it. There

are (so far) seven manufacturers and private brand sellers of commercial baby food products that have been named as defendants in cases in the MDL. These Defendants are separate companies, with different ingredient sources, product formulas, and product offerings intended for different stages of infant and toddler development. Indeed, each company on its own produces dozens, or in some cases hundreds, of unique baby food products to meet different dietary needs during different developmental time frames, and that may contain different trace levels and types of heavy metals, if any at all. Plaintiffs cannot treat all these products as identical for general causation purposes, irrespective of amount, duration, and timing of exposure to one or more metals naturally occurring in the various ingredients present in each unique baby food product. Were Plaintiffs claiming that every single one of these many hundreds of products are defective, unsafe, and can cause ASD, then they would need to provide reliable expert opinions to that effect, on a defendant-by-defendant and product-by-product basis.

The truth, however, is that Plaintiffs are not making this sweeping claim—their counsel have repeatedly stated, before Judge Riff and the JPML, that "80 percent, 70 percent" of Defendants' baby food products are "perfectly safe,"[12] and Plaintiffs' statements above confirm there are only "some products" they claim can cause harm – as they note, "[b]aby food is just food." For purposes of a general causation analysis, therefore, Plaintiffs' experts must identify which specific baby food products from each specific Defendant they claim can cause ASD (with or without ADHD) and, as to each such product, provide a reliable basis for the opinion. Contrary to Plaintiffs' suggestion, Defendants do not "want the Court to focus on whether 'baby food,' in general and regardless of heavy metal content, can cause the alleged injuries." Just the opposite: Defendants want (and the law requires) Plaintiffs to specify which specific products they claim can cause the injury they put at issue.

Plaintiffs' argument that product-by-product expert evidence is required only at the specific causation phase is mistaken. In a toxic tort products liability action, a plaintiff must provide

[12] Hr'g Tr. (6/29/23) at 40:2–3, *N.C. v. Hain et al.*, 21STCV22822 (Cal. Super. Ct., Los Angeles Cty.); *see also* Hr'g Tr. (3/28/24) at 25:13–14, *In re Baby Food Mktg., Sales Practices & Products Litig. (No. II)*, MDL No. 3101 (J.P.M.L.) ("Most baby food is actually safe.").

competent expert testimony that exposure to the product can cause the injury at issue (general causation), and that it did cause the plaintiff's injury (specific causation). And where, as here, Plaintiffs have sued multiple different defendants, each of which makes or sells multiple different products, with each product having different ingredients and different levels of heavy metals, Plaintiffs must prove, separately, that each product can cause the alleged injury. For example, when Plaintiffs file their Master Complaint, they presumably will include causes of action sounding in strict liability and negligence, among others. Under any state law governing those claims, Plaintiffs will need to show (for strict liability) that each baby food product at issue, in and of itself, is defective and unreasonably dangerous because it can cause ASD, and (for negligence) that the defendant failed to exercise reasonable care by selling a product that can cause ASD. Either way, Plaintiffs will need competent proof of general causation on a product-specific basis. To be sure, Plaintiffs *also* will need to show specific causation—that baby food product(s) eaten months or years after birth were a cause of a particular plaintiff's ASD—although even in that context, the plaintiff will need reliable expert evidence to show that each product consumed by that plaintiff, in and of itself, was a cause of the plaintiff's ASD. Again, the *NC v. Hain* case is a good example: another reason why Judge Riff granted defendants summary judgment was that plaintiff's specific causation experts opined that all baby food products that the plaintiff allegedly consumed, collectively, were the cause of plaintiff's ASD; as Judge Riff held, under California law plaintiff was required to provide expert causation opinions as to each defendant and its products separately. *NC v. Hain, et al.*, Order Granting Defendants' Motion for Summary Judgment (Sept. 1, 2023) at 5 ("Neither of [plaintiff's specific causation experts] analyzed whether exposure to a dose of heavy metals *in any one* defendants' product or products was a substantial factor in bringing about Plaintiff's ASD or ADHD.") (emphasis in original).

3. **The Proper General Causation Question Must Address the Actual Injury at Issue**

Plaintiffs' formulation describes the injury that would be subject to the general causation question as "neurodevelopmental harm sufficient to result in a child's diagnosis of ASD/ADHD." Despite disclaiming semantic wordplay, the fact of the matter is that the Plaintiffs in this MDL allege

they have one diagnosed medical condition: ASD, either alone or with co-occurring ADHD.[13] ASD is a distinct disorder, diagnosed by clinicians using specific criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) to assess deficits in social communication and interaction and restricted, repetitive patterns of behavior. The question of what can cause ASD can be reliably answered only with scientific research and data specific to ASD, not with data related to other medically distinct neurodevelopmental conditions or issues. Plaintiffs' general causation experts, therefore, will have to produce reliable scientific evidence that consuming any of Defendants' baby food products can cause ASD—not some amorphous "neurodevelopmental harm."

It is not lost on Defendants that rather than grappling with the complexity of ASD, a highly genetic condition with prenatal roots, Plaintiffs want to sweep ASD within a broad umbrella of generic "neurodevelopmental harms," including very small and clinically not relevant IQ loss. They also want to rely on studies that describe behavioral symptoms sometimes seen in ASD (but also seen in many other conditions), but do not have an endpoint of properly diagnosed ASD itself. That is why they argue that exposure to heavy metals from unidentified sources can result in "various types of neurodevelopmental harm, *some of which* are sufficient enough to manifest as an ASD or ADHD diagnosis." But Plaintiffs' strategy does not change the correct framing of the general causation question. Putting aside whether the premise of Plaintiffs' framing makes sense (i.e., that ASD is just one of many neurologic harms that have the same underlying cause and can happen on a continuum of injury if there is "enough" exposure to certain metals), and Defendants maintain that is not the case, the only diagnosed injury alleged in the complaints filed to date is ASD, with or without ADHD, and therefore the general causation question should be limited to that injury. For example, in the recent Tylenol/acetaminophen MDL, Judge Cote found that one of plaintiffs' general causation experts offered unreliable opinions in part because the expert conducted analyses and relied on studies of generalized neurodevelopmental disorders, not the specific disorders being

[13] ADHD commonly co-occurs in children with ASD. There is substantial overlap in genetic traits that cause each condition, and impairments associated with ASD often make attention and activity control more challenging as a child matures.

alleged—diagnosed ASD and/or ADHD. *See In re Acetaminophen*, 2023 WL 8711617, at *20-23 ("After all, this litigation is brought to obtain recovery on behalf of those who have been diagnosed with ASD or ADHD, not on behalf of anyone with, for example, a deficit in communication or self-regulation."). Again, if Plaintiffs' experts intend to opine that studies about other types of "neurodevelopmental harm" are relevant to a *bona fide* medical diagnosis of ASD, they are free to offer that opinion, Defendants can challenge it, and the Court can evaluate it under Rule 702.

Plaintiffs' leadership counsel also suggest that cases alleging injuries other than ASD *will be* filed at some time in the future; but even if that were true, ASD undoubtedly will continue to be the predominant injury alleged in this MDL. It was presented to the JPML as the principal injury at issue, and therefore the threshold general causation proceeding should be specific to that injury. There are many products liability MDLs in which different plaintiffs allege various scattered injuries, but where (as here) one injury dominates the cases on the docket, MDL courts typically focus the initial general causation proceeding on that injury, as an efficient case management matter. If needed, of course, the Court can conduct general causation proceedings as to any other alleged injuries properly introduced into the MDL *after* resolving Rule 702 challenges to general causation expert testimony directed to ASD, the main injury alleged.

II. The Status of the Consolidated California Proceeding and Proposals Regarding Discovery and General Causation Coordination

A petition to form a California Judicial Council Coordinated Proceeding ("JCCP") was granted by the Hon. David Cunningham, with a recommendation to place the JCCP in Los Angeles Superior Court. It is anticipated that the JCCP will be placed before the Hon. Lawrence Riff. The process of officially forming the JCCP may take a few months. Pending official formation, all cases (except one) pending in California are stayed. The one action that is not stayed (*Landon R. v. Hain Celestial, et al*. Case No. 23STCV24844) is before Judge Riff and currently has a trial date of January 21, 2025. The parties in the *Landon R.* matter are amid discovery in preparation for the January 21, 2025 trial date.

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A. Discovery Coordination

1. Plaintiffs' Position

Plaintiffs believe that coordination between discovery in the JCCP and the MDL is important. It simply makes no sense to silo discovery efforts in the respective litigations, especially when there is overlapping attorneys on both sides. That said, Plaintiffs believe the lion share of general discovery left to be completed will likely occur in the MDL. This is because Defendants in the California cases have refused to engage in discovery unless it is tethered to a specific plaintiff. For example, Defendants in the JCCP refuse to produce all metal testing for all products—instead, they have limited production of testing data to the specific products that the plaintiff (N.C. and Landon) consumed and to self-imposed time limits. Defendants also limited production of product formulations (i.e., ingredient lists with percent of product) to only those products consumed by a plaintiff and only to the time-period the specific plaintiff consumed that food. Because this discovery has only been conducted for two plaintiffs (N.C. and Landon) in California state court, this means the discovery, to date, has been highly restricted. Further, the discovery in both N.C. and Landon was/has been conducted under the extremely accelerated schedule of California's trial preference statute, thus many discovery needs were abandoned in favor of meeting the preference schedule. That said, as Plaintiffs conduct discovery in the MDL, it will be cross-noticed and/or produced in the California state court litigation contemporaneously—and vice-versa. Plaintiffs intend to serve all written discovery in both proceedings. Additionally, Plaintiffs Leadership will create an online platform that will be accessible to both JCCP and MDL counsel seeking to review documents produced in either case. This repository will also include copies of all depositions taken of any company witnesses and, where appropriate, common third parties.

2. Defendants' Position

Defendants agree with Plaintiffs that discovery should be coordinated between the MDL and the JCCP, especially discovery pertaining to the threshold general causation question in each proceeding. Plaintiffs mischaracterize the discovery that has already been produced in the pending California cases. As the Court observed during the initial case management conference, this is a

"mature" litigation. See May 16, 2024 Hearing Tr. at 6:15-17. Significant and expansive discovery has already taken place. Plaintiffs received voluminous document productions and took dozens of depositions on general liability issues that were not "tethered to a specific plaintiff" or limited to specific time periods. Thus, Defendants disagree that discovery was "highly restricted" in the California cases and that "the lion share of general discovery" is left to be completed in this MDL. In the *NC* and *Landon R.* cases, all Defendants produced tens of thousands of documents related to heavy metals in their baby food products that were not tethered to any particular products consumed. Some Defendants also produced testing data beyond a particular plaintiff's usage period while some Defendants' position as to specific categories of discovery—product information and heavy metal test results—was (depending on how the data were maintained and the particular inquiry) to limit discovery to the products and timeframes at issue for these two individual plaintiffs because no JCCP existed at that time. In fact, for most of the time when *N.C.* was pending, there were no other active cases at all in California. Now that a JCCP has been formed and will presumably soon be assigned to Judge Riff, Defendants agree that it will be most efficient to complete discovery on product testing issues as to all parties to the MDL and JCCP as a whole and already have suggested to Judge Riff (as discussed below and despite Plaintiffs' objections) that a JCCP may require re-thinking of the prioritization of a single case in favor of a threshold review of the general causation issue across cases.

In sum, Defendants propose that general causation discovery should be prioritized given this Court's desire to address general causation as a threshold issue and that the scope of discovery required to litigate general causation (discussed later in this Statement) be the same in the MDL and the JCCP. Defendants also propose that discovery in the MDL and JCCP proceed on the same schedule. Finally, Defendants agree with Plaintiffs that discovery requests and responses should be cross-noticed as applicable to both the MDL and JCCP.

B. General Causation Coordination

1. Plaintiffs' Position

Plaintiffs welcome coordination between the MDL and California JCCP as it relates to general causation. In the JCCP, general causation will not be litigated independently—at least, not

as it relates to the trial proceeding in January 2025. To the extent that there is a *Daubert*-like proceeding in the JCCP (called *Sargon*), Plaintiffs' counsel intends to invite this Court's participation in that process, subject to Judge Riff's agreement. It is unknown when that will occur. Under California's Code of Civil Procedure, expert disclosures will occur in early December, with any *Sargon* hearing to occur in the week leading up to trial (early/mid January). That schedule, however, may change should Judge Riff order it. Once a concrete schedule is in place, Plaintiffs Leadership will notify the Court. It is worth noting, however, that any *Sargon* hearing in *Landon* will involve all experts—general causation, specific causation, regulatory, and liability experts—and will involve a different legal standard of admissibility.

Below, Defendants claim that Plaintiffs are resistant to coordination. Not true. Defendants openly state that they intend to leverage "coordination" with the MDL to delay trial the *Landon R.* case. Defendants have repeatedly sought to delay any trial, having requested continuances and delays at nearly every hearing before Judge Riff. There is no "resistance" to coordination; there is simply resistance to Defendants' acknowledged stratagem to leverage the MDL to prejudice Landon, a nine-year-old boy, from getting his day in Court.

Separately, in this MDL, when the general causation issue is argued and presented, Plaintiffs in the JCCP would like to invite Judge Riff to participate in these proceedings, again, subject to this Court's agreement and Judge Riff's willingness. This will be a valuable experience, even if Judge Riff will have already presided over an entire trial.

2. Defendants' Position

As the Court and parties discussed at the Initial Case Management Conference, the threshold general causation issue in the MDL and JCCP may be resolved through coordination between this Court and the judge overseeing the JCCP. As Plaintiffs note, the schedule leading up to the currently scheduled trial date in *Landon R.* may be subject to amendment, and Defendants believe that it would be most efficient to align the MDL and JCCP schedules so as to allow the joint consideration of the expert admissibility issues across the two forums. To be sure, Plaintiffs appear to be resistant to such an approach, but Defendants propose such alignment because of the efficiencies, especially if Judge Riff is assigned the JCCP given that he already has been through

Sargon motions in one of the two products liability cases to be litigated to a judgment.

The most sensible approach is to adjust the *Landon R.* trial date so that a joint proceeding is feasible, and Defendants intend to seek that relief before Judge Riff. Accordingly, given the state of flux in the state court schedule, the prudent approach would be for this Court first to determine the scope of the general causation issue and any necessary general causation discovery in the MDL, which would allow time for the California state court timeline to be more definitively established and enable this Court to coordinate with the state court as to a briefing and hearing schedule on the general causation question.

III. The Status of the Production of Defendants' Discovery Produced in Other Actions

A. Plaintiffs' Position

Defendants refuse to reproduce all discovery from prior state court litigations in this MDL unless Plaintiffs agree to allow that production under the ESI protocols, Protective Orders, and Privilege Orders from the state court proceedings. As explained in the submissions related to those orders, Plaintiffs cannot agree to import the state court pretrial orders into this MDL. Those orders were negotiated in the context of expedited trials, and under the non-transparent rules that govern discovery under California law. Here, in federal court, we want to implement transparent and state of the art protocols and procedures—modeled after the Northern District's model orders. This is essential in the context of an MDL, where Plaintiffs would like to conduct and complete common discovery one time—instead of the piecemeal approach taken, to date, in state court.

Once the ESI, protective, and privilege orders are entered by the Court, Plaintiffs' first requests for production will seek disclosure of all prior discovery in other baby food litigation (including the class actions) and for those productions to be produced consistent with this Court's ESI, protective, and privilege orders.

B. Defendants' Position

Plaintiffs' suggestion that the existing ESI Protocol and Protective Orders are somehow inconsistent with or noncompliant with modern federal court litigation has no basis. The same counsel, experienced lawyers on both sides, negotiated these agreements over months, including in a federal court case (*Watkins*) in which the court largely adopted them. Plaintiffs' "start from

scratch" approach cannot be reconciled with Rule 1 or common sense. Nor is Plaintiffs' 33-page proposed ESI Order somehow in-line with this Court's model ESI Order (a 3-page document) as Plaintiffs claim; it is a one-sided document that explicitly carves Plaintiffs out from its requirements and is designed to be as onerous as possible on Defendants without any consideration of the actual needs of the parties addressed in prior ESI protocols entered and approved in both state and federal court.

As set forth below, Defendants have previously produced substantial documents, discovery responses, and witness testimony in three cases. With the exception of the *Watkins* case, no Defendant has produced discovery to date in any of the Related Actions currently before this Court.

Seven MDL defendants that manufacture or sell baby food products—Beech-Nut, Gerber, Hain, Nurture, Plum, Sprout, and Walmart—were named as defendants in the *NC* case. All but one of those defendants, Walmart, is also named in the presently pending California state court case, *Landon R.* Four MDL defendants (Nurture, Hain, Amazon.com Services LLC ("Amazon") and Whole Foods Market Services, Inc. ("Whole Foods")) are named as defendants in the *Watkins* case, which has since been transferred to the MDL. Between those three cases, the defendants produced the following documents:

- **Beech-Nut** – In the *N.C.* and *Landon R.* cases, Beech-Nut produced from non-custodial sources its ingredient test results for all products beginning in 2016 through December 31, 2021 that could be located after a reasonable and diligent search. Beech-Nut also conducted targeted searches from non-custodial sources to locate and produce ingredient test results dating back to 2014 for the products at issue in *N.C.* and is in the process of producing all ingredient test results for the products at issue in *Landon R.* prior to 2016 it was able to locate after a reasonable and diligent search. Beech-Nut also produced product formulas and labels for the products at issue in *N.C.* and *Landon R.* during the period of consumption. In addition to non-custodial files, Beech-Nut also searched for and produced documents across 7 individual custodial files, including test results, based on

agreed-upon search terms and custodians from 2012 through June 30, 2021. In *N.C.*, Plaintiff deposed a total of 6 current and former Beech-Nut employees over 7 days, including Beech-Nut's "Person Most Qualified" witness, amounting to a total of 2,245 pages of deposition transcript.

- **Gerber** – In the *NC* and *Landon R.* cases, Gerber produced finished product and ingredient test results that could be located after a reasonable and diligent search for over 100 products allegedly consumed by one or both of those plaintiffs through targeted non-custodial searches from 2012 to 2021. In the *NC* case, Gerber also produced documents from custodial files, including test results for the products allegedly consumed, based on agreed-upon search terms and custodians. Gerber has agreed that plaintiff Landon R. may use the documents produced in the *NC* case as if produced in the *Landon R.* case, pursuant to the terms of a stipulation. Additionally, Gerber produced product formulas for the products allegedly consumed by NC and Landon during their respective alleged periods of consumption. Plaintiff NC deposed six current and former employees, two of whom testified as a "Person Most Qualified" witness pursuant to California Code of Civil Procedure section 2025.230, amounting to a total of 1,829 deposition transcript pages.
- **Hain** – Hain has produced extensive finished product heavy metal test results, ingredient heavy metal test results, and finished product specifications for the Hain baby food products that the *NC*, *Landon R.*, and *Watkins* plaintiffs allege they consumed. These productions have included testing conducted from 2012 through 2021 and finished product specifications for the products alleged from July 2014 through 2020. In total, Hain has produced heavy metal testing and finished product specifications for over 60 products and 110 ingredients collectively spanning a decade. Hain has also produced additional non-custodial documents pertaining to the presence of heavy metals in certain baby food products, including deviation reports and ingredient supplier documents. Further, in *NC*, Hain reviewed the custodial files of six-agreed upon custodians and produced over 20,000 non-

privileged custodial documents relating to the presence of heavy metals in certain baby food products. Hain also produced and Plaintiff NC deposed four Hain corporate witnesses in their individual capacities and two witnesses as "Persons Most Qualified" on topics pertaining to heavy metals in baby food over six days of testimony.

- **Nurture** – Nurture has participated in discovery in three cases, *NC, Watkins*, and *Landon R.* In those three cases, Nurture has produced responsive documents from the files of 13 individual custodians as well as thousands of pages of documents from non-custodial sources. Nurture has produced over 440,000 pages of documents in total from custodial and non-custodial sources. Among those documents are finished good and ingredient heavy metals testing results, product labels, product formulas, and product and ingredient specifications, as well as emails and correspondence about the same. To date, Nurture has produced finished good and heavy metal ingredient testing for all products Nurture manufactures from at least 2012 through December 31, 2021. Nurture has recently agreed in principle to produce the same documents for the entire period from January 31, 2010 through December 31, 2023. Nurture has also produced formulas for approximately 36 products in use between April 2018 and February 2020 (Landon R.'s consumption period) and has recently agreed in principle to produce formulas for the same products from January 1, 2010 to December 31, 2023, to the extent they exist. Additionally, over a span of 19 deposition days, Nurture produced and Plaintiff deposed a total of ten employees and former employees in their individual capacity, three "Person Most Qualified" witnesses, and one witness pursuant to Federal Rule of Civil Procedure 30(b)(6), resulting in approximately 5,790 pages of testimony. Several of Nurture's witnesses sat for multiple days of deposition testimony.
- **Plum** – In *NC*, Plum's document productions have included heavy metals testing for the years 2010 through 2021 that Plum located following a reasonably diligent search inclusive of all finished products Plum sold, as well as all ingredients Plum used

during that twelve-year time period across both non-custodial and 8 identified custodial sources. Plum has agreed that Plaintiff may use these produced ingredient and finished product test results as if produced in the *Landon R.* case, pursuant to the terms of a stipulation in that case. Additionally, Plum produced product formulas and product labels for the baby foods allegedly consumed by NC and Landon R. for their respective periods of consumption. Further, Plum's *NC* document production included documents related to a broad range of other issues and topics implicated by plaintiff's discovery requests not tied to any specific baby food product allegedly consumed. Thus, Plum's total production is in excess of 30,000 documents. All of the 8 individual custodians whose files were produced in *N.C.* were deposed – over multiple days and topics and in many cases both individually and as "Persons Most Qualified."

- **Sprout** – In addition to non-custodial documents, Sprout produced documents from the custodial files of nine individuals in NC. These document productions included all heavy metals testing for the years 2013 through 2021 that Sprout located following a reasonably diligent search as to all Sprout products produced during that time period and allegedly consumed by the plaintiff in NC. Sprout also produced product formulas for the products allegedly consumed by the plaintiff in NC. Sprout produced and plaintiff's counsel deposed a total of seven employees and former employees in their individual capacity, three "Person Most Qualified" witnesses, and one third-party witness who worked for Sprout's consumer relations agency.
- **Walmart** – In the *N.C.* case, Walmart produced documents from non-custodial sources and 7 individual custodial files. These document productions included heavy metal testing from 2012 through June 30, 2021 that Walmart was able to locate following a reasonably diligent search as to all products Walmart produced during that time period based on agreed-upon search terms and custodians. Walmart also produced the labels and formulas for the products at issue in *N.C.*

during the period of consumption that it was able to locate after a reasonably diligent search. In *N.C.*, Plaintiff deposed a total of 5 current and former Walmart employees over 6 days, including Walmart's "Person Most Qualified" witness, amounting to a total of 1,383 pages of deposition transcript.

- **Amazon** – Discovery in *Watkins* was set to close on May 15, 2024 and thus was nearly complete at the time of the stay on April 12, 2024. The discovery process also included motion practice resulting in a Protective Order addressing and limiting discovery from the Retailer Defendants. [Case No. 2:22-551, ECF. No. 337]. Amazon conducted a diligent records and email search in response to numerous discovery requests from the *Watkins* plaintiff. Amazon produced records related to plaintiff, including records reflecting all products plaintiff's parents purchased during the relevant time period. Amazon produced records of all sales of the products at issue during the relevant time period, as well as records regarding customer feedback on those products, including all customer comments on the product pages for the products, all customer complaints and comments about the products related to heavy metals, and records reflecting actual returns and/or refunds for the products at issue related to heavy metal concerns. Amazon also produced general protocols and standard operating procedures applicable to the products at issue.
- **Whole Foods Market Services, Inc. ("WFMSI") –** Discovery in *Watkins* was set to close on May 15, 2024, and thus was nearly complete at the time of the stay on April 12, 2024. WFMSI produced all records regarding the purchases made by Plaintiff. The discovery process also included motion practice resulting in a Protective Order addressing and limiting certain discovery from the Retailer Defendants. (Case No. 2:22-551, ECF. No. 337). In accordance with the Protective Order issued by the Court and the search terms proposed by Plaintiff, WFMSI conducted a diligent search in response to numerous discovery requests from the *Watkins* plaintiff and produced responsive documents pursuant to the parties' Joint

Stipulation and Protective Order (Case No. 2:22-551, ECF No. 71).

IV. Proposal as to Additional Discovery Needed for the General Causation Proceeding

Because the parties did not reach agreement on the general causation question, they also did not reach agreement on any additional discovery (beyond what Plaintiffs' leadership counsel has received in prior or ongoing baby food litigation) that would be needed for the general causation proceeding. The parties' respective positions on this issue are below.

A. Plaintiffs' Position

In addition to prior discovery being reproduced in this MDL, Plaintiffs narrowed the scope of anticipated discovery for the general causation phase to four categories of discovery:

1. List of all products Defendants sold/manufactured between January 1, 1990 and the present
2. List of all ingredients and formulations for products identified in No. 1
3. All heavy metal testing related to products identified in No. 1, to include third party testing when Defendants have possession, custody, or control;
4. Discovery (email/communication/documents) related to targeted test results, as specified by Plaintiffs

These categories *do not* include marketing materials, all email and/or communications about ingredients, suppliers, heavy metals, etc., all regulatory materials, all field testing and supplier correspondence, all communications related to metal standards, or all communications with third parties (including Congressional investigations) related to heavy metals in baby food products. Instead, these categories are targeted to product identification, product formulation, testing, and, when needed to understand a document, communications related to specific testing results. Plaintiffs anticipate that two to three depositions may be needed per defendant, but generally, Plaintiffs do not anticipate needing to take many depositions and will endeavor to focus any depositions on topics related to general causation.

From this discovery, Plaintiffs would like to work with Defendants to construct two databases. The first is a product identification database, which will allow any party to input the Defendant and dates of use and generate a complete list of products sold by that defendant during

that period of time, with specific information related to that product's formulation. This database will ensure everyone is on the same page regarding which products were or were not available at various times. The second is a metal testing database, which will include all testing on every product conducted by the Defendants or their respective third-party suppliers / growers / co-manufacturers. All parties will have a compete database of testing data, which can be used by respective experts as they see fit.

Once Defendants have produced the above discovery, Plaintiffs anticipate their experts will need approximately 3-4 months to review the data and prepare expert reports. Following that, expert discovery could easily be completed within sixty days.

Regarding the first, second, and third categories, Defendants make three arguments.

First, they argue that they might not have records going back to 1990 about what products they sold, their formulation, or the metal testing results. This is difficult believe; but if true, then Plaintiffs cannot force Defendants to disclose information they do not possess. That is discovery 101—they must produce what they can. To the extent such documents were destroyed, Plaintiffs will likely need to understand the nature of that destruction to ensure there has been no spoliation (which, at this time, Plaintiffs are not averring).

Second, Defendants make a "burden" argument about having to produce information and documents going back to 1990. Obviously, this sort of argument cannot be fully addressed without proof from the party resisting discovery. In passing, Defendants claim that looking back to 1990 could involve employee and/or attorney time of up to 100 hours. Assuming that is correct, 100 hours of work hardly rises to the level of an "undue" burden in a case involving thousands of children alleging lifetime, permanent brain injury.

Third, Defendants argue that the product list, formulations, and metal testing should be limited to the arbitrary date of January 1, 2012 and cut off on December 31, 2021. That arbitrary time restriction does not work; nor is there a reasonable basis the impose such a restriction. As openly conceded below, Defendants did not regularly test their products for heavy metals. Moreover, many of these Defendants have started regular testing following the congressional report and the attendant lawsuits—indeed, one Defendant (Hain) even cites to metal results after

2021 to argue that their previous results were artificially high. In the face of incomplete testing and more recent claims of testing, Plaintiffs need a complete dataset to make heads or tails of the levels of toxic heavy metal in Defendants' baby food products. For example, when missing data, Plaintiffs' experts will need to look at similar products, with similar ingredients that have testing results and, when necessary, extrapolate. Such extrapolation, however, cannot happen unless Plaintiffs know the universe or products sold by Defendants (category 1) and their attendant formulations (category 2) and metal testing results (category 3). Plaintiffs chose 1990 because that is sufficiently far back enough to allow Plaintiffs' experts to construct a complete picture of the nature and scope of the toxic heavy metal contamination of the baby food products sold by these Defendants.

Remarkably, Defendants suggest that the discovery produced to date, in prior state court litigation, is sufficient. And yet, above, Defendants boldly assert that, at the general causation phase, Plaintiffs must not only identify all "defective products" but also prove that each product, itself, is capable of causing ASD and/or ADHD. As discussed above, this is not an appropriate way to consider general causation, but such a task is impossible absent full discovery about each product, including identification, formulations, and testing.

Regarding the fourth category, Defendants object because it gives Plaintiffs the right to specify what additional information they believe they need without restriction. Defendants take issue with this, even though that is how discovery requests normally work, and want to reverse the burden. Instead of the party resisting discovery showing good cause as to why discovery should not be allowed, Defendants want to impose the good cause restriction on Plaintiffs, i.e., Plaintiffs must demonstrate good cause as to why they should get discovery. This is simply not appropriate, nor consistent with the liberal thrust of discovery in federal court. If Defendants believe that Plaintiffs request too much, they should demonstrate good cause and resist discovery. That showing of good cause need not be a high burden if the information requested by Plaintiffs is not relevant to proportional to the needs of the general causation proceeding.

B. Defendants' Position

Plaintiffs claim they need more than three decades of discovery related to Defendants'

finished products, ingredients, proprietary formulas, and testing in order to respond to the general causation question. In this "mature" litigation (*see* May 16, 2024 Hearing Tr. at 6:15-17), Defendants generally maintain that Plaintiffs already have and/or will have shortly, as a result of significant and expansive discovery in the California state cases, more than ample product, ingredient, formula, and testing discovery for general causation purposes. Defendants note that Plaintiffs also have testing from a range of non-company sources including FDA and third-party advocacy groups that have published the results of testing of Defendants' products and/or of ingredients found in Defendants' products (like sweet potatoes, carrots, spinach, and rice). This third-party testing can be compared to the results Defendants generated themselves. Indeed, Plaintiffs' counsels' repeated acknowledgement that "80 percent, 70 percent" of Defendants' products are perfectly safe is surely because they have already seen so much data. With this background, Defendants respond to each of Plaintiffs' document requests below.

1. **Discovery of Defendants' Product Lists:** Plaintiffs seek to have Defendants create a master list of all baby food products sold by Beech-Nut, Hain, Gerber, Nurture, Plum, Sprout, and Walmart starting in 1990 and continuing through the present. Many Defendants in this MDL did not even come into existence until the mid- or later 2000s, or they did not sell certain products or product lines until the mid- or later 2000s or after. Further, given the nature of Defendants' businesses, they did not necessarily maintain records of every finished product ever sold in any reasonably retrievable and reliable form. Thus, it is unlikely that Defendants have or can reliably generate records of all products back to 1990. Also, this kind of extensive effort going back more than three decades is not likely fruitful. All of the Plaintiffs who have filed claims in the MDL to date are minors. Defendants are not aware of any federal case where product usage goes back to the 1990s. Also, because of the California state cases, Plaintiffs' counsel have information identifying hundreds of products going back to 2012 and through December 31, 2021—which post-dates by several months the Congressional Subcommittee Staff Report that triggered this litigation. To the extent Plaintiffs nevertheless claim they need Defendants to identify the universe of marketed products (versus Plaintiffs knowing what products they used and telling Defendants which of those are or are not at issue), Defendants see no reason why a 10-year time period from 2012 to 2021 is

not more than sufficient. As noted above, however, the ability to create such a list that truly captures all products being put at issue for general causation purposes for all companies over this time period will be constrained by the availability of this information following a reasonably diligent search.

2. **Discovery of Defendants' Ingredients and Formulas:** Plaintiffs likewise seek identification of all ingredients used in and formulas for each Defendant's baby food products from 1990 through present. All of the challenges in identifying products manufactured back to 1990 also exist with respect to identifying ingredients and formulas dating back to 1990—indeed, identifying ingredients may be even more challenging because of the sheer number of them. Formulas and ingredient lists predating 2012 are, for some Defendants, stored in archived databases or locations that are difficult to search or may not be available at all, particularly for products that are discontinued. Defendants changed suppliers and/or modified product formulas over time. Also, not all Defendants directly sourced ingredients for all products at all times or owned the formulas for their products. Searching for ingredient lists and formulas dating back to 1990—or through a company's entire existence for some Defendants—presents a significant burden (likely more than 100 hours of employee time, plus attorney review time, for some Defendants) and is likely not entirely achievable. This issue already has been extensively briefed in multiple state and federal courts.

Instead, the most reasonable and reliable means of conducting ingredient and formula discovery for general causation purposes is as follows: Defendants will make a reasonably diligent search under the circumstances, in accordance with the Federal Rules, of non-custodial sources (*i.e.*, data sources that are not kept or maintained by any particular individual custodian, but rather department, business unit, or division-level data sources) and, to the extent locatable, produce a single copy of the product label (to the extent it exists) for the specific products identified by Plaintiffs that were sold by Defendants in the United States from January 1, 2012 through December 31, 2021. These product labels will identify finished products available at different times and also contain ingredient lists and, in some cases, amounts of each ingredient included. With respect to formulas, from which Plaintiffs also can identify finished products available at different times as well as ingredients used, Defendants will make a reasonably diligent search under the circumstances,

in accordance with the Federal Rules, of non-custodial sources (defined above), and, to the extent locatable, will produce, subject to a heightened protective order with the same terms as the heightened protective order used in the *Landon R.* state case, a single copy of each available product formula for the specific products identified by Plaintiffs that were sold by Defendants in the United States from January 1, 2012 through December 31, 2021. Defendants believe this ten-year production window would give Plaintiffs as comprehensive a finished product and ingredient list as can reasonably be created for the period that is apt to be relevant to virtually all cases, as well as information regarding how ingredients were used/combined in different products at the likely relevant times.

Defendants emphasize that they cannot currently represent that they possess a product label and formula for all products manufactured between January 2012 to December 2021.

3. **Production of Testing Data for Finished Products and Ingredients:** Third, Plaintiffs seek all company-maintained testing of both finished products and ingredients going back to 1990 through the present. Defendants believe the same 10-year time period (January 1, 2012 to December 31, 2021) should apply for the production of test results for the products Plaintiffs claim are at issue, for the same reasons discussed above. Additionally, the first proposed regulatory action level in the U.S. for any heavy metal in any baby food product was in 2016, for inorganic arsenic in rice cereal—a product not all of the Defendants sold. As a result, for some Defendants testing prior to 2016 will be sparse, sporadic, and/or may not be easily locatable even with a reasonably diligent search. Moreover, given that document retention policies do not span decades and that the Congressional Subcommittee Staff Report was not published until February 2021, testing results from prior to 2012 may no longer be available, and where they are, they may be sparse, sporadic, and extremely burdensome for Defendants to attempt to locate and produce. Further, the reliability of testing methods for heavy metals and the lower limits of detection of different metals was a known challenge even into the 2010s and has materially changed over time—such that it can be extremely difficult (if not entirely infeasible) to compare results from one time period with those from another. Defendants believe that, even if earlier test data may exist for some Defendants, trying to compare results to later periods will likely result in any number of "side show" issues.

4. **Discovery Related to Targeted Test Results:** Plaintiffs propose that they, subject to their own discretion, should also be able to obtain undefined discovery, including emails and other communications, related to particular test results as they request. Plaintiffs' proposal is too broad, burdensome, and ambiguous as worded. Defendants understand that Plaintiffs are concerned that they not be prevented from seeking further documentation (such as email correspondence) if a genuine question is raised as to a specific heavy metal test. For example, if a Defendant produced a test result that showed a number but not a unit of measure for a heavy metal test, Plaintiffs would like to be able to request that the Defendant produce a document showing what the unit of measure was. Or, if a Defendant produced a test result but it was unclear what product was tested, Plaintiffs would be able to request documents identifying the product.

Defendants have no objection in principle to this type of reservation of rights. But Plaintiffs' paragraph 4 goes far beyond that and seems to allow Plaintiffs to request any type of documentation, in any volume, for any reason—all "as specified by Plaintiffs." That type of nebulous parameter would only invite disputes over what should be a limited production of test results Plaintiffs do not already have, plus any targeted documents needed to understand those results. Further, it ignores the fact that significant – and indeed, expansive – discovery has already taken place. From prior cases, Plaintiffs already have from Defendants large document productions (containing emails, test results, policies and procedures, and other documents) and depositions of over 50 current and former employees totaling over twenty thousand pages of testimony over more than 60 days relating to Defendants' baby food products and the subject of heavy metals in such products. Virtually all test results are self-explanatory on their face, so Plaintiffs should not need any substantial number of additional documents to answer the general causation question—especially given that the parties have not had any issues with respect to the thousands of tests results Defendants have already produced and Plaintiffs' leadership counsel has had access to for years.

As a result, Defendants propose that Plaintiffs' paragraph 4 be modified to read: "If there is a genuine question about understanding a specific test result that a Defendant has produced, Plaintiffs and the Defendant will meet and confer in good faith about whether there is good cause to produce any additional document(s) relating to that result and, if so, which document(s)."

Finally, Defendants object to Plaintiffs taking fact witness depositions of company employees, beyond the large number of depositions they have already conducted in the *NC* case, because any such depositions would not be relevant to the general causation question. As to Plaintiffs' request to work with Defendants to construct two databases that could be jointly used, Defendants believe that the respective sides should organize discovery materials and data in whatever fashion they see fit, using their own vendors. Moreover, for the reasons discussed above, Defendants would not be able to construct databases that they could agree contain "complete" information as to all time periods and all products; the level of completeness would depend on the product, time period, and Defendant.

V. The Proposed Filing of a Master Complaint and Scheduling of Motions to Dismiss on Jurisdictional and 12(b)(6) Grounds.

A. Plaintiffs' Position

Plaintiffs intend to prepare a Master Complaint by July 15, 2024, which will name the following entities as Defendants:

1. Beech-Nut Nutrition Company
2. Campbell
3. Danone, S.A.
4. Gerber Products Company
5. Hain Celestial Group, Inc.
6. Nestle, S.A.
7. Nurture LLC
8. Plum, PBC
9. Sprout Foods, Inc.
10. Walmart

Once the Master Complaint is filed, Plaintiffs will serve the Master Complaint on all the above entities. Although most of the Defendants agree to electronic service of the Master Complaint though email, the international defendants (Danone S.A. and Nestle S.A.), Campbell, Amazon, and Whole Foods refuse to accept electronic service. Campbell, Amazon, Whole Foods,

and the international defendants have been served in at least one case that has been transferred to this MDL. But, for whatever reason, Campbell, Amazon, Whole Foods, and the international defendants refuse to accept electronic service of the Master Complaint.

As such, Plaintiff proposes the following schedule to address the Rule 12 issues and tee up whether allowing alternate electronic service of Campbell and the international defendants is appropriate.

Rule 12 Motion: After filing the Master Complaint on July 15, 2024, Plaintiffs will expeditiously effect service of the Master Complaint on all named Defendants, including the international defendants.[14] Once all Defendants have been served, Plaintiffs will file a notice of completed service with attached proofs of service. Defendants will then file an omnibus Rule 12 motion[15] (including all jurisdictional challenges) by September 16, 2024 or within twenty-one days after filing the notice of completed service, whichever is later. Plaintiffs will respond to the Omnibus Rule 12 motion by October 28, 2024 or within 45 days of the motion, whichever is later. Any Omnibus reply should be filed by November 18, 2024 or 21 days after the filing of the opposition, whichever is later.

Alternate Service of Process Motion: MDL courts frequently enter order requiring electronic service on international defendants that have been previously served in the MDL. So, to mirror the Rule 12 briefing, Plaintiffs propose that by September 16, 2024 or within twenty-one days after filing the notice of completed service, whichever is later, Plaintiffs file an omnibus motion for alternate service of process on the international defendants and Campbell, seeking a court order allowing for electronic service of all future pleadings (i.e., any amended complaints or future short form complaints) in this MDL. The international defendants and Campbell will respond to the motion by October 28, 2024 or within 45 days of the filing of the motion,

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[14] Plaintiffs anticipate that effecting international service of the Master Complaint will take approximately three weeks, based on having previously effected international service on these international defendants in *Mosley v. Hain Celestial Group, Inc.*, 3:23-cv-06176 (W.D. Wash.).

[15] Provided Defendants can coordinate on briefing to avoid needless duplication, Plaintiffs do not object to two omnibus motions, one for manufacturers and one for all other Defendants. Plaintiffs suggest one single brief to facilitate the logistics of briefing.

whichever is later. Any Omnibus reply should be filed by November 18, 2024 or 21 days after the filing of the opposition, whichever is later.

The following chart depicts this proposal:

Filing		**Date**
Master Complaint		July 15, 2024
Notice of Completed Service		ASAP
Rule 12 Motion(s)	Motion for Alternate Service of Process	*Later of:* September 16, 2024 21 days after Notice of Completed Service
Opposition(s) to Rule 12 Motion(s)	Opposition to Motion for Alternate Service of Process	*Later of:* October 28, 2024 45 days after filing of motion
Repl(ies) to Rule 12 Motion	Reply to Motion for Alternate Service of Process	*Later of:* November 18, 2024 45 days after filing of motion
Hearing on Motions		TBD

Regarding *Watkins v. Nurture*, LLC, 2:22-cv-00551-DJP-DPC (E.D. La.), which is the only case to name Amazon and Whole Foods as Defendants, Plaintiffs have no objection to having the Court rule on the fully-briefed motions related to them that were pending before the case was transferred to the MDL.

B. Defendants' Proposal

Manufacturers: The manufacturer defendants agree to Plaintiffs' proposed schedule for the filing of Plaintiffs' Master Complaint and briefing of any motions to dismiss.

Retailers: Retailers Amazon and Whole Foods have been named in only a single complaint, *Watkins v. Nurture*, LLC, 2:22-cv-00551-DJP-DPC (E.D. La.) and have moved to dismiss the negligence claim in its entirety, which, if granted, would leave only a Louisiana redhibition claim. The Rule 12 Motion has been fully briefed by all parties. Amazon and Whole Foods propose that the MDL Court take the prior briefing under submission and that the MDL Court decide the motion at its earliest convenience. Amazon and Whole Foods also object to their inclusion in the Master Complaint. The claims against these retailers are unique to Louisiana law,

relevant to only a single plaintiff, and do not belong in a Master Complaint.

Current and former parents: Defendants Campbell Soup Company ("Campbell"), Danone S.A. (a French entity), and Nestlé S.A. (a Swiss entity) are the current or former ultimate parent companies of certain baby food manufacturers. The parent defendants are amenable to Plaintiffs' proposed schedule for the filing of a Master Complaint and briefing motions to dismiss, on the understanding that (1) the parent defendants will not be subject to short-form complaints while the parent defendants' Rule 12(b) motions and Plaintiffs' motion for alternate service of process are pending and (2) that the parent defendants expressly preserve, and do not waive, all rights and defenses associated with any individual action that has been centralized with, consolidated with, or transferred into this MDL.

In addition, while the parent defendants have no objection to other defendants filing an omnibus Rule 12 motion in response to the contemplated Master Complaint, the parent defendants are not amenable to forgoing their ability to file their own Rule 12(b) motions. Each of the parents has distinct defenses—including personal jurisdiction defenses in the case of the foreign parent entities that sound in due process. These defenses warrant individual Rule 12(b) motions and are not well-suited for presentation in an omnibus motion. Indeed, in the one action where each of three parents were named and putatively served—*Mosley v. Hain Celestial Group, Inc.*, 3:23-cv-06176 (W.D. Wash.)—each of the parent defendants had filed or intended to file its own Rule 12(b) motion, whereas the manufacturer defendants moved jointly.

As an alternative approach and to the extent Plaintiffs are not amenable to the above, the Court could use the *Mosley* action as an exemplar to adjudicate the parents' Rule 12(b) motions, rather than involving the parent companies in the Master Complaint process at this time. This approach would allow the parties to proceed on a complaint where Plaintiffs have already undertaken foreign service efforts, to tee up the issues in a more expeditious and streamlined way, and to avoid any service-related complexities and objections associated with a short-form complaint process unless and until such issues are ripe. The parent defendants would be amenable to employing the same amendment and briefing schedule proposed by Plaintiffs in connection with their contemplated Master Complaint.

Alternate Service of Process Motion: Plaintiffs have indicated they intend to seek relief from the standard service of process requirements under the Federal Rules of Civil Procedure and the Hague Convention on the Service Abroad of Judicial and Extrajudicial Documents in Civil or Commercial Matters, Nov. 15, 1965, 20 U.S.T. 361. These service rules and protections exist for a reason and are of particular salience in a case in which (1) plaintiffs are seeking to sue foreign parent companies that are asserting personal jurisdictional challenges, and (2) two retailer defendants are named in only one case where they face unique Louisiana law claims. Defendants are amenable, however, to Plaintiffs' proposed briefing schedule for their contemplated motion.

VI. <u>Any other issue the parties would like to address at the conference.</u>

Defendants propose the Court address the following additional topics:

1) **Unfiled Cases and Bellwether Selection**

Defendants' Position:

Defendants would like to discuss a process to ensure that any order entered by the Court is binding on Plaintiffs and the Court's efforts are not wasted. Because the minor Plaintiffs' statutes of limitations are arguably tolled in most states, Plaintiffs have no incentive to file their cases and are taking a "wait and see" approach, holding the bulk of cases on the sidelines until they have a general causation Rule 702 ruling. Indeed, when this issue was raised with the Court during the last CMC, Plaintiff responded: "Candidly, it's my favorite part of this litigation, is I get to pick the cases that go to trial." 5/16/24 Hearing Tr. at 26:12-13.

Defendants would like to address, through briefing, the implications raised by Plaintiffs' position. In other product liability litigations, MDL courts have imposed a requirement on counsel as a condition of leadership to file all cases in the MDL absent a showing of good cause. *See*, *e.g.*, *In re: Acetaminophen – ASD-ADHD Products Liability Litigation*, Case No. 1:22-md-03043-DLC at ECF 200 (Judge Cote). Defendants believe an appropriate limitation on collateral filings during the pendency of this MDL for those in leadership is an issue that the Court should address.

Another related issue to be briefed is how best to ensure, through the administration of this MDL, that the goals of having an MDL are reasonably achieved – *e.g.*, to avoid discovery duplication, to prevent inconsistent pretrial rulings, and to conserve the resources of the parties

and the judiciary. Defendants do not believe that Plaintiffs' position that they have a unilateral right to pick bellwether cases or that they can keep the bulk of their cases on the sidelines until after this Court rules on general causation is correct. These issues are of such significance Defendants propose the parties set a briefing schedule in order to present these issues to the Court for its consideration at the next CMC.

Plaintiffs' Position:

This proposal has never been discussed during any meet and confer. Defendants attempted to raise this topic in a "gotcha" moment at the last CMC and it went nowhere. They appear to be rehashing this issue, again, here. To begin, it is *offensive* to suggest that Plaintiffs' Counsel are doing something unethical by being mindful about which Court they file their cases, waiting to see where that plaintiff has the best opportunity for success. To claim that doing so is somehow wrong misapprehends Plaintiffs' counsel's fiduciary duty to their clients. Selecting the best forum for a plaintiff is one of the most important decisions a plaintiff's attorney makes.[16]

Respectfully, this Court does not have the authority to dictate how Plaintiffs' counsel chooses to exercise that duty for unfiled cases. Defendants cite an order in the *In re: Acetaminophen* litigation. Ex. 5, Order: Plaintiffs' Proposed Leadership Appointments, *In re: Acetaminophen*, 22-MDL-3043 (DLC) (S.D.N.Y.). However, that order merely indicated that should a member of the leadership file a case in state court, they were required to submit a letter explaining whether there was good cause to file that case in state court. *Id.* at 2. The order did not prohibit or make leadership appointment contingent upon filing all one's cases in federal court. Moreover, the order did not attempt to dictate how plaintiffs' counsel would practice law for unfiled cases. Such an order would, on its face, be unenforceable and unconstitutional. It would also create a fundamental tension between federal and state court litigation that undermines coordination. Defendants also raise concern about bellwether selection, and the concern that by

[16] Also, most fundamentally, Defendants' request eliminates plaintiff's right to meaningfully participate in basic elements of their case – selection of counsel and where the case is litigated. Indeed, there are properly situated state court plaintiffs who do not wish to be filed in federal court, for one reason or another.

being able to control which cases are filed, Plaintiffs' Counsel effectively can dictate which cases are available for bellwether selection. This Court cannot force Plaintiffs to file cases in federal court, just as this Court cannot force Defendants to waive *Lexicon*. It is not clear what Defendants envision this Court can do—indeed, they have never mentioned this on any meet and confer. Absent some concrete non-offensive basis to actively restrict Plaintiffs' Counsel's practice of law, it is unclear what Defendants are trying to accomplish with this. If the Court would like to have briefing on this—i.e., Defendants motion to enter a proposed PTO of some sort—Plaintiffs would be happy to meet and confer with the Defendants and propose a briefing schedule.

2) Preservation of Information

Defendants' Position:

Defendants would like the Court's assistance with enforcing Plaintiffs' and their counsel's obligation to preserve relevant information relating to product consumption by current and prospective Plaintiffs. Specifically, both the existing filed Plaintiffs, and the many alleged prospective Plaintiffs that counsel has publicly stated they have under a retainer agreement, have the obligation to contact retailers where they allegedly purchased baby food products and ask those retailers to preserve Plaintiffs' customer loyalty data. Customer loyalty data (purchasing information tied to a customer's account or phone number) is the strongest evidence of purchasing history, and many retailers have document retention policies that result in deleting such data after a certain number of years. Without loyalty data, Defendants are often left to rely on plaintiffs' parents' imperfect memories of what they fed their babies over the course of several years. Because of the importance of customer loyalty data to the most basic question of whether any plaintiff consumed any Defendant's products, Defendants have twice raised the known risk of non-preservation with Plaintiffs' counsel, but have not received any response. Defendants accordingly request that all filed Plaintiffs be ordered to contact the retailers at which Plaintiffs allege they purchased Defendants' products to request that Plaintiffs' customer loyalty data be preserved for the duration of the litigation. Moreover, all Plaintiffs' counsel, whether in leadership or otherwise, should be ordered to work with their clients without filed cases to contact retailers and request the preservation of these materials Defendants do not know where Plaintiffs

allegedly purchased baby food products and therefore cannot subpoena retailers or otherwise seek preservation of Plaintiffs' loyalty data, and of course do not have the identities of any of the unfiled prospective Plaintiffs.

Plaintiffs' Response:

Again, this is another topic that has not been the subject of any meet and confer. Counsel from Covington sent a letter on April 24, 2024, but never requested a meet and confer; merely threatened "raising this issue with Judge Corely" at the initial CMC, but then never did. To be clear, it is a complicated issue that cannot be adjudicated in a Joint Statement. That said, defendants' argument concerning preservation of third-party records of which they have no possession, custody or control finds no support in the law. "The fundamental factor is that the document, or other potential objects of evidence, must be in the party's possession, custody, or control for any duty to preserve to attach." *Phillips v. Netblue, Inc.*, No. C-05-4401 SC, 2007 WL 174459, at *3 (N.D. Cal. Jan. 22, 2007) (citing cases). "[T]he duty [to preserve evidence] does not extend to evidence which is not in the litigant's possession or custody and over which the litigant has no control." *Towsend v. American Insulated Panel Co.*, 174 F.R.D. 1, *5 (D. Mass. 1997). "One cannot keep what one does not have." *Phillips*, 2007 WL 174459, at *3. There are narrow exceptions to this rule; for example, when the party had "possession, custody, or control" over the evidence and relinquished that control to a third party knowing it would be destroyed. *See Ortiz v. City of Worcester*, No. 4:15-CV-40037-TSH, 2017 WL 2294285, at *4 (D. Mass. May 25, 2017) (discussing narrow exception). However, unless a Party has possession, custody, or control over evidence, there is no duty to preserve. And, that makes sense.

Here, whether loyalty records exist or not is unknown to Plaintiffs. And, most assuredly, no Plaintiff has possession, custody, or control of such records. There is no duty to preserve that which one does not have.[17] Indeed, taken to its logical end, Defendants' view of preservation

[17] To the contrary, Defendants have possession, custody, and control over the metal testing results of their third third-party suppliers and manufacturers and, thus, are under an obligation to preserve that data—a duty that began (at least) as soon as the Congressional investigation began in 2019. That data will be the subject of numerous third-party subpoenas.

would expand the duty beyond commonsense. It would apply not just to retailer loyalty records, but *any* record in the possession, custody, or control of *any* third-party that Defendants could conceivably believe is relevant. That is a staggering scope of potential third-party discovery, assuming the documents collected in *NC* are any indication. The law does not impose a duty to preserve documents outside of their possession, custody, or control—nor should it; it would effectively force one party to conduct all third-party discovery for the other party. Indeed, Defendants' proposal, without citing any caselaw or authority, effectively seeks to force discovery on unfiled cases, and puts the onus on Plaintiffs to do that discovery for Defendants. It finds no support in the law.

Dated: June 18, 2024

Respectfully submitted,

WISNER BAUM, LLP

By: */s/ R. Brent Wisner*

R. Brent Wisner (SBN: 279023)
rbwisner@wisnerbaum.com
100 Drakes Landing Rd., Suite 160
Greenbrae, CA 94904
Telephone: (310) 207-3233
Facsimile: (310) 820-7444

By: */s/ Aimee H. Wagstaff*

Aimee H. Wagstaff (SBN: 278480)
940 N. Lincoln Street
Denver, Colorado 80203
Telephone: 303.376.6360
Facsimile: 303.376.6361
awagstaff@wagstafflawfirm.com

Co-Lead Counsel for Plaintiffs in MDL 3101

Dated: June 18, 2024

COVINGTON & BURLING LLP

By: */s/ Michael X. Imbroscio*

Michael X. Imbroscio (*pro hac vice*)
Phyllis A. Jones (*pro hac vice*)
David N. Sneed (*pro hac vice*)
850 Tenth Street NW
Washington, DC 20001

Telephone: (424) 332-4800
Facsimile: (424) 332-4749
E-mail: mimbroscio@cov.com
E-mail: pajones@cov.com
E-mail: dsneed@cov.com

Attorneys for Defendant The Hain Celestial Group, Inc.

DLA PIPER LLP (US)

By: */s/ Brooke Killian Kim*
Brooke Killian Kim (CA Bar No. 239298)
4365 Executive Drive, Suite 1100
San Diego, CA 92121
Telephone: (619) 699-3439
Facsimile: (858) 677-1401
E-mail: brooke.kim@dlapiper.com

Mary Gately (*pro hac vice*)
500 Eighth Street NW
Washington, DC 20004
Telephone: (202) 799-4507
Facsimile: (202) 799-5507
E-mail: mary.gately@dlapiper.com

Loren H. Brown (*pro hac vice*)
1251 Avenue Of The Americas
New York, NY 10020
Telephone: (212) 335-4846
Facsimile: (212) 884-8546
E-mail: loren.brown@dlapiper.com

Attorneys for Defendant Nurture, LLC

KING & SPALDING LLP

By: */s/ Livia M. Kiser*
Livia M. Kiser (CA Bar No. 285411)
Michael Anthony Lombardo (CA Bar No. 311365)
110 N. Wacker Drive, Suite 3800
Chicago, IL 60606
Telephone: (312) 764-6911
Facsimile: (312) 995-6330
E-mail: lkiser@kslaw.com
E-mail: mlombardo@kslaw.com

Todd P. Davis (*pro hac vice*)

1180 Peachtree Street NE, Suite 1600
Atlanta, GA 30309
Telephone: (404) 572-4600
Facsimile: (404) 572-5100
E-mail: tdavis@kslaw.com

Attorneys for Defendants Beech-Nut Nutrition Company and Walmart Inc.

WHITE & CASE LLP

By: */s/ Bryan A. Merryman*
Bryan A. Merryman (CA Bar No.134357)
555 South Flower Street, Suite 2700
Los Angeles, CA 90071
Telephone: (213) 620-7700
Facsimile: (213) 452-2329
E-mail: bmerryman@whitecase.com

Attorneys for Defendant Gerber Products Company

GORDON REES SCULLY MANSUKHANI, LLP

By: */s/ Michael R. Klatt*
Michael R. Klatt (*pro hac vice*)
2705 Bee Caves Road, Suite 220
Austin, TX 78746
Telephone: (512) 582-6485
Facsimile: (512) 391-0183
E-mail: mklatt@grsm.com

Nancy Mae Erfle (*pro hac vice*)
1300 SW Fifth Avenue, Suite 2000
Portland, OR 97201
Telephone: (503) 382-3852
E-mail: nerfle@grsm.com

Attorneys for Sprout Foods, Inc.

DECHERT LLP

By: */s/ Hope Freiwald*
Hope Freiwald (*pro hac vice*)
Katherine Unger Davis (*pro hac vice*)
2929 Arch Street
Philadelphia, PA 19104
Telephone: (215) 994-2514
E-mail: hope.freiwald@dechert.com

E-mail: katherine.ungerdavis@dechert.com

Attorneys for Defendant Plum, PBC

COZEN O'CONNOR

By: */s/ Peter M. Ryan*
Peter M. Ryan (*pro hac vice*)
Joan M. Taylor (*pro hac vice*)
One Liberty Place
1650 Market Street, Suite 2800
Philadelphia, PA 19103
Telephone: (215) 665-2130
E-mail: pryan@cozen.com
E-mail: joantaylor@cozen.com

Attorneys for Defendant Campbell Soup Company

ATTESTATION OF CONCURRENCE IN FILING

In accordance with the Northern District of California Local Rule 5-1(i)(3), I attest that concurrence in the filing of this document has been obtained from each of the signatories who are listed on the signature page.

Dated: June 18, 2024

WISNER BAUM, LLP

By: *R. Brent Wisner*
R. Brent Wisner (SBN 279023)

Attorneys for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that on June 18, 2024, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system which will send a notice of electronic filing to all counsel of record registered in the federal CM/ECF system.

R. Brent Wisner
R. Brent Wisner (SBN 279023)

EXHIBIT 1

National Institute of Environmental Health Sciences
Your Environment. Your Health.

Autism Spectrum Disorder and the Environment

Research shows that both genetics and environmental factors likely play a role in autism spectrum disorder (ASD). The National Institute of Environmental Health Sciences (NIEHS) supports research to discover how the environment may influence ASD.

What is autism spectrum disorder?

Autism spectrum disorder is a developmental brain disorder that generally appears in the first two years of life and affects communication and behavior. The term spectrum refers to the wide range of symptoms, skills, and levels of impairment that may challenge those with ASD. Some are mildly impaired by their symptoms, while others are severely disabled.

By the numbers

- Autism affects about one in 59 children.[1]
- The number of children identified with autism nearly tripled from 2000 to 2014.[2]
- Nearly four times more boys than girls have autism — one in 38 boys and one in 152 girls.[1]
- People with autism have, on average, more medical expenses per year than people without autism.[1]
- Nearly half of children with autism have average or above-average intellectual ability.[1]

What are the symptoms?

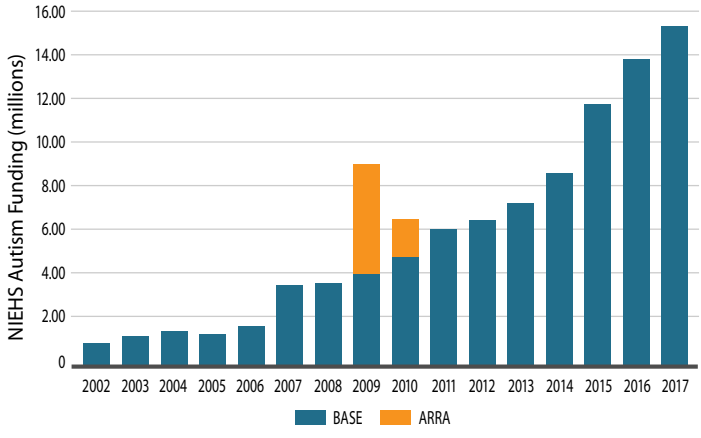
People with autism spectrum disorder often have problems with social and communication skills, as well as restricted and repetitive patterns of behavior. Early, intensive intervention can improve communication, learning, and social skills in children with ASD. Additionally, the disorder may come with other conditions, such as epilepsy, sleep disturbances, and gastrointestinal problems.

How is NIEHS contributing to research?

NIEHS steadily increased funding of ASD research over the last decade, and this investment is yielding important new discoveries that may help prevent the disorder. The NIEHS autism research program attracts talented scientists from toxicology, epidemiology, and other areas. These researchers are using new ways to measure prenatal exposures, screen for contaminants that may affect brain development, and understand how environmental factors interact with genes in ways that may lead to ASD.

NIEHS autism research funding

NIEHS funding of autism research reached $15.7 million in 2017.



ARRA indicates funds from the American Recovery and Reinvestment Act of 2009.

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National Institutes of Health
U.S. Department of Health and Human Services

April 2019

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Environmental factors play a role

Air pollution

Research supported by NIEHS indicates that early-life exposure to air pollution may be a risk factor for autism spectrum disorder.

- Children of mothers living near a freeway or traffic-related pollution during the third trimester of pregnancy were twice as likely to develop ASD. A distance of 1,014 feet, or a little less than 3.5 football fields, was considered near a freeway.[3]
- Exposure of the mother just prior to birth, and of the child shortly after, to several air pollutants, was associated with increased ASD risk and severity.[4]
- Children with a mutation in a gene called MET, combined with exposure to high levels of air pollution, may have increased risk of autism spectrum disorder.[5]

Prenatal conditions and maternal factors

Problems with a mother's immune system, certain metabolic conditions, or inflammation during pregnancy may be linked to higher ASD risk for her children.

- Some mothers of children with autism spectrum disorder have autoantibodies, or proteins produced by the immune system that attack tissues or organs in the body, that may interfere with their child's brain development. Research suggests that autoantibodies may be linked to the disorder.[6]
- Maternal diabetes or obesity may be linked to increased likelihood of having a child with ASD or other developmental disability.[7]
- Fever during pregnancy may be associated with increased risk of autism spectrum disorder in children.[8]

Metals, pesticides, and other contaminants

Prenatal and early childhood exposure to heavy metals, altered levels of metals in the body, pesticides, and other contaminants may be linked to autism spectrum disorder.

- Researchers used baby teeth that had fallen out to compare levels of lead, manganese, and zinc in children with ASD to their twin without the condition. They found children with autism spectrum disorder were low on manganese and zinc, metals essential to life, but had higher levels of lead, a harmful metal, during specific time periods of development.[9]
- Another study found that zinc-copper cycles, which regulate metal metabolism in the body, were altered in children with ASD.[10]
- Additionally, maternal exposure to insecticides during early pregnancy was associated with higher risk of the disorder in their children.[11]
- Researchers are also studying chemicals, such as bisphenol A, phthalates, flame retardants, and polychlorinated biphenyls, to see if they affect early brain development and possibly play a role in ASD.

No link has been found between autism and vaccines, including those containing thimerosal, a mercury-based compound.[12]

Nutrition

NIEHS-funded studies found that taking recommended levels of prenatal vitamins may help lower the risk of autism spectrum disorder. Furthermore, research suggests taking vitamins and supplements might provide protection from certain environmental contaminants during pregnancy.

- Women who took the daily recommended dosage of folic acid during the first month of pregnancy had a reduced risk of having a child with ASD.[13]
- Researchers found pregnant mothers who took multivitamins, with or without additional iron or folic acid, were less likely to have a child with ASD or intellectual disability.[14]
- Prenatal vitamin intake during the first month of pregnancy may also reduce ASD risk in siblings of children with the disorder.[15]

Collaborations

The Interagency Autism Coordinating Committee (IACC) is a federal advisory committee that coordinates federal efforts and provides advice to the secretary of the U.S. Department of Health and Human Services on issues related to autism spectrum disorder. NIEHS partners with members of IACC to summarize advances in autism research and participate in strategic planning for research needs. The committee works closely with the public to hear their concerns and recommendations for research.

Population-based research

Studies with large numbers of people have revealed patterns that may indicate the involvement of environmental factors in ASD. NIEHS funds several studies that include participants from across the United States, as well as in Australia, Denmark, Finland, Israel, Norway, Sweden, and South Korea, including the following:

CHARGE – The Childhood Autism Risks from Genetics and the Environment (CHARGE) study seeks to identify causes and contributing factors to autism spectrum disorder. Launched in 2003, this study enrolls children with autism, with developmental delay but not autism, and with typical development. CHARGE conducts medical exams and collects blood and urine samples from the children, and also obtains information on environmental exposures, health, lifestyle, and behavior from their parents.

MARBLES – The Markers of Autism Risk in Babies – Learning Early Signs (MARBLES) study follows women at high risk of giving birth to a child with autism. Women are enrolled during early pregnancy and their children are followed to age 3. By collecting data from mothers and their babies throughout critical periods, these studies can help identify and measure environmental exposures that may affect early stages of brain development.

EARLI – The Early Autism Risk Longitudinal Investigation (EARLI) study enrolled a large group of pregnant mothers of children with autism. Siblings born after the child with autism spectrum disorder were subsequently followed through 3 years of age, to see if they developed the disorder. The EARLI study continues to follow the children and examine possible environmental risk factors to ASD, as well as possible links between genes and the environment, known as gene-environment interactions.

What's next?

In addition to identifying environmental factors that may affect the risk of autism spectrum disorder, NIEHS-funded researchers continue to investigate how these factors may interact with a person's genes. This information may help lead to prevention strategies and treatments, and also pinpoint areas that need further research.

- NIEHS continues to promote collaboration and dialogue among researchers. Combining data from different studies may help facilitate identification of ASD risk factors.
- Using data on genes known to be involved with ASD, scientists are screening chemicals that could interact with those genes. This research may help reveal environmental factors that increase risk, as well as provide information about specific gene-environment interactions.
- NIEHS is also interested in learning more about environmental exposures, such as air pollution and related changes at the cellular level, that affect brain development.

For more information on the National Institute of Environmental Health Sciences, go to **www.niehs.nih.gov**.

To learn more about NIEHS autism research, visit **www.niehs.nih.gov/research/supported/health/autism**

1. CDC (Centers for Disease Control and Prevention). 2014. Autism Spectrum Disorder – Data and Statistics. Available: http://www.cdc.gov/ncbddd/autism/data.html [accessed 8 January 2019].
2. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, Kurzius-Spencer M, Zahorodny W, et al. 2018. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. MMWR Surveill Summ 67:1–23.
3. Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. 2011. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect 119(6):873-877.
4. Kalkbrenner AE, Windham GC, Zheng C, McConnell R, Lee NL, Schauer JJ, Thayer B, Pandey J, Volk HE. 2018. Air Toxics in Relation to Autism Diagnosis, Phenotype, and Severity in a U.S. Family-Based Study. Environ Health Perspect 126(3):037004.
5. Volk HE, Kerin T, Lurmann F, Hertz-Picciotto I, McConnell R, Campbell DB. 2014. Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. Epidemiology 25(1):44-47.
6. Jones KL, Van D Water J. 2018. Maternal autoantibody related autism: mechanisms and pathways. Mol Psychiatry 24(2):252-265.
7. Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, Hertz-Picciotto I. 2012. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 129(5):e1121-e1128.
8. Brucato M, Ladd-Acosta C, Li M, Caruso D, Hong X, Kaczaniuk J, Stuart EA, Fallin MD, Wang X. 2017. Prenatal exposure to fever is associated with autism spectrum disorder in the Boston birth cohort. Autism Res 10(11):1878-1890.
9. Arora M, Reichenberg A, Willfors C, Austin C, Gennings C, Berggren S, Lichtenstein P, Anckarsater H, Tammimies K, Bolte S. 2017. Fetal and postnatal metal dysregulation in autism. Nat Commun 8:15493.
10. Curtin P, Austin C, Curtin A, Gennings C, Arora M, Tammimies K, Wilfors C, Berggre S, Siper P, Rai D, Meyering K, Kolevzon A, Mollon J, David AS, Lewis G, Zammit S, Heilbrun L, Palmer RF, Wright RO, Bolte S, Reichenberg A. 2018. Dynamical features in fetal and postnatal zinc-copper metabolic cycles predict the emergence of autism spectrum disorder. Sci Adv 30:4(5).
11. Brown AS, Cheslack-Postava K, Rantakokko P, Kiviranta H, Hinkka-Yli-Salomäki S, McKeague IW, Surcel HM, Sourander A. 2018. Association of Maternal Insecticide Levels With Autism in Offspring From a National Birth Cohort. Am J Psychiatry; doi: 10.1176/appi.ajp.2018.17101129 [online 16 August 2018].
12. CDC (Centers for Disease Control and Prevention). 2018. Autism Spectrum Disorder – Related Topics. Available: https://www.cdc.gov/ncbddd/autism/topics.html [accessed 4 April 2019].
13. Schmidt RJ, Tancredi DJ, Ozonoff S, Hansen FL, Hartiala J, Allayee H, Schmidt LC, Tassone F, Hertz-Picciotto I. 2012. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr 96(1):80-9.
14. DeVilbiss EA, Magnusson C, Gardner RM, Rai D, Newschaffer CJ, Lyall K, Dalman D, Lee BK. 2017. Antenatal nutritional supplementation and autism spectrum disorders in the Stockholm youth cohort: population based cohort study. BMJ 359:j4273.
15. Schmidt RJ, Iosif AM, Guerrero AE, Ozonoff S. 2019. Association of maternal prenatal vitamin use with risk for autism spectrum disorder recurrence in young siblings. JAMA Psychiatry; doi: 10.1001/jamapsychiatry.2018.3901 [epub ahead of print].

EXHIBIT 2

ment to compare outcomes in auctions with secret versus public reserve prices, two common approaches used to auction goods on the Internet. They auctioned 50 matched pairs of Pokemon trading cards on eBay: one with a minimum bid of 30% of the card's book value, and one with a minimum bid of $0.05 and a secret reserve price equal to 30% of the card's book value. Keeping the reserve price secret reduced the probability of selling any card, the number of serious bidders in an auction, and the amount of the winning bid. Thus, contrary to the beliefs of many eBay sellers and to the predictions of models of rational bidder behavior, using secret reserve prices instead of public reserve prices actually lowers a seller's expected returns.

An example of a natural field experiment designed to measure key parameters of a theory is (*6*), where parameters associated with why people give to charities are estimated. In this study, Karlan and I worked with a private charity to explore the effects of different matching rates on charitable giving by soliciting contributions from more than 50,000 supporters. In one group, solicitees were informed that for every dollar contributed, an outside donor would match the contribution 1:1. A control group received no match, and other groups received more generous matching rates (such as 2:1 or 3:1). Simply announcing that a match is available increases the revenue per solicitation by 19%. In addition, the match offer increases the probability that an individual donates by 22%. These estimates shed light on a key parameter for fundraisers: how sensitive contributions are to the "price" of giving.

In the examples above, I have focused on natural field experiments; similar examples can be found for artifactual and framed field experiments. The various field experimental approaches, lab experiments, and econometric methods using naturally occurring data should be thought of as strong complements—much like theory and empiricism. Combining insights gained from each methodology will permit scholars to develop a deeper scientific understanding. For example, economists have shown that there is much to be gained from gathering data from a variety of settings, both controlled and uncontrolled. In those cases where behaviors are robust, the advice to policy-makers can be unequivocal. In other instances, behaviors might differ systematically, and developing theory to explain such discrepancies deepens our economic understanding. Similar gains can accrue within the sciences more broadly.

References

1. J. J. Heckman, *Int. Stat. Rev.* **76**, 1 (2008).
2. G. W. Harrison, J. A. List, *J. Econ. Lit.* **42**, 1009 (2004).
3. J. A. Hausman, D. A. Wise, *Social Experimentation* (Univ. of Chicago Press, Chicago, 1985).
4. E. T. Anderson, Y. Hu, E. Brynjolfsson, D. Simester, *Econ. Inq.* **46**, 3 (2008).
5. D. Reiley, R. Katkar, *Adv. Econ. An. Pol.* **6**, 7 (2006).
6. D. Karlan, J. A. List, *Am. Econ. Rev.* **95**, 1688 (2007).

10.1126/science.1156716

GENETICS

Insights into the Pathogenesis of Autism

Genetic analysis of inbred families reveals genes associated with susceptibility to autism.

James S. Sutcliffe

Autism is a common developmental disorder that profoundly impairs the emergence of social behaviors and communication in children before 3 years of age. Repetitive, stereotyped, and obsessive-compulsive–like behaviors are also prominent features of the disorder (*1*), and are often accompanied by cognitive impairment, seizures or epilepsy, gastrointestinal complaints, disordered sleep, and other problems. Identifying risk factors for autism has become a high priority of scientists, lay groups, and parents of autistic children. On page 218 of this issue, Morrow *et al*. (*2*) add several more genes to a growing number of genetic abnormalities that correlate with susceptibility to autism (see the figure).

Twin and family studies demonstrate that the etiology of autism has a substantial genetic component. Current estimates of sibling recurrence risk—the likelihood that a younger sibling of an autistic child will also have autism—is greater than 15% (*3*–*5*). Comparing this to population rates of approximately 1 per 500 children for narrowly defined autism or 1 per 150 children for the more broadly defined autism spectrum disorders indicates a high degree of heritability in families.

Determining specific genetic changes that increase the risk of developing disorders like autism is extraordinarily complex (*6*) due to heterogeneity—different kinds of variation at many underlying genes are involved. One type of variation consists of rare disease-causing or highly penetrant mutations, and these have implicated specific biological processes. Similarly, common variation—usually discrete changes in DNA sequence—has been identified in autism, but only a few specific findings have been replicated. Other important clues to genetic factors in autism include abnormalities such as chromosomal translocations, inversions, and large deletions or duplications, which are more frequent in individuals that present clinically with dysmorphic features and severe cognitive impairment. Geneticists have long hypothesized that genes disrupted by chromosomal abnormalities in isolated cases may play a role in susceptibility to autism more broadly and have pursued experiments toward this end.

Recent advances in DNA microarray technologies have revealed a substantial etiological role for small losses and gains of DNA—so-called copy number variation—in autism (*7*–*12*). All individuals harbor this common form of genetic variation, which can be inherited from a parent or can arise as a sporadic event de novo. However, a large and growing number of deletions and duplications of DNA have been found in people with autism. As comparisons to control samples identify which variants are unique, more frequent, or equal in autism versus control cases, we will be better able to interpret the observed copy number variation.

Much discussion has focused on whether a copy number variant is inherited or arises de novo, with greater interpretive weight vis-à-vis disease association given to the latter. As with large chromosomal abnormalities, it may be that the disruption or dysregulation of gene expression underlies the risk or causal effect for a given copy number variant. Genes may be lost or an extra copy may be present on a given chromosome; genes flanking a DNA

Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN 37232–8548, USA. E-mail: james.s.sutcliffe@vanderbilt.edu

PUTATIVE AND KNOWN AUTISM-RELATED GENES

Glutamatergic synapse function and/or neuronal cell adhesion	
FMR1[A,B]	Fragile X mental retardation 1
NLGN3[B]	Neuroligin 3
NLGN4[B]	Neuroligin 4
NRXN1[B,C]	Neurexin 1
SHANK3[B,C]	SH3 and mulitple ankyrin repeat domains 3
CNTNAP2[B,C,D]	Contactin-associated protein-like 2
PCDH10[C]	**Protocadherin 10**
CNTN3[C]	**Contactin 3**
Endosomal trafficking	
NHE9 (SLC9A9)[B,C]	**Na^+/H^+ exchanger isoform 9**
NHE6 (SLC9A6)[B]	Na^+/H^+ exchanger isoform 6
***DIA1* (c3orf58)**[C]	**Deleted in autism 1**
A2BP1[C]	Ataxin 2-binding protein 1
Neuronal activity regulation	
FMR1[A,B]	Fragile X mental retardation 1
MECP2[B,C]	Methyl CpG binding protein 2
***DIA1* (c3orf58)**[C]	**Deleted in autism 1**
PCDH10[C]	**Protocadherin 10**
NHE9 (SLC9A9)[B,C]	**Na^+/H^+ exchanger isoform 9**
A2BP1[C]	Ataxin 2-binding protein 1
UBE3A[B,C]	Ubiquitin protein ligase E3A
Implicated in related disorders	
FMR1[A,B]	Fragile X mental retardation 1
MECP2[B,C]	Methyl CpG binding protein 2
NHE6 (SLC9A6)[B]	Na^+/H^+ exchanger isoform 6
A2BP1[C]	Ataxin 2-binding protein 1
UBE3A[B,C]	Ubiquitin protein ligase E3A
Other functions	
EN2[D]	Engrailed homeobox 2
SLC6A4[B,D]	Serotonin transporter (SERT, 5-HTT)
MET[D]	Met proto-oncogene (c-Met, HGFR)
SCN7A[C]	**Na^+ channel, voltage-gated, type VII**
RNF8[C]	**Ring finger protein 8**

Genes implicated in autism pathogenesis. Genes have been implicated in autism (*1*, *2*) on the basis of different functions and forms of genetic variation, and also on their association with disorders that show features of autism. They share common or related pathways, as shown. A, genes showing triplet repeat expansion; B, genes with rare mutations or coding variants; C, genes with copy number variation or chromosomal abnormality; D, association of common alleles. Genes implicated from (*2*) are shown in bold.

deletion or duplication may be subject to dysregulation because of altered local chromatin structure or separation from key enhancer elements (which regulate gene expression). Thus, copy number variation is a major category of genetic risk for autism spectrum disorders, and is implicated in 10 to 20% (or more) of cases (*7*–*12*). The genetic heterogeneity of autism, however, greatly complicates the task of identifying genes that increase susceptibility to the disorder.

Morrow *et al.* use the powerful genetic technique of homozygosity mapping to identify autism genes. Geneticists have long taken advantage of the statistical power afforded by genetic analysis of families in which parents of affected individuals share a common ancestry (e.g., first cousins). Such consanguineous families, more common in the Middle East, are at substantially increased risk for autosomal recessive conditions [traits that are expressed when an individual is homozygous (has two identical copies) for a particular gene]. There is a growing recognition that inbred families are also useful in identifying genes for complex disorders, such as autism.

Morrow *et al*. use DNA microarrays to study numerous consanguineous families from the Middle East. By analyzing the inheritance of DNA throughout the genome in these pedigrees, they identify chromosomal regions that are inherited in common by the affected individuals who share the same two copies of these regions. These homozygous segments, which are heterozygous in the related parents, are likely to represent a causal or risk factor. In several of these families, the regions linked to the autism spectrum disorder and inherited "identical by descent" contained deletions. Thus, the affected individuals were completely deficient for the genes (or potential regulatory DNA) that lie within the deleted intervals. By extension, the absence of those gene products, and/or the possible altered expression of genes in the immediate vicinity of the deletion, is predicted to cause the autism spectrum disorder in that family.

An important question is whether a gene identified as causing disease in a single inbred family has any relevance to autism in nonconsanguineous families. In addition, establishing which gene (or genes) lies within or near a deleted interval—the disruption of which is causing the disorder—is not trivial. Here, a nice story is developed for one such region on chromosome 3q containing a large (~886 kilobase) deletion. A gene called *DIA1* (*deleted in autism1*; also known as *c3orf58*) encoding an uncharacterized protein is completely removed, whereas *NHE9* (*Na^+/H^+ exchanger 9*), a nearby gene encoding a membrane protein that exchanges intracellular H^+ for extracellular Na^+, remains intact but could be dysregulated. To assess the broader relevance of these genes in autism, Morrow *et al.* sequenced the coding regions of *NHE9* in affected subjects from nonconsanguineous U.S. families and found a loss-of-function mutation in one family. Similar mutations cause an epilepsy phenotype in mice, and for the related *NHE6* gene, they cause a phenotype with autistic symptoms and epilepsy. In addition, other variation is implicated, because a focus on autism families with epilepsy led the authors to observe a much greater number of coding variants in cases compared with controls. Taken together, these findings support dysregulation of *NHE9* as a contributing or causal factor in that family.

The most provocative observations from this study point to an important functional class of genes involved in autism susceptibility. The authors show that several of the genes identified in or likely affected by homozygous deletions are regulated by neuronal activity—that is, their expression changes in response to stimulation of neuronal activity. Because autism is a neurodevelopmental disorder, emphasis has been placed on prenatal development, which is guided by intrinsic gene-expression patterns. The brain continues to develop long after birth, however, and experience and environmental input play an important role in subsequent development. Synapses (connections between neurons) mature partly as a function of experience-dependent neuronal activity and of the gene-expression changes that accompany it. But if those genes are disrupted by mutation or copy number variation, that could suggest that the process of activity-regulated synaptic development itself is disrupted in some way. Indeed, this is the authors' hypothesis.

Dysregulation of synaptic development is an established idea in autism research. Although it is conceptually a big step, and the authors are cautious in their conclusions, the possibility that dysregulation of these genes results in disruption of synaptic development in response to early-life environment and experiences is an intriguing proposal, whose validity must await the results of further research.

References

1. L. Kanner, *Nerv. Child* **2**, 217 (1943).
2. E. M. Morrow *et al.*, *Science* **321**, 218 (2008).
3. R. J. Landa, *Nat. Clin. Pract. Neurol.* **4**, 138 (2008).
4. R. J. Landa, K. C. Holman, E. Garrett-Mayer, *Arch. Gen. Psychiatry* **64**, 853 (2007).
5. M. B. Lauritsen, C. B. Pedersen, P. B. Mortensen, *J. Child Psychol. Psychiatry* **46**, 963 (2005).
6. B. J. O'Roak, M. W. State, *Autism Res.* **1**, 4 (2008).
7. J. Sebat *et al.*, *Science* **316**, 445 (2007).
8. P. Szatmari *et al.*, *Nat. Genet.* **39**, 319 (2007).
9. C. R. Marshall *et al.*, *Am. J. Hum. Genet.* **82**, 477 (2008).
10. S. L. Christian *et al.*, *Biol. Psychiatry* **63**, 1111 (2008).
11. R. A. Kumar *et al.*, *Hum. Mol. Genet.* **17**, 628 (2008).
12. L. A. Weiss *et al.*, *N. Engl. J. Med.* **358**, 667 (2008).

10.1126/science.1160555

Science

Insights into the Pathogenesis of Autism

James S. Sutcliffe

Science, 321 (5886), • DOI: 10.1126/science.1160555

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EXHIBIT 3

in linkage and association analyses, will have to be collected prospectively to avoid biases associated with amnestic information, use of proxy informants, and physiological changes that are a consequence of, rather than a cause of, the disease process. Family-based designs will be particularly attractive because they more effectively control for differences in the genetic background among affected and unaffected persons and for measured nongenetic risk factors (*50*, *51*). Such an effort will require collaborations between clinicians, epidemiologists, and geneticists to develop and standardize the collection of phenotypes and to design new statistical approaches that can model complex multifactorial and polygenic causologies (*52*, *53*). This will be useful not only for the adult-onset neuropsychiatric disorders discussed here but also for most other common, complex disorders.

References and Notes

1. W. A. Rocca, L. A. Amaducci, B. S. Schoenberg, *Ann. Neurol.* **19**, 415 (1986).
2. N. T. Lautenschlager *et al.*, *Neurology* **46**, 641 (1996).
3. M. T. Tsuang, M. Tohen, *Textbook in Psychiatric Epidemiology* (Wiley, Weinheim, Germany, ed. 2, 2002).
4. P. McGuffin, M. J. Owen, I. I. Gottesman, *Psychiatric Genetics and Genomics* (Oxford University Press, Oxford, 2002).
5. A. M. Goate *et al.*, *Nature* **349**, 704 (1991).
6. R. Sherrington *et al.*, *Nature* **375**, 754 (1995).
7. E. I. Rogaev *et al.*, *Nature* **376**, 775 (1995).
8. M. Citron *et al.*, *Nature Med.* **3**, 67 (1997).
9. A. Saunders *et al.*, *Neurology* **43**, 1467 (1993).
10. P. Poorkaj *et al.*, *Ann. Neurol.* **43**, 815 (1998).
11. C. M. Clark, J. H. Karlawish, *Ann. Intern. Med.* **138**, 400 (2003).
12. D. F. Levinson, M. D. Levinson, R. Segurado, C. M. Lewis, *Am. J. Hum. Genet.* **73**, 17 (2003).
13. C. M. Lewis *et al.*, *Am. J. Hum. Genet.* **73**, 34 (2003).
14. R. Segurado *et al.*, *Am. J. Hum. Genet.* **73**, 49 (2003).
15. D. Botstein, N. Risch, *Nature Genet.* **33** (suppl.), 228 (2003).
16. K. E. Lohmueller, C. L. Pearce, M. Pike, E. S. Lander, J. N. Hirschhorn, *Nature Genet.* **33**, 177 (2003).
17. M. C. O'Donovan, N. M. Williams, M. J. Owen, *Hum. Mol. Genet.* **12** (suppl. 2), R125 (2003).
18. S. A. Crone, K. F. Lee, *Ann. N.Y. Acad. Sci.* **971**, 547 (2002).
19. M. A. Benson, S. E. Newey, E. Martin-Rendon, R. Hawkes, D. J. Blake, *J. Biol. Chem.* **276**, 24232 (2001).
20. R. E. Straub *et al.*, *Am. J. Hum. Genet.* **71**, 337 (2002).
21. F. Karoum, S. J. Chrapusta, M. F. Egan, *J. Neurochem.* **63**, 972 (1994).
22. J. A. Gogos *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 9991 (1998).
23. T. E. Goldberg *et al.*, *Arch. Gen. Psychiatry* **60**, 889 (2003).
24. S. Shifman *et al.*, *Am. J. Hum. Genet.* **71**, 1296 (2002).
25. N. J. Bray *et al.*, *Am. J. Hum. Genet.* **73**, 152 (2003).
26. I. Chumakov *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 13675 (2002).
27. M. A. Pericak-Vance *et al.*, *JAMA* **278**, 1282 (1997).
28. E. Rogaeva *et al.*, *JAMA* **280**, 614 (1998).
29. M. A. Pericak-Vance *et al.*, *Exp. Gerontol.* **35**, 1343 (2000).
30. A. Myers *et al.*, *Science* **290**, 2304 (2000).
31. L. Bertram *et al.*, *Science* **290**, 2302 (2000).
32. R. Mayeux *et al.*, *Am. J. Hum. Genet.* **70**, 237 (2002).
33. D. Blacker *et al.*, *Hum. Mol. Genet.* **12**, 23 (2003).
34. U. Finckh, *J. Neural. Transm.* **110**, 253 (2003).
35. E. Hattori *et al.*, *Am. J. Hum. Genet.* **72**, 1131 (2003).
36. M. F. Egan *et al.*, *Cell* **112**, 257 (2003).
37. M. Neves-Pereira *et al.*, *Am. J. Hum. Genet.* **71**, 651 (2002).
38. P. Sklar *et al.*, *Mol. Psychiatry* **7**, 579 (2002).
39. A. Caspi *et al.*, *Science* **301**, 386 (2003).
40. I. I. Gottesman, T. D. Gould, *Am. J. Psychiatry* **160**, 636 (2003).
41. N. Ertekin-Taner *et al.*, *Science* **290**, 2303 (2000).
42. H. Stefansson *et al.*, *Am. J. Hum. Genet.* **71**, 877 (2002).
43. A. Petronis, *Trends Genet.* **17**, 142 (2001).
44. A. Petronis, *Neuropsychopharmacology* **23**, 1 (2000).
45. A. Petronis *et al.*, *Schizophr. Bull.* **29**, 169 (2003).
46. O. C. Stine *et al.*, *Am. J. Hum. Genet.* **57**, 1384 (1995).
47. F. J. McMahon *et al.*, *Am. J. Hum. Genet.* **61**, 1397 (1997).
48. S. D. Detera-Wadleigh *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 5604 (1999)
49. D. A. Lewis, P. Levitt, *Annu. Rev. Neurosci.* **25**, 409 (2002).
50. L. Farrer, in *Cerebral Cortex: Neurodegenerative and Age-Related Changes in Structure and Function of the Cerebral Cortex*, A. Peters, J. Morrison, Eds. (Plenum, New York, 1999), vol. 14, pp. 433–459.
51. N. J. Risch, *Nature* **405**, 847 (2000).
52. N. J. Cox *et al.*, *Nature Genet.* **21**, 213 (1999).
53. Y. Shao *et al.*, *Am. J. Hum. Genet.* **72**, 539 (2003).
54. P. H. St George-Hyslop *et al.*, *Science* **263**, 536 (1994).
55. M. Citron *et al.*, *Neurobiol. Dis.* **5**, 107 (1998).

56. Supported by grants from the Canadian Institutes of Health Research, Howard Hughes Foundation, Alzheimer Society of Ontario, Canadian Genetic Diseases Network, NIH (R01-AG09029, P30-AG95004, U01-AG17173, AG15473, AG07232, MH31593, MH40856, and MH43271), Philip Morris External Research Program, Banbury Fund, Taub Foundation, and Rockefeller Foundation.

VIEWPOINT

Postnatal Neurodevelopmental Disorders: Meeting at the Synapse?

Huda Y. Zoghbi

We often think of neurodevelopmental disorders as beginning before birth, and many certainly do. A handful, however, strike many months after birth, following a period of apparently normal growth and development. Autism and Rett syndrome are two such disorders, and here I consider some of their similarities at the phenotypic and pathogenic levels. I propose that both disorders result from disruption of postnatal or experience-dependent synaptic plasticity.

Falling silent. After a child is born, parents watch with anticipation the normal developmental program that ensues. The baby smiles and follows faces at 6 weeks, acquires sufficient motor control to sit and transfer toys by 6 months, and typically walks and says a couple of words by 12 to 15 months. Language and thought continue to develop as children begin to understand make-believe play, to use verbs to describe a mental state, and to imitate complex actions.

Ashley delighted her parents as she progressed through early developmental milestones. She learned to crawl, babble, walk, and sing nursery rhymes, all at the expected ages. At 18 months, however, her progress ceased. No more songs or words, only a vacant stare. Ashley's ability—or inclination—to use her hands was overwhelmed by incessant hand-wringing; tremors, rocking, and loss of balance robbed her of normal motor control; apnea and hyperventilation indicated autonomic control was going haywire, too. Her head growth slowed, and her social interactions became almost nonexistent.

Alex, born to a different family at a different time, has a similar story. He was a healthy boy who smiled and followed faces by 6 weeks, made eye contact, and enjoyed interactive games. At 10 months of age he showed an unusually intense interest in wheels, but he continued to interact socially and was saying several words and walking by 13 months. Some time between 15 and 18 months, however, Alex, like Ashley, fell si-

Departments of Pediatrics, Neurology, and Molecular and Human Genetics, Division of Neuroscience, and Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX 77030, USA. E-mail: hzoghbi@bcm.tmc.edu

Table 1. Postnatal neurodevelopmental phenotypes associated with mutations in genes for MECP2 and NLGN-3 and -4, and 15q duplications.

Gene	Females	Males
MECP2	Rett syndrome including more severe congenital form or milder preserved speech variant	Fatal encephalopathy Rett if 47, XXY, or somatic mosaicism
	Angelman syndrome phenotype	Mental retardation, tremors, and seizures
	Autism	
	Mental retardation Mild learning disability	Mental retardation, spasticity, and psychosis
NLGN-3	Asymptomatic	Autism or Asperger
NLGN-4	Asymptomatic	Autism or Asperger
Duplications of 15q11–q13 (especially maternally inherited)		Autistic spectrum disorder or autism plus one or more of the following: Mental retardation, hypotonia, seizures, short stature, and abnormal epicanthal folds

lent. He stopped trying to communicate through gestures or words. He lost interest in social interactions and became utterly absorbed with lines on a tile or wheels on a toy. He seemed less sensitive to pain but hypersensitive to heat. He flapped his hands constantly and picked at his skin.

Similar histories, different diagnoses: Ashley has Rett syndrome and Alex is autistic. Both disorders become manifest after a period of apparently normal development. Both disrupt social and language development and are accompanied by unusual stereotypies. Despite the intellectual regression that marks the majority of Rett patients and ~30% of autistic patients (*1, 2*), neither disease is neurodegenerative in nature. Many children can improve somewhat as they get older. Although neither Ashley nor Alex have any language skills, they do have better eye contact now and seem to recognize family and friends at their respective ages of 23 and 11 years. The onset of both disorders after neurogenesis, neuronal migration, and maturation have occurred suggests that these disorders might affect synaptic maturation, connectivity, or stabilization.

Rett Syndrome: One Gene, Many Phenotypes

Rett syndrome was first described by the Austrian pediatrician Andreas Rett (*3*), but skeptical clinicians doubted its identity as a distinct syndrome until 1983, when Hagberg and colleagues reported on 35 patients with an undeniably unique postnatal developmental disorder (*4*). One difficulty in diagnosis was (and is) that clinical and laboratory tests are nonspecific. The electroencephalogram (EEG) is typically normal the first 2 to 3 years of life (*5, 6*), after which the background activity gradually slows, and repetitive high-amplitude spike and wave discharges appear in 60 to 70% of these patients. Imaging studies reveal changes in blood flow reminiscent of patterns seen in young infants, suggesting some arrest in development (*7, 8*). Pathological studies show other changes, also nonspecific. Neurons are abnormally small and densely packed, and have markedly shortened and simplified dendritic arbors, although migration seems to be normal (*9–11*). A degenerative process is unlikely, because brains of Rett syndrome children weigh about 30% less than normal at any given age (*12, 13*).

Mutations in the X-linked methyl-CpG–binding protein 2 (*MECP2*) gene cause the majority of Rett syndrome cases (*1, 14*). Both mutation type and, in females, patterns of X chromosome inactivation (XCI) create a surprisingly wide range of phenotypes. Females with favorably skewed XCI can be asymptomatic or have mild learning disability, autism, or mild, later-onset versions of Rett (*15–20*). In males, the range is even wider: mutations that would cause classic Rett in females produce severe neonatal encephalopathy, motor abnormalities, respiratory dysfunction, and death by the second year. Mutations that cause little or no phenotype in female carriers cause male children to develop X-linked mental retardation with seizures, tremors, spasticity, macrocephaly, or bipolar disease (*21–25*). One boy with a receptive language disorder developed childhood-onset schizophrenia (*26*). This phenotypic diversity (Table 1) raises questions about the differential effects of the mutations, regional or neuronal vulnerability to MeCP2 dysfunction, effects of genetic modifiers, and the nature of MeCP2's role in the brain.

MeCP2 was first identified as a member of the methyl-CpG–binding domain (MBD) protein family (*27*) and has been thought to serve as a methylation-dependent repressor (*28, 29*). MeCP2 dysfunction could thus disrupt the normal developmental program of gene silencing, but how this might result in a predominantly neurological phenotype has been a pressing question. It is interesting that MeCP2 is more abundant in brain tissue than most peripheral tissues (*30, 31*), is expressed in neurons but not in glia, and is localized to cell nuclei (*30–32*). Even more interesting, MeCP2 levels increase in cortical neurons throughout development (*31–34*) (Fig. 1). In addition to providing one possible explanation to the postnatal onset of symptoms, this expression pattern suggests that MeCP2 might help maintain or modulate neuronal maturity and plasticity.

Evidence from animal models and hu-

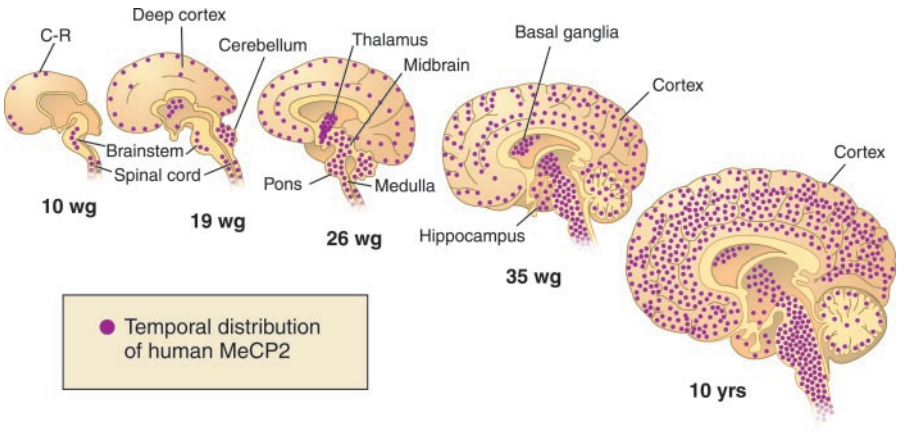


Fig. 1. Spatial and temporal distribution of MeCP2 during human development. MeCP2 is abundant in mature neurons and has an expression pattern that correlates with the ontogeny of the CNS—spinal cord first, cerebral cortex last. Cajal-Retzius (C-R) neurons are the first cortical neurons to mature and express MeCP2, followed by midbrain, thalamus, cerebellum, and deep cortical neurons. Expression in basal ganglia, hypothalamus, hippocampus, and superficial cortical layers appears later, and the number of MeCP2-positive neurons in the cerebral cortex continues to increase until 10 years of age. Wg, weeks of gestation.

mans supporting transcriptional alteration of neuronal genes is somewhat mixed. Human brain tissues show alterations in gene expression (*35*), but the role of these changes in pathogenesis is difficult to ascertain because of the confounding effects of chronic disease. Male *Mecp2*-null mice are small, hypoactive, clasp their hind limbs, have breathing abnormalities, and die by 3 months of age; female mice develop similar features but a bit later than males (*36, 37*). Conditional deletion of *Mecp2* in postmitotic neurons recapitulates these features, albeit more slowly (*36*). Yet transcriptional profiling of brain tissue from *Mecp2*-null mice has revealed no dramatic changes in gene expression (*38*). Elevated levels of acetylated histone H3, however, were found in brains of mice bearing a truncating mutation similar to one found in classic Rett patients ($Mecp2^{308}$). These mice develop a progressive neurological phenotype reminiscent of Rett syndrome, and that supports the hypothesis that transcriptional misregulation could account for at least some aspects of the phenotype (*39*).

In *Xenopus,* absence of xMeCP2 function disrupts normal neuronal differentiation mediated by the Notch-Delta signaling pathway. Normally, xMeCP2 interacts with the SMRT (silencing mediator for retinoid and thyroid-hormone receptors) corepressor complex and silences *xHairy2a* by binding a methylated CpG site in its promoter. Expression of MeCP2 lacking a transcriptional repression domain causes an increase in the number of differentiated neurons due to abnormal regulation of *xHairy2a* expression (*40*). Whether similar specific neuronal targets will be identified in mice and human remains to be seen. Loss of MeCP2 in mammals does not alter neurogenesis, probably because the timing of its expression in the CNS is different from that of its *Xenopus* homolog, but it is conceivable that misregulation of *HES1* (the mammalian homolog of *Hairy2a*) contributes to neuronal dysfunction. The future of Rett research clearly depends on identifying MeCP2 targets in the CNS and understanding the cascade of events that follows their dysregulation.

Autism: Many Genes, One Family of Phenotypes

Like Rett syndrome, autism covers a range of phenotypes. Infantile autism, described in 1943 by Leo Kanner as an inability of affected children to develop social reciprocity (*41*), is the more severe form. Hans Asperger used the term "autistic psychopathy" to describe similar patients in 1944; Asperger syndrome patients typically do not have significant delay in language or cognitive development—indeed, they can function at quite a high level—but suffer social deficits and various stereotypies.

Unlike Rett children, autistic individuals tend to have larger head size than expected for a given age (*42–44*). Autistic brains are larger; the white matter is more prominent, although the cerebral cortex, hippocampus, and amygdala are smaller than normal (*44, 45*). It is interesting that, at birth, the brains of autistic children tend to be smaller than those of healthy infants, but between 6 and 14 months of age they undergo abnormally accelerated growth (*46*). Whether the increase in brain size is due to the formation of too many connections or poor elimination of inappropriate connections is not known. A study aimed at understanding the neuroanatomical basis of spatial working deficits in autism found decreased activation in the dorsolateral prefrontal cortex and posterior cingulate cortex with the use of functional magnetic resonance imaging (MRI) (*47*). Functional imaging studies during tasks that invoke mentalizing show that Asperger patients have less activation in the critical medial prefrontal region, superior temporal sulcus, and peri-amygdaloid cortex (*48*). Neuropathological studies show fewer Purkinje cells than normal, small neuronal size, and increased packing density in several nuclei of the amygdala (*49*); small neurons with decreased dendritic branches have occasionally been observed in CA1 and CA4 (*50*).

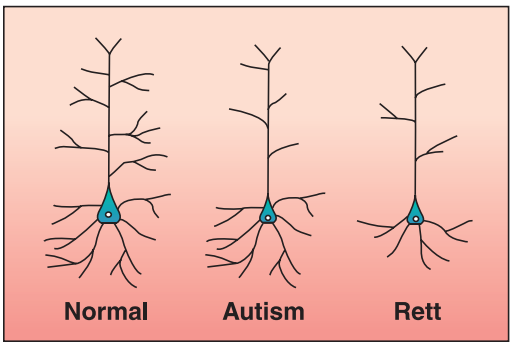


Fig. 2. Schematic representation of pyramidal neurons from control, autism, and Rett brains. In autism, the cell body is small and there is reduced dendritic branching. Similar changes occur in Rett, along with reduction in basilar dendritic branching. The reported changes are subtle and apply to a few neurons in selected brain regions in each disorder (*50, 81*).

Twin studies provide the most compelling evidence for a genetic origin of autism (*51*). The concordance rate in monozygotic (MZ) twins is 70 to 90% and for dizygotic (DZ) twins is 0 to 10% (*52–55*). The high concordance rate in MZ twins suggests either de novo sporadic mutations in a single gene for a particular autism locus or a multilocus model involving two or more interacting loci (*56*). Although these models are not mutually exclusive, the data thus far support the existence of several autism loci with mutations in a single gene underlying the etiology for a specific locus.

A variety of chromosomal rearrangements have been reported in autistic children, with extra copies of 15q11–q13 being the most frequently reported (*57–68*). Nullisomy, disomy, trisomy, and tetrasomy of 15q11–q13 have all been associated with classic autism or other developmental disabilities, which suggests that dosage of one or more genes in 15q11–q13 is critical for neuronal function. Because many of the duplications causing an autism phenotype are of maternal origin, one cannot help but consider the *UBE3A* gene, mutated in Angelman syndrome, a prime candidate for mediating some of the phenotypic features. *ATP10C* is another gene that is maternally expressed in some tissues and may contribute to the phenotype (*69*).

Single gene mutations can also produce an autistic phenotype. A recent study identified *MECP2* mutations in 2 out of 68 females with an autistic disorder (*20*). These two females had mutations that typically cause classic Rett syndrome, so it is likely that modifier genes and/or regional-specific differences in XCI patterns are responsible for their autism phenotype. Mutations in neuroligin-3 (NLGN-3) and NLGN-4, mapping to Xp22.3 and Xq13, respectively, can cause autism or Asperger syndrome (*70*). A screen of 140 male and 18 female siblings and twins identified a frame-shifting mutation in NLGN-4 and missense mutations in an evolutionarily conserved residue in NLGN-3. That both mutations were found in asymptomatic mothers could be explained by XCI, but it is possible that the missense mutation is a benign variant. The case of the truncating mutation in NLGN-4 is more convincing, given that its de novo nature has been established. These data show that mutations in a single gene can indeed reproduce all the classic features of autism and, for some cases, provide a genetic mechanism for the high male-to-female (4:1) ratio in autism. They also provide neurobiologists with two excellent molecules with which to begin studying pathophysiologic mechanisms in autism. It is tempting to speculate that additional autism genes might be soon identified by following the pattern of Rett research, i.e., by focusing on cases with a strictly defined phenotype (e.g., classic autism with or without regression) to decrease the effects of genetic heterogeneity. As causative genes are found, they can be tested in patients with variant phenotypes.

Do Rett and Autism Meet at the Synapse?

For all the apparent differences, there are striking similarities between Rett syndrome and autism. Indeed, Rett has been classified

as a pervasive developmental autistic spectrum disorder in the ICD-10 (*71*). The timing of disease onset is similar; some neurons show reduced dendritic arborization (Fig. 2); and both disorders manifest abnormal social reciprocity, lack of communication, and stereotyped behaviors. Could there be mechanistic relationships between the two diseases? The continuous increase in abundance of MeCP2 in cortical neurons throughout childhood (*31*) (Fig. 1) points to the dynamic regulation of this protein, perhaps as neurons form new synaptic connections that might be experience-dependent. I suggest that both Rett and autism could be disorders of synaptic modulation or maintenance.

Recent data consistent with such a hypothesis came from a study of MeCP2 expression in olfactory receptor neurons (ORNs), which display postnatal neurogenesis (*72*). MeCP2 expression localizes to mature ORNs. After ablation of ORNs, which induces neurogenesis, MeCP2 expression gradually reaches prelesion levels unless the ORN targets are removed by bulbectomy. Without ORN targets, and thus without functional synaptogenesis, the levels of MeCP2 in the mature ORN are not completely restored (*72*). Thus, MeCP2 is expressed in mature neurons before synaptogenesis and might be critical for maintaining or modulating synapses. In human patients, the data are consistent with the idea that MeCP2 is not essential for initiating synaptogenesis—clearly, there are enough viable synapses that Rett patients can function at some level—yet the precipitous loss of learned skills (and even the loss of learning itself) hint that the ability of Rett patients to maintain or form new synapses is impaired.

In autism, mutations in two different neuroligins draw attention to the synapse. NLGN-3 and -4 belong to a larger family of postsynaptic cell adhesion molecules, some of which are known to interact with β-neurexin (*73, 74*). Neurexins are encoded by three large genes that each give rise to α and β (short) isoforms, depending on the choice of promoter (*75, 76*). α-Neurexins are essential for calcium-triggered neurotransmitter release through their ability to cluster or activate calcium channels at presynaptic terminals near the synaptic vesicles and release machinery (*77*). They have no effect on synapse formation. In contrast, the smaller β-neurexins induce presynaptic differentiation in immature cerebellar granule neurons and hippocampal neurons through their interaction with neuroligin-1 (*74*). Neuroligin-1 stimulates presynaptic differentiation and synaptic vesicle recruitment by clustering β-neurexin; furthermore, overexpression of neuroligin-1 induces postsynaptic differentiation based on the increase in PSD-95 and puncta positive for glutamate receptors GluR2/3 (Fig. 3). Focusing attention on the synapse provides molecular targets that deserve to be thoroughly investigated in autism (Fig. 3). Because of the extensive alternative splicing that occurs in this family of genes, some cases of autism might be due to tissue-specific splicing defects. Such abnormalities might be harder to detect by sequencing of coding regions and/or might result from dysfunction in RNA-binding proteins that mediate processing of such RNAs.

Although we have not yet identified neuronal MeCP2 targets in mammals, I suspect that some of its targets will directly or indirectly regulate gene products involved in autism. These interactions might occur at the synapse or regulate synaptic functions.

In contemplating possible pathogenetic relationships between Rett syndrome and autism, the *UBE3A* gene (located on 15q11–13), which causes Angelman syndrome, emerges as a tantalizing, if highly speculative, link. Angelman syndrome resembles both autism and Rett syndrome: Affected children suffer developmental delay, movement disorder, tremulousness, hand-flapping, short attention span, slowed head growth, increased sensitivity to heat, stereotypic mouthing behaviors, and a fascination with water. Indeed, several patients with Angelman syndrome meet the behavioral criteria for the diagnosis of autistic spectrum disorder, and *MECP2* mutations have caused some children to display an Angelman phenotype (*78–80*). Given the importance of DNA methylation in regulating neuronal expression of this gene, could it be that MeCP2 regulates *UBE3A* expression? As for autism, loss of function, duplications, and triplications of *UBE3A* have been associated with autistic features in patients with 15q11–q13 anomalies; could *UBE3A*, a ubiquitin ligase, be involved in the degradation of NLGN and/or one of its partners? We can now test whether some molecular pathways are shared by these three disorders (or groups of disorders), because specific molecules are in hand, and there are excellent mouse models for Rett and Angelman syndrome. Although there are other causes of autism (and possibly Rett) that remain to be discovered, knowing the genetic basis of some cases is sufficient to allow us to begin unraveling the complex and fascinating pathogenesis of these unusual and devastating disorders.

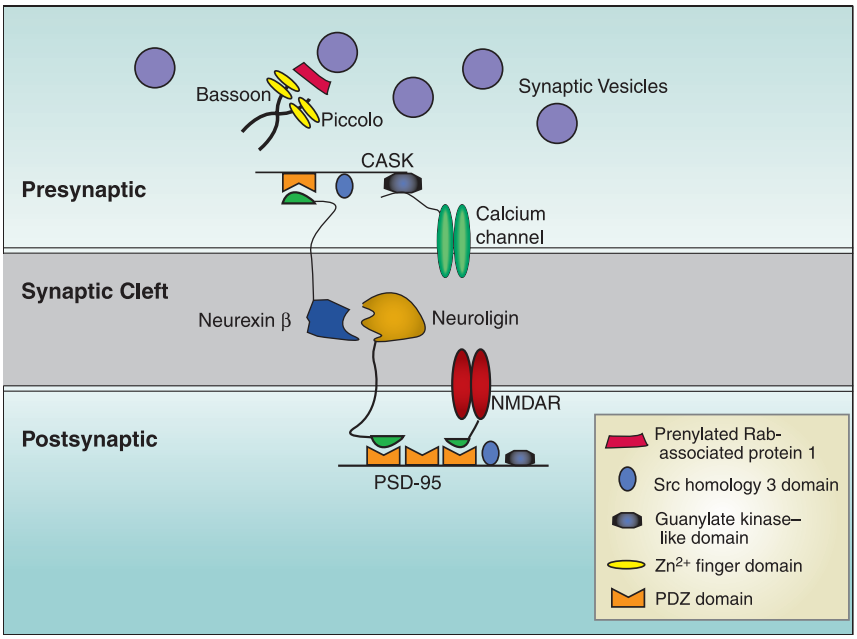


Fig. 3. A model depicting the role of neuroligins for clustering β-neurexin and inducing presynaptic differentiation. Neuroligin in the postsynaptic membrane recruits β-neurexin molecules in the presynaptic membrane and leads to their clustering. Clustered β-neurexin molecules recruit scaffolding and signaling molecules that, in turn, signal the recruitment of synaptic vesicles. Neuroligin might contribute to postsynaptic differentiation by interacting with scaffolding proteins such as PSD-95, which also interact with glutamate receptors. This model is based on data from a study of neuroligin-1 and β-neurexin (*74*). Whether NLGN-3 and NLGN-4, mutated in autism, have similar or related functions needs to be investigated.

References and Notes

1. M. D. Shahbazian, H. Y. Zoghbi, *Am. J. Hum. Genet.* **71**, 1259 (2002).
2. S. Wilson, A. Djukic, S. Shinnar, C. Dharmani, I. Rapin, *Dev. Med. Child. Neurol.* **45**, 508 (2003).
3. A. Rett, *Wien. Med. Wochenschr.* **116**, 723 (1966).
4. B. Hagberg, J. Aicardi, K. Dias, O. Ramos, *Ann. Neurol.* **14**, 471 (1983).
5. N. P. Verma, R. L. Chheda, M. A. Nigro, Z. H. Hart, *Electroencephal. Clin. Neurophysiol.* **64**, 394 (1986).

6. D. G. Glaze, J. D. Frost Jr., H. Y. Zoghbi, A. K. Percy, *Arch. Neurol.* **44**, 1053 (1987).
7. A. L. Reiss *et al.*, *Ann. Neurol.* **34**, 227 (1993).
8. J. B. Nielsen, L. Friberg, H. Lou, N. A. Lassen, I. L. Sam, *Arch. Neurol.* **47**, 982 (1990).
9. M. L. Bauman, T. L. Kemper, D. M. Arin, *Neuropediatrics* **26**, 105 (1995).
10. J. Armstrong, M. Pineda, E. Aibar, E. Gean, E. Monros, *Ann. Neurol.* **50**, 692 (2001).
11. P. V. Belichenko, A. Oldfors, B. Hagberg, A. Dahlstrom, *Neuroreport* **5**, 1509 (1994).
12. K. Jellinger, F. Seitelberger, *Am. J. Med. Genet. Suppl.* **1**, 259 (1986).
13. D. D. Armstrong *et al.*, *Pediatr. Neurol.* **20**, 125 (1999).
14. R. E. Amir *et al.*, *Nature Genet.* **23**, 185 (1999).
15. M. Wan *et al.*, *Am. J. Hum. Genet.* **65**, 1520 (1999).
16. R. E. Amir *et al.*, *Ann. Neurol.* **47**, 670 (2000).
17. T. Bienvenu *et al.*, *Hum. Mol. Genet.* **9**, 1377 (2000).
18. L. Villard *et al.*, *Neurology* **55**, 1188 (2000).
19. K. Hoffbuhr *et al.*, *Neurology* **56**, 1486 (2001).
20. R. M. Carney *et al.*, *Pediatr. Neurol.* **28**, 205 (2003).
21. A. Orrico *et al.*, *FEBS Lett.* **481**, 285 (2000).
22. I. Meloni *et al.*, *Am. J. Hum. Genet.* **67**, 982 (2000).
23. P. Couvert *et al.*, *Hum. Mol. Genet.* **10**, 941 (2001).
24. S. M. Klauck *et al.*, *Am. J. Hum. Genet.* **70**, 1034 (2002).
25. B. Winnepenninckx, V. Errijgers, F. Hayez-Delatte, E. Reyniers, R. Frank Kooy, *Hum. Mutat.* **20**, 249 (2002).
26. D. Cohen *et al.*, *Am. J. Psychiatry* **159**, 148 (2002).
27. B. Hendrich, S. Tweedie, *Trends Genet.* **19**, 269 (2003).
28. A. Bird, *Genes Dev.* **16**, 6 (2002).
29. F. Fuks *et al.*, *J. Biol. Chem.* **278**, 4035 (2003).
30. J. M. LaSalle, J. Goldstine, D. Balmer, C. M. Greco, *Hum. Mol. Genet.* **10**, 1729 (2001).
31. M. D. Shahbazian, B. Antalffy, D. L. Armstrong, H. Y. Zoghbi, *Hum. Mol. Genet.* **11**, 115 (2002).
32. S. Akbarian *et al.*, *Neurobiol. Dis.* **8**, 784 (2001).
33. D. Balmer, J. Goldstine, Y. M. Rao, J. M. LaSalle, *J. Mol. Med.* **81**, 61 (2003).
34. B. P. Jung *et al.*, *J. Neurobiol.* **55**, 86 (2003).
35. C. Colantuoni *et al.*, *Neurobiol. Dis.* **8**, 847 (2001).
36. R. Z. Chen, S. Akbarian, M. Tudor, R. Jaenisch, *Nature Genet.* **27**, 327 (2001).
37. J. Guy, B. Hendrich, M. Holmes, J. E. Martin, A. Bird, *Nature Genet.* **27**, 322 (2001).
38. M. Tudor, S. Akbarian, R. Z. Chen, R. Jaenisch, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 15536 (2002).
39. M. Shahbazian *et al.*, *Neuron* **35**, 243 (2002).
40. I. Stancheva, A. L. Collins, I. B. Van den Veyver, H. Y. Zoghbi, R. R. Meehan, *Mol. Cell*, **2**, 425 (2003).
41. L. Kanner, *Nervous Child* **2**, 217 (1943).
42. A. Bailey *et al.*, *Lancet* **341**, 1225 (1993).
43. A. Y. Hardan, N. J. Minshew, M. Mallikarjuhn, M. S. Keshavan, *J. Child Neurol.* **16**, 421 (2001).
44. M. R. Herbert *et al.*, *Brain* **126**, 1182 (2003).
45. E. H. Aylward *et al.*, *Neurology* **53**, 2145 (1999).
46. E. Courchesne, R. Carper, N. Akshoomoff, *JAMA* **290**, 337 (2003).
47. B. Luna *et al.*, *Neurology* **59**, 834 (2002).
48. U. Frith, *Neuron* **32**, 969 (2001).
49. T. L. Kemper, M. Bauman, *J. Neuropathol. Exp. Neurol.* **57**, 645 (1998).
50. G. V. Raymond, M. L. Bauman, T. L. Kemper, *Acta Neuropathol.* (*Berlin*) **91**, 117 (1996).
51. A. L. Beaudet, *Genet. Med.* **4**, 399 (2002).
52. S. Folstein, M. Rutter, *J. Child Psychol. Psych.* **18**, 297 (1977).
53. A. Bailey *et al.*, *Psychol. Med.* **25**, 63 (1995).
54. S. Steffenburg *et al.*, *J. Child Psychol. Psych.* **30**, 405 (1989).
55. S. E. Folstein, B. Rosen-Sheidley, *Nature Rev. Genet.* **2**, 943 (2001).
56. A. Pickles *et al.*, *Am. J. Hum. Genet.* **57**, 717 (1995).
57. P. Baker, J. Piven, S. Schwartz, S. Patil, *J. Autism Dev. Disord.* **24**, 529 (1994).
58. S. D. Cheng, N. B. Spinner, E. H. Zackai, J. H. Knoll, *Am. J. Hum. Genet.* **55**, 753 (1994).
59. M. Hotopf, P. Bolton, *J. Autism Dev. Disord.* **25**, 41 (1995).
60. E. H. Cook Jr. *et al.*, *Am. J. Hum. Genet.* **60**, 928 (1997).
61. R. J. Schroer *et al.*, *Am. J. Med. Genet.* **76**, 327 (1998).
62. F. Gurrieri *et al.*, *Neurology* **52**, 1694 (1999).
63. M. M. Konstantareas, S. Homatidis, *J. Autism Dev. Disord.* **29**, 275 (1999).
64. C. M. Wolpert *et al.*, *Am. J. Med. Genet.* **96**, 365 (2000).
65. P. F. Bolton *et al.*, *Am. J. Med. Genet.* **105**, 675 (2001).
66. F. Z. Boyar *et al.*, *Clin. Genet.* **60**, 421 (2001).
67. A. E. Silva, S. A. Vayego-Lourenco, A. C. Fett-Conte, E. M. Goloni-Bertollo, M. Varella-Garcia, *Arq. Neuropsiquiatr.* **60**, 290 (2002).
68. J. A. Thomas *et al.*, *Am. J. Med. Genet.* **119A**, 1110 (2003).
69. A. Kashiwagi *et al.*, *J. Hum. Genet.* **48**, 194 (2003).
70. S. Jamain *et al.*, *Nature Genet.* **34**, 27 (2003).
71. *International Statistical Classification of Diseases and Related Health Problems, 1989 revision* (World Health Organization, Geneva, ed. 10, 1992) (ICD-10).
72. D. R. Cohen *et al.*, *Mol. Cell Neurosci.* **22**, 417 (2003).
73. P. Scheiffele, J. Fan, J. Choih, R. Fetter, T. Serafini, *Cell* **101**, 657 (2000).
74. C. Dean *et al.*, *Nature Neurosci.* **6**, 708 (2003).
75. R. Klein *et al.*, *Cell* **75**, 113 (1993).
76. K. Tabuchi, T. C. Sudhof, *Genomics* **79**, 849 (2002).
77. M. Missler *et al.*, *Nature* **423**, 939 (2003).
78. S. Steffenburg, C. L. Gillberg, U. Steffenburg, M. Kyllerman, *Pediatr. Neurol.* **14**, 131 (1996).
79. L. A. Laan, A. A. Vein, *Epilepsia* **43**, 1590 (2002).
80. P. Watson *et al.*, *J. Med. Genet.* **38**, 224 (2001).
81. D. Armstrong, J. K. Dunn, B. Antalffy, R. Trivedi, *J. Neuropathol. Exp. Neurol.* **54**, 195 (1995).
82. Supported by HHMI and NIH (HD 40301). I thank D. Sweatt, J. Neul, and J. Young for comments on the manuscript, V. Brandt for editorial assistance, and J. Neul for the illustrations.

REVIEW

Looking Backward to Move Forward: Early Detection of Neurodegenerative Disorders

Steven T. DeKosky[1]* and Kenneth Marek[2]

Early detection of neurodegenerative disorders would provide clues to the underlying pathobiology of these diseases and would enable more effective diagnosis and treatment of patients. Recent advances in molecular neuroscience have begun to provide the tools to detect diseases like Alzheimer's disease, Parkinson's disease, and others early in their course and potentially even before the development of clinical manifestations of disease. These genetic, imaging, clinical, and biochemical tools are being validated in a number of studies. Early detection of these slowly progressive diseases offers the promise of presymptomatic diagnosis and, ultimately, of disease-modifying medications for use early in disease and during the presymptomatic period.

In the past decade, an explosion of information in molecular neuroscience has markedly enhanced our understanding of and potential therapy for neurodegenerative disorders. These diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), motor neuron disease, Huntington's disease (HD), and other neurodegenerative dementias, generally begin late in life and slowly but inexorably cause progressive neuronal degeneration and result in disability or death. Recent studies have demonstrated that these disorders are characterized by a presymptomatic phase, likely lasting years, during which neuronal degeneration is occurring but before clinical symptoms appear. This presents both a challenge—How do we identify individuals during this preclinical period—and an opportunity: Can preventive therapy be started during the preclinical period before disease symptoms appear? Therefore, a major goal of clinical research is to improve early detection of these diseases by developing tools to move diagnosis backward in the neurodegeneration temporal course (Fig. 1). These tools would enable us to (i) identify at-risk groups both for disease onset and progression during the preclinical period; (ii) accelerate and enhance the accuracy of diagnosis in the early clinical phase to ensure appropriate treatment; and (iii) speed the development of drugs that might modify disease progression during the (earlier) preclinical and clinical periods and, ultimately, enable these therapies to be directed at individuals in the preclinical phase of illness to prevent or slow the onset of clinical manifestations of disease. Strategies might include therapies specific for the disease pathobiology, such as anti-amyloid medications for AD, or interventions that address nonspecific disease mechanisms, such as inflammation or oxidative stress. In the case of AD, a delay in onset by 5 years could translate into a 50% decrease in disease prevalence (*1*). A delay of 10 years would result in virtual disappearance of the disease.

These tools emerging from many new technologies are biomarkers for neurodegeneration and/or for clinical manifestations of disease. Biomarkers are broadly defined as characteristics that can be objectively measured and evaluated

[1]Department of Neurology and Alzheimer Disease Research Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. [2]Institute for Neurodegenerative Disorders, New Haven, CT, USA.

*To whom correspondence should be addressed. E-mail: DeKoskyST@upmc.edu

Science

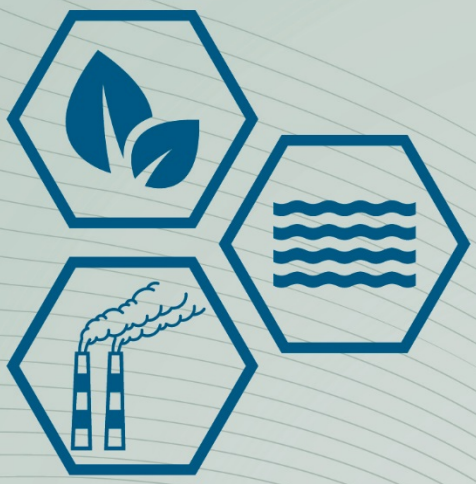
Postnatal Neurodevelopmental Disorders: Meeting at the Synapse?

Huda Y. Zoghbi

Science, 302 (5646), • DOI: 10.1126/science.1089071

Science (ISSN 1095-9203) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.
American Association for the Advancement of Science

EXHIBIT 4



Toxicological Profile for Lead

August 2020

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

2.16 NEUROLOGICAL

Overview. The literature on the neurobehavioral effects of Pb is extensive. With the improvement in analytical methods to detect Pb in the various biological media and in study designs, the concentrations of Pb, particularly in blood, associated with alterations in neurobehavioral outcomes continue to decrease, suggesting that there may be no threshold for the effects of Pb on intellectual function (CDC 2012d). Due to the enormous size of the database on neurobehavioral effects of Pb, this discussion has been limited to representative and/or major studies published on specific topics crucial to understanding dose-response relationships in the lower exposure ranges (e.g., PbB ≤10 µg/dL). For additional information, the reader is referred to a recent review of this topic (EPA 2014c).

Numerous epidemiological studies have evaluated effects of Pb on neurological function in children and adults. These studies show consistent evidence of associations between decrements in cognitive and neuromotor/neurosensory function with PbBs that range from ≤10 to >50 µg/dL. The PbB-effect relationship for cognitive effects in children extends well below 10 µg/dL, with no evidence for a threshold. In several PbB-effect models, the slope for decrements in cognitive function in children show greater increases at lower PbB ranges. These models predict that larger decrements in cognitive function would occur when PbB increases from 1 to 10 µg/dL, than when PbB increases to levels >10 µg/dL. All of the cognitive and neurobehavioral effects of Pb observed in children have also been observed in adults; however, it is not certain what life-stage exposures contribute most to outcomes in adults. A few studies that have followed children to early adulthood provide evidence of associations between childhood Pb exposure (e.g., PbB) and behavioral and neuroanatomical changes in adults, suggesting a possible role of exposures in childhood to adult outcomes. Other studies have found evidence of associations between cumulative Pb exposures (e.g., bone Pb) and neurological outcomes in adults.

The following neurobehavioral effects in children have been associated with PbB:

- ≤10 µg/dL:
  - Decreased cognitive function including full scale IQ (FSIQ).
  - Altered mood and behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency.
  - Altered neuromotor and neurosensory function, including gross and fine motor skills, visual-motor integration, and hearing threshold.

EXHIBIT 5

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen - ASD-ADHD Products Liability Litigation	22md3043 (DLC) 22mc3043 (DLC)
	ORDER: PLAINTIFFS' PROPOSED LEADERSHIP APPOINTMENTS

DENISE COTE, District Judge:

On November 2, 2022, Mikal C. Watts, Ashley C. Keller, and W. Mark Lanier submitted a proposal for a leadership structure for plaintiffs' counsel ("Structure") and nominated attorneys for appointment to positions within the Structure. An Order of November 16 approved that Structure and the nominees to serve a one-year term. Through a submission of November 20, plaintiffs' Co-Lead Counsel seek to amend the Structure and revise the appointments. Accordingly, it is hereby

ORDERED that any objection to the following proposal be filed by **November 30, 2022.** It is proposed by Co-Lead Counsel that for one year, subject to renewal by Court Order, the following lawyers are appointed as plaintiffs' leadership team ("Leadership Team"):

1. Plaintiffs' Co-Lead Counsel ("Co-Lead Counsel"): Mikal C. Watts, Ashley C. Keller, and W. Mark Lanier.

2. Plaintiffs' Liaison Counsel ("PLC"): Daniel Sullivan.

3. Plaintiffs' Executive Committee ("PEC"): The PEC shall

be composed of Plaintiffs' Co-Lead Counsel, Plaintiffs' Liaison Counsel, and the following committee chairs:

a. Law & Briefing Committee: Ashley Barriere.
b. Early Vetting/Bellwether Selection Committee: Sean Tracey.
c. Discovery/ESI Committee: Eric Holland.
d. Science & Expert Committee: W. Roger Smith.
e. Settlement/Lien Resolution Committee: Zoe Littlepage.
f. Federal/State Court Liaison Committee: Ann Callis.

4. Plaintiffs' Steering Committee ("PSC"): The PSC shall be composed of Julien Adams, Tricia Campbell, Charles J. Cooper, Eric W. Cracken, Paul Danziger, Richard Golomb, Patrick Luff, David P. Matthews, Neal Moskow, Richard M. Paul III, Ruth Rizkalla, and Lindsey Scarcello.

IT IS FURTHER ORDERED that any plaintiffs' attorney who seeks appointment to the Leadership Team and who has not yet submitted an application for such appointment shall submit such an application by **November 30, 2022.** No attorneys shall be added to the Leadership Team without prior application to and approval from this Court.

IT IS FURTHER ORDERED that Co-Lead Counsel shall advise the Court by the first of each month whether any member of the Leadership Team, or any attorney at the law firm to which that member belongs, has filed an action related to this MDL in state court. If such a filing has been made, the member of the Leadership Team shall submit a letter to the Court explaining whether good cause exists for the state court filing. Counsel are reminded that the transfer of an action to the MDL or the direct filing of an action in the MDL (pursuant to an Order to

be issued by this Court) do not constitute, for any party, a waiver pursuant to Lexecon, Inc. v. Milberg Weiss Bershad Hynes & Lerach, 523 U.S. 26 (1998).

Dated: New York, New York
November 22, 2022

DENISE COTE
United States District Judge