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

FOOD & WATER WATCH, et al.,

Plaintiffs,

vs.

U.S. ENVIRONMENTAL PROTECTION AGENCY, et al.

Defendants.

Civ. No. 17-CV-02162-EMC

PLAINTIFFS' TRIAL BRIEF

Judge: Hon. Edward M. Chen
Date: Jan 16, 2023 (Pretrial Conference)
Time: 2:30 p.m.
Courtroom: 5 - 17th Floor

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INTRODUCTION

The resolution of this case rests on the answers to three questions. First, is neurotoxicity a *hazard* of fluoride exposure? Second, does the condition of use at issue (water fluoridation) present a *risk* of this hazard? Third, is the risk an *unreasonable* one? EPA has well-established methods for answering these three questions, as set forth and detailed in the Agency's first ten final risk evaluations under the Amended TSCA. Yet, once again, EPA's litigation experts have eschewed EPA's risk assessment framework, and have opted instead to use an onerous causation standard that is foreign and antithetical to the way EPA evaluates hazard and risk under TSCA.

KEY EVIDENCE

A. Despite the Court's Admonition, the EPA Is Still Using an Improper Standard

At the first trial, EPA's experts used a "causation" standard to assess the neurotoxic risk posed by water fluoridation: i.e., whether the available studies *prove* that fluoride at 0.7 mg F/L *causes* reductions in IQ. During cross examination, EPA's risk assessment expert, Dr. Tala Henry, admitted EPA had never before held any other chemical under TSCA to this exacting standard of proof:

> Q. You held the plaintiffs to a burden of proof that EPA has not held a single chemical under Section 6 before; correct?
> A. *By the words on the page, I guess that's – that's true* but it was really my -- my opinion was based mostly on the methodological problems. ECF No. 244, at 987.

At the close of the first trial, the Court agreed that EPA had "applied a standard of causation which, from my read of TSCA, is not accurate. . . . It's not the proper standard." ECF No. 245 at 1131:5-9, 1132:20-21, 1137:20-22. Given this, the Court urged EPA to "relook at [the evidence] under the proper standard of review." *Id.* at 1132:18-21, 1142:4-9. The Court also encouraged Plaintiffs to submit a supplemental petition to EPA, which the Plaintiffs did, so that the Agency could give the new science a "serious look" at the administrative level. ECF No 245 at 1132:15-21; 1137:20-24; 1142:4-9. The EPA declined, however, to conduct a new administrative review and, now, in this second phase of the litigation, EPA's experts are continuing to use the very same causation standard that the Court correctly observed is "not the proper standard" under TSCA.

In his textbook INTERPRETING EPIDEMIOLOGIC EVIDENCE, EPA's retained expert, Dr. David Savitz, recognized that "[t]he amount of epidemiologic evidence may be sufficient for some purposes and insufficient for others." Yet, for this case, Dr. Savitz admitted he does not know what level of

epidemiological evidence is sufficient for a hazard or risk determination under TSCA, and has not read any of EPA's guidance on these crucial points. Savitz Dep. Tr. at 164:12-166:2. Dr. Savitz further admitted that he conducted a "general *causation*" analysis to determine "whether fluoride in the range of *under* 1.5 milligrams per liter is capable of *causing* adverse neurodevelopmental effects." *Id.* at 30:7-20.

EPA's risk assessment expert, Dr. Stanley Barone, conducted a similar causation analysis. Thus, although Dr. Barone found the evidence "*suggestive*" of neurodevelopmental effects from *low-dose* fluoride, he concluded there is no risk because the evidence is not yet "causal or likely causal."

Not only did Drs. Savitz and Barone both use a causation standard, they limited their assessment to *low dose* fluoride studies. Both Drs. Savitz and Barone thus required proof of causation at the human exposure level in order to find risk from fluoridation – a standard that EPA has never used for its assessment of other chemicals under TSCA.

B. EPA's Experts Have Admitted that Fluoride Is a Neurotoxicant

In discovery, EPA's experts made important admissions about the neurotoxicity of fluoride. Indeed, EPA's risk assessment and developmental neurotoxicity expert, Dr. Barone, admitted there is now "sufficient evidence" to demonstrate that fluoride is a neurotoxicant under *EPA's Guidelines for Neurotoxicity Risk Assessment* – which are the Guidelines that EPA uses for assessing neurotoxicity hazards under TSCA. The following are some of the admissions that Dr. Barone provided on fluoride's neurotoxicity:

> *Q. So you would agree, Dr. Barone, that the NRC concluded that fluoride has the ability to interfere with the functions of the brain, correct?*
> *A. Yes, I believe their findings are correct. And the question is at what dose.*[1]
> ###
> *Q. Do you have any reason to dispute the conclusion here that fluoride has been demonstrated to cause developmental neurotoxicity in animals?*
> *A. No, but that's not the point of this paper.*
> *Q. But you don't disagree with that conclusion?*
> *A. I don't disagree with that conclusion.* [2]
> *Q. Do you dispute, Dr. Barone, that high doses of fluoride cause neurodevelopmental effects?*
> *A. Do I dispute that high doses of fluoride cause neurodevelopmental effects? I don't dispute that. I think there's evidence of that and the NTP report addresses that.*[3]
> ###

[1] Barone Dep. Tr. at 44:22-45:3.
[2] Barone Dep. Tr. at 52:17-25.
[3] Barone Dep. Tr. at 78:6-12.

> *Q. [Y]ou would agree that the literature that NTP reviewed up through April 2021 meets EPA's sufficient human evidence standard under the guidelines?*
> *A. For hazard ID.*
> *Q. You agree with that?*
> *A. I would agree that there's significant evidence there for a sufficiency call.*
> *Q. And you agree that it meets the sufficient human evidence standard?*
> *A. It meets the sufficient evidence standard.*[4]

EPA's non-retained expert, Dr. Jesus Ibarluzea, offered similar admissions about fluoride's neurotoxicity:

> *Q. Do you agree that at least at high doses, the epidemiological evidence is consistent in showing an association between fluoride and adverse neurodevelopmental effects?*
> *A. Definitely.*
> *Q. Given the findings for the high dose epidemiological literature, do you agree that at least at high doses, fluoride is a neurotoxin?*
> *A. I will say yes.*[5]

C. EPA's Risk Assessment Expert Has Admitted that an Uncertainty Factor (aka Margin of Safety) of at Least Ten Is Necessary to Protect Against Fluoride Neurotoxicity

EPA's risk assessment expert, Dr. Barone, made an important admission that will help guide the Court's assessment of neurotoxic risk from fluoride exposures. Dr. Barone agreed that a risk assessment for fluoride neurotoxicity should incorporate an "uncertainty factor" of at least 10 to account for "intraspecies" differences in susceptibility to fluoride toxicity across the human population. To quote:

> *Q. Did you give any consideration as to what an appropriate benchmark MOE should be for fluoride neurotoxicity?*
> *A. Yeah, I did. Given the -- given that the critical studies in question are probably epidemiological studies, human studies,* ***uncertainty factor of 10****, which is appropriate for all life stages, inclusive of all life stages and vulnerabilities at face value would be the benchmark MOE.*
> *Q. Okay. Would that apply whether we used a BMCL, a LOAEL, or a NOAEL?*
> *A. It would apply to all of them. Whether we're using a LOAEL or a NOAEL, that would potentially be another uncertainty factor.* [6]

In lay terms, an uncertainty factor is a "margin of safety" which is a "health protective" approach to evaluating risk that EPA routinely uses in its risk assessments, including in each and every one of its risk evaluations under TSCA.

As a practical matter, an uncertainty factor of 10 reduces the risk threshold by a factor of 10. Ergo,

[4] Barone Dep. Tr. at 135:23-136:22.
[5] Ibarluzea Dep. Tr. at 111:20-112:3.
[6] Barone Dep. Tr. at 163:1-16.

if 1.5 mg/L of fluoride in water is selected as the Hazard Level,[7] a *risk* of this hazard will exist for humans drinking water with >0.15 mg F/L (i.e., >1/10th of the Hazard Level). By extension, a risk of the neurotoxicity hazard will exist for humans drinking "optimally" fluoridated water (0.7 mg/L) so long as the Hazard Level is less than 7.0 mg/L. The evidence at trial will overwhelmingly support the conclusion that the Hazard Level for fluoride neurotoxicity is well below 7.0 mg/L. Indeed, there are high-quality prospective cohort studies associating fluoride with neurotoxic effects under the condition of use.

D. The NTP's Assessment Supports an Unreasonable Risk Determination

1. Background

One of the principal reasons the Court placed this case in abeyance for two years was to consider the findings of the National Toxicology Program (NTP). As the Court noted, the NTP's review is "likely to add substantially to the body of scientific analysis relevant to the precise questions before this court." ECF No 262 at 4:19-22.

On May 11, 2022, almost two years after the completion of the first trial, the NTP announced that its systematic review (i.e., the "State of the Science" Monograph) was complete and slated to be released in 7 days. Trial Ex. 74. The NTP, however, was prevented from publishing the Monograph by political leadership at the Department of Health & Human Services (HHS). Trial Exs. 75 & 76. Almost two additional years have now passed, and the Monograph has still not been published.

2. EPA's Experts Agree that NTP's Monograph Is a High-Quality Systematic Review

Although the NTP's May 2022 Monograph represented a completed assessment by NTP's scientists, it is still technically a "draft" report.[8] Nevertheless, EPA's experts in this case agree it is a "high quality" systematic review. Here, for example, is an excerpt from Dr. Barone's deposition:

> *Q. You would agree that NTP's review of the literature is a high-quality review, correct?*
> *A. I think it's a high-quality review.*
> *Q. Dr. Savitz wrote in his report that NTP follows the rules that have been developed by NTP for conducting systematic reviews. Do you agree with Dr. Savitz on that point?*
> *A. I do.*
> *Q. Dr. Savitz also wrote that NTP complied with the formal requirements for conducting systematic reviews. Do you agree with Dr. Savitz on that point?*
> *A. I do.*

[7] A hazard level, otherwise known as the "Point of Departure," can be a Benchmark Concentration Level (BMCL), No Observed Adverse Effect Level (NOAEL), or Lowest Observed Adverse Effect Level (LOAEL).

[8] The NTP issued another draft of the Monograph in September 2022, but this report is virtually identical, with no material changes.

> *Q. Dr. Savitz wrote that NTP had a "rigorous approach to assembling the evidence." Do you agree with Dr. Savitz?*
> *A. I do.*
> *Q. Dr. Savitz wrote that NTP's review of the literature was "thorough." Do you agree?*
> *A. I do.*
> *Q. Dr. Savitz wrote that NTP's "search of the literature is likely to have identified essentially all relevant studies published by the closing date of April 2021." Do you agree?*
> *A. I do.*
> *Q. Dr. Savitz also wrote that NTP used "clearly defined rules for identifying and evaluating studies." Do you agree?*
> *A. I do.*
> *Q. And lastly, Dr. Savitz agreed that NTP had a "well-defined protocol for drawing inferences from studies." Do you agree?*
> *A. I do.*[9]

3. NTP Has Concluded that Fluoride Is Consistently Associated with Reduced IQ, and that This Association Is Unlikely to Be Explained by Confounding, or Other Forms of Bias

The NTP identified a total of 72 studies that have examined the relationship between fluoride and IQ in children, which the NTP described as a "large body of evidence." Trial Ex. 67, at xiii. According to the NTP, the "vast majority" of the 72 studies found an association between fluoride and childhood IQ loss, including 18 of the 19 "high quality" studies. Trial Ex. 67, at xii; Trial Ex. 69, at 65. Importantly, the NTP concluded that the association between fluoride and reduced IQ is unlikely to be explained by confounding or other forms of bias:

> Taken together and considering the consistency in the results despite the variability across studies in which covariates were accounted for, **bias due to confounding is not considered to be a concern in the body of evidence.** The potential for the consistency in results to be attributable to bias due to confounding in the 19 low risk-of-bias studies is considered low. Trial Ex. 67, at 49.

The NTP similarly concluded that errors in exposure assessment are unlikely to explain the inverse association between fluoride and IQ:

> In general, there were **few, if any, risk-of-bias concerns regarding exposure characterization in the low risk-of-bias studies.** These studies mainly had individual exposure data based on urine or water measures with appropriate analyses. Although there are concerns related to using urine samples . . . , the evidence suggests that urinary fluoride is a reasonable measure of exposure. Trial Ex. 67, at 51 (citations omitted).

In its responses to HHS's criticisms, the NTP expounded on the above conclusions, by noting:

> The consistency in direction of the association in the studies with heterogeneity in methods of exposure and outcome assessment, in 5 different countries, and accounting for a wide variety of covariates **all serve to rule out the possibility that there is a common factor other than fluoride exposure that can account for this outcome**. Trial Ex. 69, at 66.

[9] Barone Dep. Tr. at 96:9-97:17.

EPA's epidemiology expert, Dr. Savitz, will not be challenging NTP's conclusion on this crucial point:

> *Q. Dr. Savitz, have you been able to identify any common flaw or any common bias that can explain the consistent association between fluoride and reduced IQ in the full body of the literature?*
> *A. I haven't undertaken the process that would allow me to do that, even if it were there.*[10]

4. The NTP Agrees that Its Findings Are Relevant to Water Fluoridation (0.7 mg F/L)

Various HHS agencies, including the CDC and NIDCR, have repeatedly urged NTP to expressly disavow the relevance of its findings to water fluoridation. The NTP, however, has refused to do so. The following is an example of the (many) requests that NTP has received from HHS agencies to remove fluoridation from the orbit of concern, along with NTP's response:

> NIDCR: The data do not support the assertion of an effect below 1.5 mg/L. Therefore, all conclusory statements in this document should be explicit that any findings from the included studies only apply to water fluoride concentrations above 1.5 mg/L.
>
> NTP: We do not agree with this comment.[11]

One reason NTP has refused to disavow the relevance of its findings to water fluoridation is because the NTP conducted a *hazard* assessment, not a *risk* assessment. Trial Ex. 80, at 1. NTP's Scientific Director, Dr. Brian Berridge, will explain the importance of this distinction at trial, and how the failure to appreciate this distinction has led to some of the misguided criticisms of NTP's work.

A second reason that NTP has refused to disavow the relevance of its findings to fluoridation is because "several of the highest quality studies showing lower IQs in children were done in optimally fluoridated (0.7 mg/L) areas in Canada," or in areas with fluoridated salt giving similar total fluoride exposures as those drinking fluoridated water. Trial Ex. 70 at 82-83 & 32. NTP has explained, therefore, that its "confidence assessment also includes findings from studies with fluoride exposures that are similar to those associated with optimally fluoridated water supplies in the United States." Trial Ex. 70 at 12-13.

A third reason that the NTP has refused to disavow the relevance of its findings to fluoridation is because "many urinary fluoride measurements" among pregnant women living in fluoridated areas "exceed those that would be expected from consuming water that contains fluoride at 1.5 mg/L." Trial Ex. 70 at 82-83.

Thus, although NTP's confidence in fluoride presenting a neurotoxic *hazard* is greatest for

[10] Savitz Dep. Tr. At 95:11-17.
[11] Trial Ex. 69 at 41 & 55; Trial Ex. 70 (identifying NIDCR as the agency who made the comment).

communities with >1.5 mg F/L, it is an *error* to conclude from this that there is no *risk* of this hazard among people drinking water with 0.7 mg F/L.

5. NTP's Meta-Analysis Supports a Dose-Response Relationship Between Fluoride & IQ Loss, Including at Low Fluoride Levels

In addition to its systematic review, the NTP has conducted a quantitative meta-analysis of the fluoride/IQ literature which "extends the findings of [NTP's] larger systematic review" and further "supports an inverse association between fluoride exposure and children's IQ." Trial Ex. 68 at 15. NTP's meta-analysis includes a dose-response analysis in which NTP (1) used both non-linear and linear models, and (2) restricted the data to studies looking at low levels of fluoride (i.e., < 4 mg/L, <2 mg/L, and <1.5 mg/L). Trial Ex. 68 at NIEHS_455.

Based on these analyses, NTP concluded there is **"a dose-response relationship** between group-level fluoride exposure measures and mean children's IQ." Trial Ex. 68, at 2. Further, NTP found that the dose-response relationship between urinary fluoride and IQ remained significant even when restricting the studies to urinary fluoride levels less than 1.5 mg/L. Trial Ex. 68, at 10 & NIEHS_455.

NTP's dose-response analysis supports the existence of a *hazard* (not just a risk) below 1.5 mg F/L. Yet, EPA's epidemiology expert, Dr. Savitz, who focused his analysis on fluoride levels less than 1.5 mg/L, was *unaware* that the NTP had conducted this analysis. Savitz Dep Tr. at 128:17-131:14.

E. New Birth Cohort Analyses Provide Further Evidence of Low Dose Fluoride Neurotoxicity

1. ELEMENT & MIREC Cohorts

The MIREC and ELEMENT birth cohort studies from Canada and Mexico were the focus of much of the expert testimony at the first trial, including testimony from the Principal Investigators of the two studies (Dr. Howard Hu & Dr. Bruce Lanphear). ECF No. 262 at 4:4-18. As the Court will recall, the MIREC and ELEMENT studies were funded by the NIH, underwent *extensive* peer review, controlled for numerous potential confounding factors, and examined the effects of so-called "optimal" fluoride levels. It was relevant, therefore, that *both* studies found significant associations between *in utero* fluoride exposures and adverse neurodevelopmental effects. As the Court noted, the ELEMENT and MIREC studies present "serious questions" about the safety of fluoridation chemicals in water. ECF No. 245 at 1133:5-23.

Subsequent to the first trial, additional analyses have been conducted on both the ELEMENT and MIREC cohorts. At trial, Dr. Hu and Dr. Lanphear will testify about these new analyses, and how they further support the conclusion that fluoride is a developmental neurotoxicant at low doses. For example, Dr. Lanphear will testify about his team's recent study of fluoride and hypothyroidism, which found a significant relationship between fluoride in water and hypothyroidism in pregnant mothers. This finding has clear implications for neurotoxicity, as hypothyroidism is an established cause of IQ loss, including intellectual disabilities, in children.

2. MADRES Cohort (Los Angeles, California)

Dr. Howard Hu has recently begun studying fluoride in the MADRES birth cohort in Los Angeles, California. Earlier this year, Dr. Hu published a study that examined the urinary fluoride levels among pregnant mothers in this cohort (Malin 2023). The study found that the urinary fluoride levels in the Los Angeles mothers were very similar to the urinary fluoride levels documented in the MIREC and ELEMENT cohorts, further supporting the generalizability of the neurodevelopmental findings from these cohorts to the United States.

Dr. Hu has also recently completed a study of fluoride and neurodevelopmental outcomes in the MADRES cohort, the first study of its kind in a US-based birth cohort. Dr. Hu has submitted this groundbreaking study for publication, and Plaintiffs may seek the Court's leave to permit Dr. Hu to testify about the findings should the study reach a status that would make such testimony appropriate.

3. PROGRESS Cohort (Mexico)

In October 2021, a study of fluoride and mental development among infants and toddlers in the PROGRESS cohort was published (Cantoral, et al. 2021). The PROGRESS cohort involves a population of pregnant women in Mexico, and their children, who are exposed to so-called "optimal" levels of fluoride. The study found a statistically significant inverse association between dietary fluoride intake and cognitive outcomes among boys. The study provides further evidence of fluoride's neurotoxicity, as well as further support for boys being potentially more susceptible.

4. OCC Cohort (Denmark)

In the fall of 2023, Dr. Philippe Grandjean and colleagues, including Dr. Hu, published the results of a new birth cohort study from a *non-fluoridated* area of Denmark – the OCC cohort (Grandjean, et al. 2023). The study did not detect a statistically significant association between maternal fluoride and IQ in this non-fluoridated population. However, the study's most comprehensive and reliable analysis (i.e., the 24-hour comprehensive model) is consistent with an inverse association:

> Q. Now, I know that these results for the 24-hour comprehensive model are not statistically significant, but are the results here consistent with a negative influence from fluoride on IQ?
> A. I would say yes. [Hu Dep. Tr. at 171:21-25]

5. Pooled Benchmark Dose Analyses

One of the studies that the Court expressed a specific interest in considering in the second phase of this litigation is the pooled benchmark dose (BMD) analysis of the ELEMENT and MIREC cohorts. ECF No. 262 at 4:23-26. This pooled analysis was published by Dr. Philippe Grandjean and his colleagues in the preeminent journal *Risk Analysis* (Grandjean, et al. 2022). Additionally, Dr. Grandjean and his colleagues have published an additional pooled BMD analysis in the *European Journal of Public Health* which incorporates data from the non-fluoridated cohort from Denmark (Grandjean, et al. 2023). Both of these pooled analyses found dose-response relationships between maternal urinary fluoride concentrations and IQ with no evidence of a threshold in non-linear or linear models, and both analyses found that the BMCL for a one-point loss of IQ is less than **0.3 mg F/L** in maternal urine. This concentration of urinary fluoride is exceeded by almost all pregnant women living in fluoridated areas.

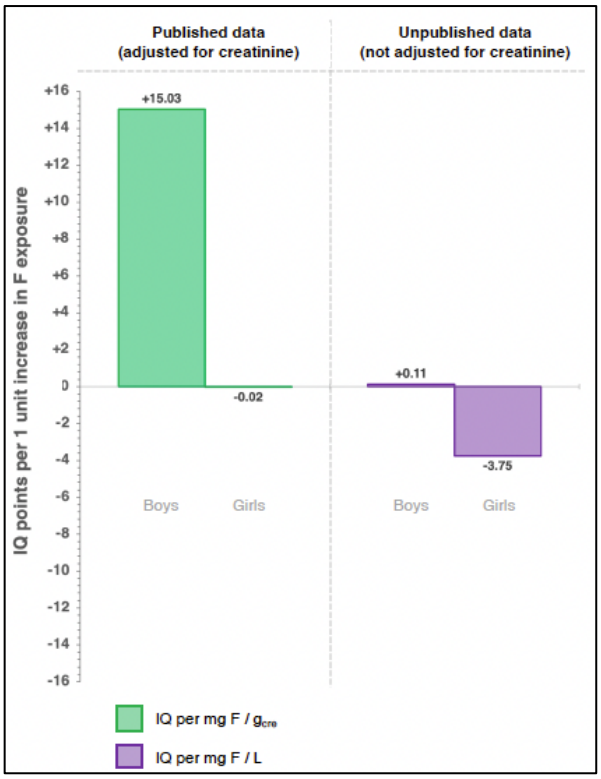
6. INMA Cohort (Basque, Spain)

EPA's experts have placed great reliance on the outlier results of the "Spanish study" by Ibarluzea (2022). The study found no significant relationship between maternal fluoride and IQ in the fluoridated part of the cohort, but a massive **28-point *increase* in IQ** among boys with each milligram of fluoride in the mother's urine in the ***non-fluoridated* areas**. A 28-point increase in IQ represents two standard deviations on the IQ scale, which is the approximate difference between an average child and a **genius**.

This result, on its face, is biologically implausible—if not *impossible*. Even when the results are averaged out across the fluoridated and non-fluoridated areas, the result is still clearly implausible: an average **15-point increase** in IQ in boys.

EPA's experts have conceded there are no other studies, in animals or humans, that have found neurological benefits from fluoride, let alone a benefit as dramatic as 15 to 28 IQ points. EPA's experts have also conceded that they are unaware of *any* substance having such a dramatic benefit.

There are other odd and *unexplained* aspects to the Ibarluzea study. For example, when the NTP asked Dr. Ibarluzea to provide his results based on a different unit of exposure[12] the results changed dramatically. Trial Ex. 87. The following figure compares Dr. Ibarluzea's published findings with the findings he shared with the NTP. Trial Ex. 86. As can be seen, the 15-point increase in IQ for boys completely *disappeared* using the different unit of exposure.



None of EPA's experts, including Dr. Ibarluzea, could provide an explanation for why the results

[12] The NTP asked Dr. Ibarluzea to provide the results using milligram of fluoride per liter of urine (which has been the most common way of presenting fluoride results in IQ studies) as opposed to milligram of fluoride per gram of creatinine. Trial Ex. 87.

would change so dramatically when adjusting for creatinine. While it is true that creatinine-adjusted data is preferable to unadjusted data, creatinine adjustment should *not* have such a radical effect on the outcome. EPA's risk assessment expert, Dr. Barone, agreed it was "a good question" as to why creatinine-adjustment had such a large effect, but Dr. Ibarluzea testified he has "no interest whatsoever" in finding the answer:

> *Q. Do you have any explanation for why adjusting for creatinine would have a such a dramatic effect on the association between fluoride and IQ in the Gipuzkoa cohort?*
> *A. No, and I have no interest whatsoever in having it. The right measurement is the adjusted one.*[13]

According to EPA's Dr. Barone, plausible findings are generally given more weight than implausible findings in hazard assessments:

> *Q. The first statement here is "In a hazard assessment plausible findings should be given more weight than implausible findings." Do you agree with that, Dr. Barone, or disagree?*
> *A. I generally agree with that.*[14]

Given the implausible and unexplained findings of the Ibarluzea study,[15] its findings should be given reduced weight in the overall weight of evidence assessment.

F. EPA Does Not Dispute that Plaintiffs Have Standing

Plaintiffs have produced an updated standing declaration by Jessica Trader, which will be entered into evidence without objection. Trial Ex. 66. Based on the facts set forth in Ms. Trader's declaration, the EPA does not dispute that Plaintiffs have standing in this case.

THE THREE KEY QUESTIONS

Pursuant to EPA's risk evaluation framework under TSCA, there are three key factual questions to the risk determination in this case. If the answer is yes to each of these questions, Plaintiffs prevail. If the answer is no to any of these questions, EPA prevails. The questions are as follows:

1. Is neurotoxicity a hazard of fluoride exposure?
2. Does water fluoridation present a risk of this hazard?
3. Is the risk posed by fluoridation an unreasonable one?

If Plaintiffs prevail on these questions, the TSCA statute commands that the Court order EPA to implement a rule-making proceeding to eliminate the risk. 15 U.S.C. § 2620(b)(4)(ii).

[13] Ibarluzea Dep. Tr. at 205:14-22.
[14] Barone Dep. Tr. at 213:1-5.
[15] There are other problems with the Ibarluzea study, including a failure to control for a key confounding factor (seafood), which is associated with both fluoride exposure and higher IQ.

CONCLUSIONS

A. Neurotoxicity Is a Hazard of Fluoride Exposure

1. The Hazard Standard

The question of whether neurotoxicity is a *hazard* of fluoride is a separate and distinct question from whether fluoridated water poses a *risk* of this hazard. Plaintiffs will emphasize this point throughout trial, as many of EPA's arguments (once again) serve to collapse the two inquiries into one.

EPA's *Guidelines for Neurotoxicity Risk Assessment* describe the criteria that EPA uses to determine whether a chemical poses a neurotoxic hazard, including under TSCA:

> *Q. If EPA is assessing a neurotoxic hazard under TSCA, will EPA follow these guidelines?*
> *A. We have and we will.*[16]

According to the *Guidelines*, a hazard exists if human studies demonstrate an "association" between the chemical and the hazard. Trial Ex. 17, at 53. The *Guidelines* do *not* require proof of causation to find a hazard:

> *Q. So would you agree that there is sufficient human evidence to support a hazard determination if there are epidemiologic studies that show an association between the chemical and the neurotoxic effects?*
> *A. That is what we call a hazard ID.*
> *Q. Okay. And in this table EPA specifically contrasts association with causality, correct?*
> *A. They do make a distinction, we do.*
> *Q. Okay. So EPA is specifically stating here we're not going to require proof of causality in the epidemiological studies, correct?*
> *A. We're not requiring causality for hazard ID.*
> *Q. Okay. So for hazard ID it's sufficient for there to be an association, correct?*
> *A. That's correct.*[17]

Additionally, EPA does not make separate hazard determinations for "high-dose" studies and "low-dose" studies; nor does EPA exclude studies because they are "high dose." To the contrary, EPA considers *all* of the hazard data, both high and low dose, and then makes a confidence determination of "Low," "Medium," or "High" as to the strength of the overall evidence.

2. EPA Has Deviated from Its Hazard Standard

In stark contrast to how EPA does hazard assessments for other chemicals under TSCA, EPA's experts in this litigation *excluded all "high-dose" fluoride studies from their consideration* (thus eliminating broad swathes of data from their assessment). Further, after excluding all of the high-dose

[16] Barone Dep. Tr. at 81:2-4.
[17] Barone Dep. Tr. at 86:11-87:4.

studies, EPA's experts required proof of *causality*, or *likely causality*, among the remaining low-dose studies. These two *major deviations* from EPA's normal analytical framework resulted in an *onerous* standard that few, if any, of the 10 prioritized chemicals under the Amended TSCA would satisfy.

The current science on fluoride neurotoxicity, as systematically reviewed by the NTP, easily satisfies EPA's hazard standard, as Plaintiffs' experts will demonstrate at trial.

B. Fluoridated Water Presents a Risk of Neurotoxicity

1. The Risk Standard

EPA uses a "Margin of Exposure" framework, or what a lay person might call a "margin of safety" approach, to assess if a Condition of Use poses a risk. Margin of Exposure refers to the difference between the Hazard Level (i.e., BMCL, NOAEL, or LOAEL) and the Human Exposure level. For example, if the hazard level for lead is 5 ug/dl in blood, and the human exposure level is 1 ug/dl, then the Margin of Exposure would be 5.

After determining the Margin of Exposure, EPA compares it against the Uncertainty Factor (i.e., Benchmark MOE). If the Margin of Exposure is less than the Uncertainty Factor, then a *risk* exists because the human exposure level is considered *unacceptably close* to the hazard level. Trial Ex. 45 at 43; Trial Ex. 97 at 411.

Finally, and importantly, EPA does not just consider "average" or "typical" exposures when assessing the risk from a Condition of Use; EPA also considers *highly-exposed* individuals. As set forth in Undisputed Fact No. 42, "EPA has made Unreasonable Risk determinations for conditions of use where average exposures did not present a risk, but highly exposed individuals (e.g., 95th percentile) had exposures of concern."

2. EPA Has Deviated from Its Risk Standard

EPA's experts in this case did not attempt to apply EPA's risk characterization framework to the hazard and exposure data on fluoride. Had they done so, the conclusion would be obvious: exposures to fluoride from fluoridated water, particularly for highly-exposed individuals, are unacceptably close to (and indeed *exceed*) the Hazard Level. This conclusion holds irrespective of whether one uses (1) the BMCLs from the pooled benchmark dose analyses, or (2) the 1.5 mg F/L figure from the NTP's assessment. This is because, as Dr. Barone has confirmed, the Uncertainty Factor for fluoride neurotoxicity should be at

least a factor of 10. Accordingly, if average *or* 95th percentile exposures in fluoridated areas are within 1/10th of the Hazard Level, a risk exists.

C. The Neurotoxic Risk Posed by Fluoridation Is Unreasonable

To determine whether a risk is "unreasonable," EPA considers various "risk-related factors," including (A) the severity of the hazard, (B) the extent of human exposure (e.g., the number of people exposed), (C) whether susceptible subpopulations are being exposed, (D) uncertainties in the data, and (E) the overall confidence in the hazard and exposure data.

Severity of Hazard: EPA considers the nature and severity of the hazard as part of its unreasonable risk determination. Here, there will be no dispute that IQ loss is a sufficiently serious effect to warrant regulatory action. According to EPA's 30(b)(6) representative, "EPA's on record for looking at IQ and IQ decrements in a number of risk assessments and that has been the critical effect in a number of risk assessments." Dep. Tr. at 58:23-59:1.

Extent of Human Exposure: The number of people exposed to a condition of use helps to identify "the extent of potential exposure and potential risk." EPA (30)(b)(6) Dep. Tr. at 93:11-15. Approximately 200 million Americans are served with community water that is treated with fluoridation chemicals. As noted by Dr. Kathleen Thiessen, "To put these numbers in perspective, EPA has found unreasonable risks for conditions of use that affect less than 500, and as few as 56 and 75 people, which is less than 0.0000025% of the population impacted by fluoridation. To put it another way, if water fluoridation caused IQ loss in only 0.0000025% of the population, it would still harm more people than the entire populations involved with conditions of use that EPA has found to present unreasonable risk." ECF No. 378-5 at 74.

Exposure to Susceptible Subpopulations: Determining whether susceptible populations are exposed to a condition of use is "an important part of the characterization for the unreasonable risk determination." EPA (30)(b)(6) Dep. Tr. at 63:16-25. Here, it is *undisputed* that susceptible populations are being exposed on a daily ongoing basis to fluoridated water, including over 2 million pregnant mothers, and over 400,000 exclusively bottle-fed babies. ECF No. 202-1 ¶ 220.

Uncertainties: Uncertainties are pervasive to risk assessment, and to be expected in the fluoride assessment. Here, for example, is a passage from the deposition of Dr. Barone:

> *Q. [A]s we talked about earlier, risk assessment is laden with uncertainties, correct?*
> *A. We did and I agree.*

Q. So it would be the exception, not the rule that you'd have a risk assessment where you have complete certainty about everything, right?
A. It's very rare.[18]

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Q. [A]s we know, data gaps are common in risk assessment, correct?
A. Data gaps and uncertainty are common in our risk assessments, yes.

As expected, there are some uncertainties in the current literature on fluoride neurotoxicity, including how to calculate a total fluoride dose from a urinary fluoride level. While these uncertainties are the appropriate subject for further research, they do not meaningfully call into question whether neurotoxicity is a hazard of fluoride, or whether human exposure levels to fluoride are unacceptably close to, or in excess of, the hazard level.

Confidence: EPA does not require "High" Confidence in either the hazard or exposure data to make a risk determination under TSCA. Undisputed Fact Nos. 38 & 40. In fact, EPA has repeatedly made unreasonable risk determinations when it has "Medium" confidence in *both* the hazard and exposure data, or even "Low" to "Low-Medium" confidence. Undisputed Fact Nos. 39 & 41; Trial Ex. 88 at 5-6; Trial Ex. 90, & Trial Ex. 91.

As the evidence will show, the exposure and hazard data for fluoride is stronger, and requires less extrapolation, than the data EPA has used to make risk determinations for other chemicals under TSCA. For example, EPA determined that PCE posed an unreasonable risk of neurotoxicity (cognitive deficits) among bystanders in the dry-cleaning industry who were exposed to **1/89th** of the level associated with neurotoxicity in several "medium" quality epidemiology studies. Trial Ex. 92. EPA had no epidemiology studies indicating harm to bystanders, but it inferred a risk based on the high dose epidemiological data. Trial Ex. 92. Dr. Kathleen Thiessen will explain that "the determination of risk for water fluoridation requires far less extrapolation, and involves far less uncertainty [than the PCE assessment], because water fluoridation has been associated with neurotoxic outcomes (in high-quality epidemiological studies) at the levels of exposure produced by the condition of use." ECF No. 378-5 at 58.

Dr. Philippe Grandjean, one of the world's leading environmental health scientists, has concurred in this assessment, noting that "[t]he evidence supporting the EPA's conclusion on the condition of PCE use is far less extensive" than the data available for fluoride. ECF No. 378-5 at 28.

The risk-related factors support a determination of an unreasonable risk.

[18] Barone Dep. Tr. at 177:8-15.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing Trial Brief was served by Notice of Electronic Filing this 22nd day of December, 2023, upon all ECF registered counsel of record using the Court's CM/ECF system.

/s/ Michael Connett
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