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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

FOOD & WATER WATCH, INC., et al.,

Plaintiffs,

v.

U.S. ENVIRONMENTAL PROTECTION AGENCY, et al.,

Defendants.

Case No. 17-CV-02162 EMC

DEFENDANTS' TRIAL BRIEF FOR SECOND PHASE OF TRIAL

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INTRODUCTION

Plaintiffs cannot prove by a preponderance of the evidence that adding fluoridation chemicals to public drinking water in the United States up to a level of 0.7 milligrams per liter (mg/L) presents an unreasonable risk of injury to health—specifically, neurodevelopment—under the Toxic Substances Control Act ("TSCA"), 15 U.S.C. § 2620(b)(4)(B). They were unable to meet this burden after the first trial in June 2020. And studies published since then only further support EPA's position that the scientific evidence for evaluating the risk of developmental neurotoxic effects from low-dose exposure to fluoride is insufficient to reach an informed risk determination under TSCA.

The most critical evidence for the Court's unreasonable risk determination at the second phase of trial will be the testimony of the parties' expert epidemiologists and risk assessors. EPA's experts will show there is not sufficient information currently available to integrate the hazards of and exposures to fluoridation chemicals, which is required for an assessment of risk under TSCA.

At the first trial, EPA demonstrated that the most comprehensive and well-conducted study of learning and memory in animals did not find evidence of developmental neurotoxicity at doses comparable to community water fluoridation in the United States. That study was in fact a suite of experiments conducted by National Toxicology Program ("NTP") researchers and published in a single article referred to as McPherson 2018 at the first trial. And most of the human epidemiological studies were conducted in populations where average fluoride exposure levels were well above those associated with artificial fluoridation in the United States. Even the recent studies in Western populations finding some statistically significant associations between early-life fluoride exposure and adverse neurodevelopmental outcomes were of limited value. And the associations found were modest and inconsistent. Some were also plagued with other issues like bias and confounding.

At the second phase of trial, EPA will present testimony on the most compelling scientific developments since June 2020. Most notably, two prospective cohort studies found no statistically significant adverse association between maternal urinary fluoride and the offspring's IQ: one study from Spain and the other from Denmark. Both studies looked at fluoridated drinking water

exposures below 1.5 mg/L, and thus offer powerful evidence against an adverse association between low-dose fluoride exposure and IQ. Additional cross-sectional studies add further support that low-dose fluoride exposure is not a hazard. Further, the NTP draft monograph characterizes the evidence of fluoride's potential developmental neurotoxicity at low levels of exposure associated with community water fluoridation as "unclear," and that analysis did not even incorporate the results of the Spain and Denmark cohort studies. The evidence is simply insufficient to support a risk evaluation for the condition of use at issue under TSCA.

At the conclusion of trial, the Court should find that Plaintiffs have not satisfied their burden and enter judgment in favor of EPA.

ISSUES FOR SECOND PHASE OF TRIAL

I. THE MOST INFORMATIVE EPIDEMIOLOGIC STUDIES PUBLISHED SINCE THE FIRST TRIAL DO NOT SUPPORT LOW-DOSE ADVERSE EFFECTS.

EPA's expert epidemiologist Dr. David Savitz will explain the epidemiological studies of fluoride and neurodevelopment published since the June 2020 trial and will offer an opinion about the cumulative evidence surrounding whether low-dose fluoride exposures have an adverse neurodevelopmental effect. Dr. Savitz is a Professor of Epidemiology at Brown University School of Public Health, a Professor of Pediatrics, Obstetrics and Gynecology at Brown University Medical School, and is an Adjunct Professor of Epidemiology at both the Dartmouth School of Medicine and the Boston University School of Public Health. He was selected to chair the National Academies of Science, Engineering, and Medicine ("NASEM") committees that conducted two independent reviews of the NTP monograph on fluoride neurotoxicity. His research focuses on environmental exposures, reproductive and perinatal outcomes, and drinking water treatment. In other words, his training and experience are perfectly suited for assisting the Court in understanding the evidence at the phase-two trial.

Not all studies are equal, as Dr. Savitz will explain. Some studies of fluoride and neurodevelopment are more informative and influential than others based on their methodologies and the scientific quality of the presented information. EPA's trial presentation will focus on the most important studies that have been published since the June 2020 trial.

First, the most notable study published since the first trial is a prospective cohort study of the association of low doses of fluoride on children's IQ from Spain published in 2022 in a peer-reviewed and well-recognized journal, Environmental Research. The lead author is Dr. Jesús Ibarluzea. The parties refer to the cohort as "INMA," which is short for Infancia y Medio Ambiente. The study focuses on a sub-cohort in the province of Gipuzkoa, which is an area of Spain that had an active community drinking water fluoridation program in place.

The INMA IQ study examined the relationship between mothers' urinary fluoride concentration, adjusted for dilution, and their offsprings' intelligence scores. The study had a large sample size and controlled for relevant confounders. It is of equal quality to the Canada (MIREC) and Mexico City (ELEMENT) cohort studies that were the focus of the first trial.

Dr. Ibarluzea and his team found no statistically significant adverse effect of fluoride on the intelligence scores of boys, girls, or boys and girls combined. In fact, by some metrics, a statistically significant beneficial effect was observed from low-dose fluoride exposure. These findings are consistent with the MIREC IQ study (Green 2019). In the MIREC study, there also was no statistically significant adverse effect of fluoride on full-scale IQ for the offspring combined. When the authors stratified the results by sex, there was a statistically significant beneficial association in full-scale IQ for girls and a negative association for boys by certain measures.

And in 2023, Dr. Ibarluzea and his team published another fluoride study in the journal Environmental Research. This study considered potential associations between prenatal maternal urinary fluoride and systems associated with attention-deficit/hyperactivity disorder ("ADHD") in the offspring. Again, Dr. Ibarluzea and his team found no statistically significant adverse relationship between fluoride exposure and ADHD symptoms.

No doubt, Plaintiffs will attempt to discredit the INMA studies. After all, the studies are detrimental to their case. Chief among Plaintiffs' anticipated criticisms is that the INMA IQ study shows a beneficial effect from low-dose fluoride exposure. Plaintiffs base their criticism on data on one of the twenty-seven tables and supplementary figures that Dr. Ibarluzea and his team published with their study in the interest of transparency. For reference, the MIREC IQ study

published only four supplementary tables. And the change in IQ points shown in the table is the mathematical function of a presumed change in exposure across all the analyzed data, as Dr. Ibarluzea will explain. No one is claiming that fluoride exposure in utero has the power to make any one person a genius but for that exposure. Moreover, the INMA IQ study should be judged on its methodology. The study design is like the MIREC and ELEMENT intelligence studies, which Plaintiffs held out to be the gold standard at the first phase of trial. The INMA IQ study similarly controlled for an extensive list of covariates—even maternal IQ, which the MIREC study lacked and acknowledged as a limitation.

Plaintiffs' other anticipated criticism of the INMA IQ study—that the results were different before and after the researchers adjusted for urinary dilution—should be dismissed out of hand. Testimony at the first trial, including by Plaintiffs' experts, established that adjusting for urinary dilution was important to the validity of the studies that Plaintiffs like—that is, the ELEMENT and MIREC studies. Those studies adjusted for urinary dilution, too.

Second, results from another prospective cohort study in Denmark are consistent with the INMA IQ study and the MIREC IQ study's combined results. Like the INMA studies, the Odense Child Cohort ("OCC") in Denmark also examined the relationship between maternal urinary fluoride, adjusted for dilution, and the offsprings' IQ scores. The study, too, had a large sample size, controlled for relevant confounders, and is relevant to low-dose exposures. It is again of equal quality to the MIREC and ELEMENT studies. And again, the Danish OCC study found no statistically significant adverse effect of fluoride on the IQ of boys, girls, or boys and girls combined.

Third, several cross-sectional studies have come out since the June 2020 trial. Those that look at low-fluoride exposures (< 1.5 mg/L) cast further doubt on fluoride being neurotoxic at low doses, as Dr. Savitz will explain.

Dewey et. al. (2023) was a natural experiment conducted in Calgary, Canada, when the city stopped fluoridating its drinking water—a change that occurred in 2011. The authors identified infants who were prenatally exposed to fluoridated water throughout the pregnancy, exposed for part of the pregnancy, or exposed for none of their pregnancy, depending on when in relation to

2011 the mother became pregnant. The drinking water fluoride level was 0.7 mg/L. The authors found no association between exposure to fluoridated drinking water and IQ, with null findings for IQ subtests and for boys and girls analyzed separately. No association was found between fluoride exposure and working memory or cognitive flexibility. This study provides meaningful evidence against an adverse effect of water fluoridation.

Do et al. (2022) measured fluoride exposure based on children's place of residence and whether that area fluoridated its drinking water. Over 2,600 children aged 5–10 years were included in the analysis and assigned fluoridation status based on where they lived at ages 0–5 years. The exposure index was "lifetime exposure to fluoridated water," and classified as 0% if there was no exposure to fluoridated water, >0–<100% if there was some but not complete exposure to fluoridated water, or 100% if always exposed to fluoridated water. Overall, there were no indications that greater exposure to fluoridated water was associated with poorer behavioral outcomes.

Finally, in addition to the INMA ADHD study, other studies published since trial considered the association between fluoride exposure and neurobehavioral outcomes. As Dr. Savitz will explain, on balance, there is little corroboration or consistency between the findings of these studies.

On the whole, therefore, studies published since June 2020 provide additional, compelling evidence that water fluoridation at 0.7 mg/L does not pose an unreasonable risk of neurotoxicity.

II. THE DRAFT NTP STATE OF THE SCIENCE MONOGRAPH DOES NOT SUPPORT LOW-DOSE ADVERSE EFFECTS.

The NTP State of the Science Monograph has not yet been published and there is no reason to think it will be published before the second phase of trial. But multiple drafts of the document have been made public and some of those drafts will be offered as evidence.

The two NASEM committees that Dr. Savitz chaired independently reviewed and were critical of two earlier drafts of the monograph. Of note, the committee that issued the second report cautioned that the NTP monograph "needs to emphasize that much of the evidence presented comes from studies that involve relatively high fluoride concentrations and that the monograph

cannot be used to draw conclusions regarding low fluoride exposure concentrations (less than 1.5 mg/L), including those typically associated with drinking water fluoridation."

In more recent drafts of the monograph dated May and September 2022, the NTP authors state unequivocally that the evidence of potential effects of low doses of fluoride on children's intelligence is "unclear." The draft provides in relevant part (emphasis added):

> Associations between lower total fluoride exposure [e.g., represented by populations whose total fluoride exposure was lower than the WHO Guidelines for Drinking-Water Quality of 1.5 mg/L of fluoride (WHO 2017)] and children's IQ remain unclear. More studies are needed to fully understand potential associations in ranges typically found in the United States (i.e., < 1.5 mg/L in water).

In May 2023, the NTP Board of Scientific Counselors Working Group finalized a report on drafts of the monograph and associated meta-analysis manuscript. The report includes interagency review comments, the NTP authors' responses to those comments, and the Working Group's assessment of the NTP authors' responses. In response to the interagency review comments, the NTP authors repeatedly stated that the scientific literature about fluoride's potential effects at low doses is inconsistent. For example, the NTP authors "tend to agree" that studies of fluoride exposures relevant to U.S. drinking water are "inconclusive" and that "more studies at lower exposure levels are needed to fully understand potential associations at fluoride levels in drinking water typically found in the United States (< 1.5 mg/L)."

What is even more remarkable about the NTP authors' conclusions about the inconclusive nature of evidence is that the draft monograph does not even consider the INMA or OCC cohort studies on children's intelligence or the INMA ADHD study. The INMA and OCC studies were published after NTP's predefined literature cut-off date. The INMA studies did not find detrimental effects from low doses of fluoride exposure and therefore inject even less certainty that low doses of fluoride are associated with adverse effects.

In sum, NTP's independent consideration of the body of evidence of fluoride's potential neurotoxic effects (at least, the body of evidence up to NTP's literature cut-off date) supports that the weight of the evidence of low-dose fluoride exposure associated with public drinking water supplies does not present an unreasonable risk of injury.

III. PLAINTIFFS CANNOT SHOW THAT FLUORIDATION CHEMICALS PRESENT AN UNREASONABLE RISK OF INJURY UNDER THE CONDITION OF USE.

EPA will offer testimony by its risk-assessment expert, Dr. Stanley Barone. Dr. Barone's career at EPA spans nearly thirty years. He is currently the Senior Science Policy Advisor and Deputy Science Integrity Official for EPA's Office of Chemical Safety and Pollution Prevention. As senior advisor, Dr. Barone provides expert technical advice and guidance to senior management concerning scientific integrity, science policy development, and science coordination. This includes an understanding of the agency's scientific integrity policy and risk evaluation procedures under TSCA and other laws.

Dr. Barone is an expert toxicologist and risk assessor with experience in EPA's first ten risk evaluations under TSCA. Dr. Barone will explain TSCA risk evaluation standards and processes and the weight of the scientific evidence of the potential developmental neurotoxicity of fluoride. Dr. Barone will describe that the scientific evidence for evaluating the risk of developmental neurotoxic effects from exposure to fluoride, especially considering the more recent scientific studies published after the first trial, is insufficient for EPA to reach an informed risk determination under TSCA. Dr. Barone will also explain there are fundamental flaws in Dr. Grandjean's and Dr. Thiessen's approaches, including their analysis and interpretation of the NTP draft monograph and meta-analysis and opinions whether community water fluoridation presents an unreasonable risk under TSCA. Dr. Grandjean also published two pooled benchmark dose analyses since the first trial, but neither incorporates the results of the INMA IQ study.

Under TSCA section 6(b), EPA must undertake a risk evaluation process to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment. Prior to the 2016 amendments to TSCA, this evaluation process required a risk assessment but not a determination of unreasonable risk. Instead, the determination of unreasonable risk part of the risk management rulemaking process. The amended statute now requires that a risk evaluation include a determination of unreasonable risk as well as a risk assessment.

Risk assessment is the process by which scientific judgments are made concerning the potential for toxicity in humans. Risk assessment involves a hazard assessment (which includes a

hazard identification and dose-response assessment), exposure assessment, and risk characterization. The risk assessment and the risk determination make up the risk evaluation. Most significantly, the risk evaluation requires that this determination be independent of consideration of cost or other non-risk factors.

As explained below, Plaintiffs did not complete a TSCA risk evaluation or any scientifically sound risk assessment.

A. TSCA Hazard Assessment

A hazard assessment includes two components: hazard identification and dose-response assessment. Hazard identification is the determination of whether a particular chemical is or is not causally linked to a particular health effect. Dose-response assessment is the determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.

This step requires identification, evaluation, and synthesis of information to describe the health effects of individual chemical substances or mixtures. In the dose-response assessment, the relationship between the exposure or dose of a contaminant and the occurrence of health or environmental effects or outcomes is assessed. The response assessed might be incidence of some endpoint or outcome or it might describe the magnitude of a response. The approaches employed for these components, including, for example, the level of detail and complexity of quantitative aspects, may vary across different risk assessments. Thus, TSCA subsections 26(h) and (i) require that all information used in TSCA section 6 risk evaluation be reviewed consistent with reliance on the best available science and a weight of the scientific evidence approach.

Dr. Barone will explain that the existing scientific studies do not provide sufficient evidence that low-dose fluoride exposure is associated with community water fluoridation in the United States for purposes of supporting a hazard assessment in a TSCA risk evaluation. In particular, he will explain that the evidence of adverse neurological effects is conflicting and not coherent across the critical prospective cohort studies, which prevent a conclusion regarding the presence or absence of an effect.

The dose-response data are deficient and thus insufficient for risk assessment. Plaintiffs' proffered dose-response evidence of developmental neurotoxicity has several critically deficient issues that prohibit its use in a risk estimate, including a lack of rationale for linear extrapolation at low doses, which was a concern raised by the NTP BSC Working Group when reviewing the draft NTP monograph and meta-analysis manuscript. In addition, there remain issues with extrapolation from urinary biomarkers of fluoride to intake and intake concentrations affecting all the epidemiological prospective cohort studies of fluoride. Urinary biomarkers are not the same as intake concentration measures, and it is currently impossible to extrapolate that information with any precision.

B. TSCA Exposure Assessment

TSCA requires that EPA "take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use" when conducting a risk evaluation, which EPA implements through an exposure assessment. 15 U.S.C. § 2605(b)(4)(F)(iv). An exposure assessment includes information on chemical-specific factors, including, but not limited to, physical-chemical properties and environmental fate and transport parameters. An exposure assessment, where relevant, includes some discussion of the magnitude, nature, duration, intensity, frequency, pattern, and number of exposures under the conditions of use. It should also include types of individuals or populations exposed to the agent, as well as discussion of the uncertainties in this information. Using reasonably available information, exposures will be estimated (usually quantitatively) for the identified conditions of use.

Plaintiffs failed to conduct an exposure assessment of fluoride in public drinking water (including artificially fluoridated and naturally occurring fluoride) and other fluoride source contributions, as Dr. Barone will explain. Thus, even if the Court found the evidence is sufficient for a hazard assessment, Plaintiffs cannot demonstrate this aspect of a risk assessment.

C. Risk Characterization

When examining neurotoxicity, risk characterization requires that the hazard assessment, including hazard identification and dose-response analysis, and exposure assessment for given populations be combined to estimate the risk for a particular endpoint (for example, neurotoxicity).

The goal of risk characterization is to compare toxicity levels with exposure doses to determine if risk may occur under a specific scenario or condition of use.

Dr. Barone will explain that to estimate noncancer risk under TSCA, EPA uses a margin of exposure ("MOE") approach. The MOE is the point of departure ("POD") (an approximation of the no-observed adverse effect level ("NOAEL") or benchmark dose level ("BMDL")) for a specific health endpoint divided by the exposure concentration for the specific scenario of concern. The POD (numerator) and relevant exposure concentration (denominator) must be in the same units (for example, mg/kg/day).

$$Margin\ of\ Exposure = \frac{Point\ of\ Departure}{Exposure\ Concentration}$$

The resulting MOEs are then compared to a benchmark MOE. The benchmark MOE accounts for the total uncertainty in a POD, including, as appropriate: (1) the variation in sensitivity among the members of the human population (i.e., intra-human/intra-species variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies variability); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4) the uncertainty in extrapolating from a lowest observed adverse effect level ("LOAEL") rather than from a NOAEL. A lower benchmark MOE (e.g., 30) indicates greater certainty in the data (because fewer of the default uncertainty factors relevant to a given POD as described above were applied). A higher benchmark MOE (e.g., 1000) would indicate more uncertainty for specific endpoints and scenarios. However, these are often not the only uncertainties in a risk evaluation.

Plaintiffs' expert Dr. Kathleen Thiessen is expected to testify that she performed an MOE analysis. But as Dr. Barone will explain, Dr. Thiessen confuses a hazard approach that considers fluoride exposure from all sources with a risk-based MOE approach that would be appropriate under TSCA for a specific condition of use (here, community water fluoridation). Neither Dr. Thiessen nor Dr. Grandjean convert urinary fluoride concentrations from study results to approximate fluoride intake from community water fluoridation.

This is just one independent reason why the evidence is not sufficient to demonstrate risk.

D. Risk Determination

Plaintiffs failed to conduct a sufficient analysis to support a risk determination for the relevant condition of use, as Dr. Barone will explain. EPA may weigh a variety of factors in determining whether a risk is unreasonable. In making this determination, EPA considers relevant risk-related factors, including, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use; the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any potentially exposed or susceptible subpopulations, magnitude, nature, duration, intensity, frequency, pattern, and number of exposures under the conditions of use in an exposure assessment); the severity of hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties.

EPA takes into consideration the Agency's confidence in the data used in the risk estimate for both exposure and hazard. This includes an evaluation of the strengths, limitations and uncertainties associated with the information used to inform the risk estimate and the risk characterization. The factors EPA may consider are the subject of considerable scientific complexity and policy debate.

Even if Plaintiffs could satisfy the other elements of a risk assessment discussed above, uncertainty in the hazard assessment and variability in response between the most reliable and robust studies at this time makes a risk estimation highly uncertain, as Dr. Barone will testify. The strength of the evidence is too weak to make a reliable risk determination based upon risk factors alone.

Finally, the draft NTP monograph and meta-analysis manuscript are not a substitute for a risk evaluation under TSCA. They address hazard identification and dose-response assessment. But they do not include an exposure assessment. And they expressly consider total fluoride exposure, not exposures from only drinking water supplies.

CONCLUSION

For the foregoing reasons, and based on the evidence that was presented at the June 2020 trial and that will be presented at the second phase of trial, the Court should find that Plaintiffs have not satisfied their burden and enter judgment in favor of EPA.

Date: December 22, 2023

Respectfully Submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this 22nd day of December, 2023, a true and correct copy of the foregoing Defendant's Trial Brief for the Second Phase of Trial was filed electronically with the Clerk of the Court using CM/ECF. I also certify that the foregoing document is being served on all counsel of record via transmission of Notices of Electronic Filing generated by CM/ECF.

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