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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' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW** Judge: Hon. Edward M. Chen Date: Jan 7, 2017 (Pretrial Conference) Time: 2:30 p.m. Courtroom: 5 - 17th Floor

TABLE OF CONTENTS

Pursuant to the Court's Order, Plaintiffs hereby submit the following Proposed Findings of Fact and Conclusions of Law.

PROPOSED FINDINGS OF FACT

I. BACKGROUND

A. The Condition of Use: Water Fluoridation

1. In the United States, approximately 200 million people drink water treated with fluoridation chemicals.

2. Up until 2011, fluoridation chemicals were generally added to U.S. drinking water supplies at a concentration of 1 mg/L. This concentration was increased to 1.2 mg/L in some colder, northern areas, and decreased to 0.7 mg/L in some warner, southern areas.

3. The fluoridation chemicals added to municipal drinking water supplies result in elevated concentrations of fluoride in many processed beverages and foods. These products are not currently labeled for their fluoride content in the U.S.

4. Due to concerns about increasing rates of dental fluorosis in U.S. children, the U.S. Centers for Disease Control and Prevention (CDC), and other federal agencies, recommended that the concentration of fluoride in water be reduced to 0.7 mg/L for all climate conditions. This recommendation was finalized in 2015.

5. Although fluoridation of water is a widespread practice in the United States, it is not so in Europe. Most European countries do not add fluoridation chemicals to their water, including Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Italy, Netherlands, Norway, Sweden, and Switzerland, as well as most of Spain and the United Kingdom. In total, less than 3% of the European population consumes water treated with fluoridation chemicals.

6. Worldwide, it is estimated that approximately 380 million people drink water treated with fluoridation chemicals. More than half of these people reside in the United States.

B. Current Fluoride Safety Standards

7. The foundational epidemiological studies in the U.S. that helped to establish the current safety standards for fluoride did not address the potential for fluoride to cause neurological effects, including IQ loss. The primary focus of these early studies was, instead, on skeletal health.

8. Although largely overlooked, some of the early studies of occupationally exposed workers, as well as some of the early studies of fluoride-exposed animals, reported central nervous system effects from fluoride exposure. In a 1953 study of monkeys, Wadhwani and Ramasway reported that monkeys with chronic fluorosis "did not conduct themselves with intelligence and agility of mind normally associated with them. There was a significant lack of co-ordination in their behaviour." These early observations, some of which remained unpublished, were largely overlooked.

9. The first known study of fluoride and intelligence in humans was published in 1989 by Ren and colleagues in China. A flurry of similar studies were published in China in the 1990s. Most of these studies were published in Chinese, and they remained largely unknown outside of China until English translations started to become available after 2006.

10. The current non-enforceable health-based limit for fluoride under the Safe Drinking Water Act ("SDWA"), or Maximum Contaminant Level Goal (MCLG), of 4.0 mg/L was promulgated in 1985 to protect against a condition known as crippling skeletal fluorosis (i.e., "stage III skeletal fluorosis"). Crippling fluorosis is the final, and most severe, stage of skeletal fluorosis.

11. In a 2006 comprehensive review, the National Research Council (NRC) of the National Academies of Science (NAS) recommended that the MCLG of 4 mg/L be lowered to prevent children from developing severe dental fluorosis and reduce the lifetime accumulation of fluoride into bone that the

majority of the committee concluded is likely to put individuals at increased risk of bone fracture and skeletal fluorosis.

12. Based on the NRC's recommendation, in 2010, EPA's Office of Water completed a dose-response analysis using available data between 2000 and 2010 to calculate a reference dose ("RfD")—an estimate of the fluoride dose protective against severe dental fluorosis, stage II skeletal fluorosis, and increased risk of bone fractures—of 0.08 milligrams per kilograms per day (mg/kg/day), a measure of daily intake by body weight.

13. Today, in determining whether adding fluoridation chemicals to drinking water presents an unreasonable risk of neurotoxic effects under TSCA, EPA has conceded that it would not rely on the 2010 RfD, but would instead apply a weight of the scientific evidence approach for identifying and characterizing the best available science from the most up-to-date scientific database of studies that have examined neurotoxicity as an effect of fluoride exposure. In other words, if EPA were to conduct a risk assessment for fluoride neurotoxicity (which the Agency has never done before), it would not rely on its existing safety standards.

14. The CDC has declared in this litigation, through its 30(b)(6) representative, that it has not conducted or sponsored research to assess the risk of neurotoxicity associated with fluoridation, and that it has not issued any position on the matter subsequent to the publication of the NIH-funded studies, which are discussed below.

15. The U.S. Food & Drug Administration (FDA), which regulates fluoride in toothpaste and other dental products, has not conducted or sponsored any research on the neurotoxicity of fluoride and has no position on the matter.

16. NSF International (NSF) is a private, quasi-public organization that certifies the safety of the chemicals added to drinking water in the United States, including fluoridation chemicals. The NSF declared in this litigation, through its 30(b)(6) representative, that it has not considered the potential for

fluoridation chemicals to cause neurotoxic effects, and has no position on the issue.

17. J.R. Simplot Company ("Simplot"), Mosaic Fertilizer and Mosaic Global Sales ("Mosaic Subsidiaries"), and Solvay Fluorides, LLC ("Solvay") are companies that manufacture and sell the chemicals used to fluoridate water in the U.S. Each of these three companies has declared in this litigation that they have made no attempt to assess whether fluoridation chemicals cause neurotoxic effects.

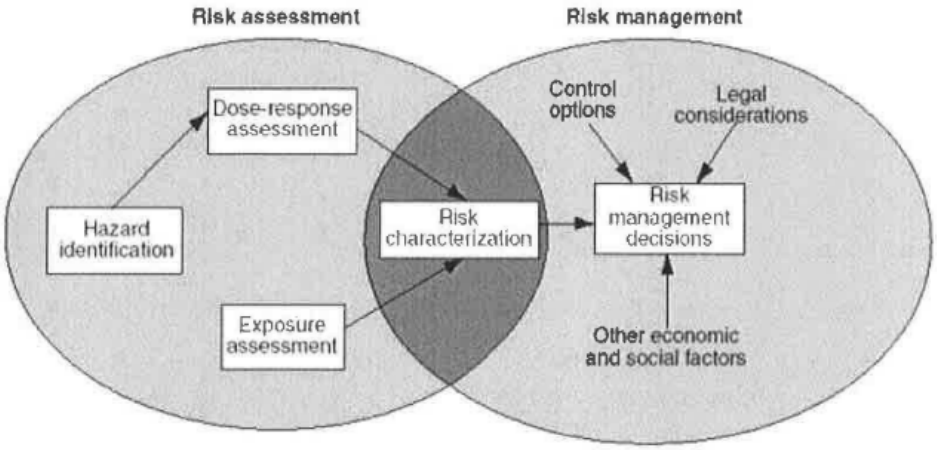
18. For the foregoing reasons, finding that fluoridation chemicals present a neurotoxic risk does not require the Court to find that any of the existing safety standards for fluoride were inadequate for the purposes established.

II. THE EPA/NRC RISK ASSESSMENT PARADIGM

19. "Risk assessment" is the dominant public-policy tool that EPA uses for "risk management" – i.e., to help inform the different policy options for protecting public health and the environment from chemical hazards.

20. EPA's framework for assessing and managing risks reflects the risk assessment and risk management paradigm set forth by the National Research Council (NRC) in 1983 (i.e., "The Red Book"), as illustrated in the following Figure:

Figure 1. Diagram of NRC risk assessment/risk management paradigm.



Source: EPA Office of Research and Development.

21. As indicated in the Figure, the NRC concluded that risk assessment and risk management are "two distinct elements" between which agencies should maintain a clear conceptual distinction. The NRC warned that "[e]ven the perception that risk management considerations are influencing the conduct of risk assessment in an important way will cause the assessment and regulatory decisions based on them to lack credibility."

22. The NRC's 1983 report identified four steps integral to any risk assessment: 1) hazard identification, 2) dose-response assessment, 3) exposure assessment, and 4) risk characterization.

23. The NRC and EPA have recognized that "uncertainty" is a pervasive aspect of risk assessment, since information in the real world is often not complete, and assumptions and inferences must be made to fill in certain evidentiary gaps.

24. One of the data gaps that is often present in a risk assessment is that EPA often does not have data demonstrating the chemical's hazards at exposure levels seen in the general population, and must thus assess risk by extrapolating from studies at higher doses.

25. Since uncertainty is an inherent feature of risk assessment, the NRC recommended that EPA establish "inference guidelines" (i.e., defaults) to ensure consistency in how EPA fills in data gaps from one chemical to the next.

26. As the NRC has explained, "without uniform guidelines, risk assessments might be manipulated on an ad hoc basis according to whether regulating a substance is thought be politically feasible." To minimize the risk of political interference, the NRC has explained that the "defaults" contained within the Agency's guidelines should be used unless there is chemical-specific data that justifies an alternative approach.

27. According to the NRC, the default options that are set forth in guidelines, "assign the burden of persuasion" to those wishing to use an alternative to the default for any given chemical.

28. In response to the NRC's recommendation to establish uniform guidelines, EPA created

Guidelines for Neurotoxicity Risk Assessment (hereafter *Guidelines*). EPA has stated it "will use" these *Guidelines* to "evaluate data on potential neurotoxicity associated with exposure to environmental toxicants."

29. Consistent with Figure 1 above, the *Guidelines* describe four steps to the risk assessment: (1) Hazard Assessment, (2) Quantitative Dose Response, (3) Exposure Assessment, and (4) Risk Characterization.

30. Neither the EPA, nor its retained experts in this case, have applied these *Guidelines* to the neurotoxicity literature on fluoride.

III. HAZARD ASSESSMENT

31. Under the *Guidelines*, the Hazard Assessment is a qualitative assessment to determine whether neurotoxicity is a *hazard* of the chemical.

32. A hazard is defined as the potential for a substance to cause an effect at a sufficiently high dose, which may or may not be relevant to a given condition of use. In other words, the focus of the hazard assessment is whether a chemical can, at some dose, cause the effect. The question of whether this hazard is a *risk* under any given condition of use is reserved for the Risk Characterization step of the analysis, which is the fourth and final step of a risk assessment under the *Guidelines*.

33. Under the *Guidelines*, neurotoxicity is considered to be a hazard of a chemical if "sufficient evidence" demonstrates an association.

34. Sufficient evidence of a hazard exists if there is "a single adverse endpoint from a well-conducted study." Alternatively, sufficient evidence exists if "the total available data may support such a conclusion."

35. The *Guidelines* identify the types of evidence that should be considered in the Hazard Assessment as well as the factors that should be considered when assessing this evidence.

36. The *Guidelines* recommend consideration of the following types of studies: animal; case reports; epidemiological, including cross-sectional and prospective cohort studies; *in vitro*; and pharmacokinetic.

A. Animal Studies

A.1 General Principles

37. Under the *Guidelines*, the hazard determination "can be based on either human or animal data." EPA has a preference for using human data if suitable data exist; in practice, however, animal data are almost always used.

38. The National Research Council has stated that "the inference that results from animal experiments are applicable to humans is fundamental to toxicologic research." Consistent with this, "EPA agrees that effects observed in animals are relevant to humans unless human data counterindicate."

39. EPA has expressly applied the *Guidelines* in 10 risk assessments. Based on these assessments, EPA established reference values—reference dose (RfD) or reference concentration (RfC)—to protect against neurotoxicity for 9 chemicals or groups of chemicals. In each of these assessments, EPA relied on animal data to establish the reference value.

40. One reason that EPA uses animal studies is that they "provide more precise exposure information, and control environmental factors better." Another reason is that human data are rarely available: for 6 of the 9 chemicals for which EPA has established reference values based on neurotoxicity endpoints, there were *no* human data on neurotoxicity.

41. Neurotoxic endpoints in animal studies fall into several categories, including neuroanatomical (i.e., structural or neuropathological), neurochemical, and behavioral.

42. Neuroanatomical endpoints include changes to the brain that are detectable under the microscope (i.e., "histological"), such as damage to brain cells. The *Guidelines* consider neuroanatomical changes to be "of concern," and EPA has established reference doses for chemicals based on

neuroanatomical effects documented in animals.

43. Neurochemical effects include biochemical changes in the brain, including alterations in neurotransmitter function and effects on enzymes. The *Guidelines* state that neurochemical changes "may be regarded as adverse because of their known or presumed relation to neurophysiological and/or neurobehavioral consequences."

44. Behavioral changes include alterations to motor activity, changes in sensory abilities or motor coordination, seizures, and impairments in learning, memory, and attention. EPA has repeatedly based reference doses on behavioral alterations documented in animals, including learning and memory impairments.

45. The principal studies which EPA has used to establish reference values have not been "perfect" studies, as EPA has generally identified a number of methodological limitations with the studies it has relied upon. Some of the principal studies did not conform to EPA's testing guidelines for animal studies, some used relatively small numbers of animals (e.g., 10 per group), and the principal studies that investigated effects from prenatal exposures did not always control for litter effects. These limitations did not stop EPA from establishing reference doses for these chemicals.

A.2 Animal Research on Fluoride Neurotoxicity

46. In 2006, the National Research Council (NRC) reviewed the existing toxicological literature on fluoride, including animal studies investigating fluoride neurotoxicity. The EPA, and other federal agencies, have accepted NRC's 2006 report as "an accurate summary of [fluoride's] hazard."

47. In its "Findings" section on neurotoxicity, the NRC 2006 report concluded that fluoride "interferes with the brain" in experimental animals, as evident by both neuroanatomical and neurochemical changes. Based on these findings, the NRC 2006 report concluded that neurotoxicity is a hazard of fluoride, at least in animals. As the NRC noted, "it is apparent that fluorides have the ability to interfere with the functions of the brain."

48. The neuroanatomical and neurochemical changes that NRC identified include, *inter alia*,

reduced phospholipid content; inhibition of acetylcholinesterase; interference with neurotransmitters; increased production of free radicals in the brain (i.e., oxidative stress); neuronal deformations; increased uptake of aluminum; and enhancement of reactive microglia.

49. It was unclear to the NRC if the brain changes seen in fluoride-treated animals would manifest into outwardly demonstrable deficits in cognition/behavior (i.e., "functional" effects), and whether these effects would occur in humans below the regulatory limit (4 mg/L) in the United States. The NRC 2006 report thus called for more animal research to examine fluoride's impact on cognitive skills.

50. Subsequent to the NRC's 2006 report, over 100 animal studies investigating fluoride's neurotoxicity have been indexed in the National Library of Medicine's online database ("PubMed"). Most of these animal studies have continued to focus on fluoride's neuroanatomical and neurochemical effects, with the overwhelming majority corroborating NRC's conclusion that fluoride affects animal brain on the neuroanatomical and/or neurochemical level.

51. Most animal studies on fluoride neurotoxicity have used subchronic exposure scenarios, which will tend to understate the effect from lifetime exposure. EPA's testing guidelines define a chronic exposure study in rodents as one that lasts at least 12 months.

52. Among studies that have tested animals at multiple points in time, effects have tended to worsen with time, with some effects not appearing at all until 3 to 6 months of chronic exposure. Most of the studies on fluoride neurotoxicity have lasted no longer than 3 months.

53. Only two studies of fluoride neurotoxicity have lasted 12 months or more. One of these two studies was coauthored by EPA neurotoxicologist Karl Jensen, and reported that rats drinking water with 1 mg/L had impaired cerebrovascular integrity, increased presence of beta-amyloid plaques, and increased uptake of aluminum. According to the NRC, these brain changes are similar to those seen in humans with dementia.

54. A subset of the post-NRC animal studies have investigated fluoride's "functional" effects on learning and memory. In 2016, the National Toxicology Program (NTP) published a systematic review of these functional studies and concluded that the overall evidence "suggests adverse effects on learning

and memory in animal [sic] exposed to fluoride."

55. The NTP had a "moderate level-of-confidence" in the studies investigating learning/memory effects in adult animals, but a "low level of confidence" in the developmental studies. The lower level of confidence for the developmental studies at that time was primarily the result of having fewer studies.

56. One of the limitations that the NTP identified is that the existing studies did not rule out the possibility that fluoride-induced "motor impairments" could be the cause of the impaired test performance. But motor impairments are themselves a form of neurotoxicity.

57. The lead author of the NTP review, Dr. Kristina Thayer, who is now the Director of EPA's IRIS Division, agrees that the animal data supports the biological plausibility of fluoride causing neurotoxic effects in humans.

58. Subsequent to the NTP's review, 11 additional developmental studies have reported learning and memory outcomes. Ten of these studies found impaired performance in the fluoride-treated groups.

59. In 2018, the NTP published an animal study on fluoride neurotoxicity, which found no impairment in learning/memory in the fluoride-treated rats.

60. While the NTP's 2018 study did not find an impairment in learning/memory, it did report a significant increase in pain sensitivity in the fluoride-treated rats, which is a manifestation of neurotoxicity that EPA considers adverse.

61. In October 2019, the NTP released a draft version of its *Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*. This report summarizes the findings of NTP's 3-year systematic review of both the animal and human evidence on fluoride neurotoxicity.

62. The NTP found that the studies still do not sufficiently rule out the possibility that the performance impairments in the fluoride-treated animals are the result of a neurotoxic effect on the motor/sensory system. Nevertheless, the NTP concluded that the collective data from the animal studies

support fluoride being a neurotoxicant in humans.

B. Human Studies

63. The *Guidelines* recognize several types of human studies that can inform the Hazard Assessment, including case reports and epidemiological studies.

64. In contrast to the 9 chemicals for which EPA has established RfDs or RfCs pursuant to the *Guidelines* (most of which did not have *any* human studies available), both categories of human studies are available for fluoride, including the most reliable kind of epidemiological study, prospective cohort studies.

B.1 Case Reports

65. The *Guidelines* note that "the first type of human data available is often the case report or case series," including clinician observations of occupationally exposed workers. This statement holds true for fluoride.

66. Case reports are generally not sufficient, by themselves, to establish a hazard, but the *Guidelines* consider them "useful when corroborating epidemiological data are available."

67. Decades before the first study of fluoride and IQ was published, case reports and clinician surveys of occupationally exposed workers identified neurological symptoms among fluoride-exposed individuals, including general malaise, fatigue, headaches, and difficulties with concentration and memory. The NRC has observed that "[t]here are numerous reports of mental and physiological changes after exposure to fluoride from various routes (air, food, and water) and for various time periods."

68. According to the NRC, several of the case reports on fluoride could be characterized as "experimental studies," since they involved "individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under 'blind' conditions. In most cases, the symptoms disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated."

B.2 Cross Sectional Studies

69. In cross-sectional studies, both the disease and suspected risk factors are ascertained at the same time.

70. A large number of cross-sectional studies on fluoride and neurotoxicity have been conducted since the first study on fluoride and IQ by Ren in 1989. Most of these studies have been conducted in China, India, and Iran, and have generally addressed higher levels of fluoride (>1.5 mg/L) than are added to water in fluoridation programs in the U.S.

71. The cross-sectional studies on fluoride have consistently reported associations between fluoride exposure and cognitive deficits, including studies with robust designs that the National Toxicology Program has found to have low risk of bias.

72. While cross sectional studies generally do not "allow the investigator to determine whether the disease or the exposure came first" (and thereby limit the ability to ascribe causality), this limitation is lessened when there is a stable population where water supplies and fluoride concentrations have remained unchanged for many years.

73. Some of the cross-sectional studies on fluoride and IQ have limited the study population to children who have lived in the same area since birth. In this context of stable populations and stable water fluoride levels, measurement of exposure at the time of the study can be a reasonable, albeit imperfect, proxy for exposure from the prenatal period onward. Imprecision in exposure estimates are generally expected to bias the results towards the null, thereby making it less likely to observe an association.

74. In 2006, the NRC report assessed the first four IQ studies to become available in English (each was conducted in China). Each of the four studies that NRC reviewed found significant associations between fluoride exposure and reduced IQ. While the studies lacked sufficient detail for the NRC to draw conclusions, the NRC found that "the consistency of the collective results warrant[s] additional research on the effects of fluoride on intelligence."

75. In 2012, Drs. Philippe Grandjean and Anna Choi from the Harvard School of Public Health published a meta-analysis of 27 studies, and found that "children in high fluoride areas had significantly lower IQ scores than those who lived in low-fluoride areas." Of the 27 studies examined, 26 found an

association between elevated fluoride and reduced IQ. The water fluoride concentrations in the studies were generally between 2 and 4 mg/L. Children in the high-fluoride areas had, on average, 7 less IQ points than children in control areas.

76. Consistent results in cross-sectional studies across different populations increases the confidence that a chemical is, in fact, causally related to the outcome, and thus increase confidence in the hazard assessment.

77. Dr. Grandjean's team recommended that future research "formally evaluate dose-response relationships based on individual level measures of exposure over time, including more precise prenatal exposure assessment." As discussed below, a number of studies have now been conducted, and add substantial confidence to the hazard assessment.

78. A more recent meta-analysis by Duan has also reported a significant association between higher fluoride concentrations in water and lower intelligence in children. Duan focused on studies published through November 2016 that examined the effects of waterborne fluoride exposures and which provided data on the water fluoride levels.

79. Each of the 26 studies that met Duan's inclusion criteria found lower IQs in the high-fluoride community when compared against the control. In a majority of these studies, the high-fluoride community had less than 4 mg/L in the water, including three studies which found significant effects at concentrations between 1 and 2 mg/L. Duan concluded that "Greater exposure to high levels of fluoride in water was significantly associated with reduced levels of intelligence in children."

80. In addition to the association with reduced IQ, cross-sectional studies have also found associations between fluoride and ADHD. Most recently, a study of a nationally representative sample of Canadian children found that an increase of 1.0 mg/L fluoride in water was associated with a 6.1 times higher odds of an ADHD diagnosis after controlling for potential confounding factors such as household income, parental educational attainment, blood lead, and secondhand smoke exposure (Riddell 2019).

B.3 Prospective Cohort Studies

81. EPA's *Guidelines* recognize that prospective cohort studies are "invaluable for determining the time course for development of dysfunction."

82. In a prospective cohort study, "a healthy group of people is assembled and followed forward in time and observed for the development of dysfunction." This study design "allows the direct estimate of risks attributed to a particular exposure, since toxic incidence rates in the cohort can be determined."

83. Short of intentionally dosing humans in controlled experiments (which are prohibited for ethical reasons), prospective cohort studies are generally considered the ideal study design for understanding the impact of environmental chemicals on human health.

84. Because prospective cohort studies "can be very time-consuming and costly," they are rarely available for neurotoxicity risk assessments.

85. None of the 9 chemicals that EPA has established reference values for under the *Guidelines* had a prospective cohort study. In the case of fluoride, there are now *six* prospective cohort studies, including five with individualized measurements of fluoride exposure. In addition, the NTP's 2019 systematic review determined that 9 of the cross-sectional studies on fluoride and IQ are "functionally prospective in nature."

86. Of the six formal prospective studies on fluoride and neurodevelopment, five have collected individual measurements of total fluoride exposure (e.g., urinary fluoride levels and fluoride ingestion from beverages). Each of these 5 prospective studies that collected individual measurements of exposure found a significant association between early-life exposure to fluoride and neurodevelopmental harm. The one study that did not assess total exposure (Broadbent, et al) did not detect a measurable effect on IQ.

87. Studies of environmental toxicants that collect data on individual exposure (versus community measures of exposure, such as water fluoride concentration) are generally considered more robust and reliable than those that do not.

88. Four of the prospective cohort studies that have collected individual measurements have been funded by the National Institutes of Health (NIH), including two studies of the "ELEMENT" cohort in Mexico City (Bashash 2017, Bashash 2018), and two studies of the "MIREC" cohort in Canada (Green

2019, Till 2019).

89. Two of the NIH-funded studies were co-funded by the EPA. According to EPA, it "generally does not fund studies on the effect of environmental toxicants on children's health unless EPA believes the proposals for the studies have reliable methods that will produce reliable results."

90. The parties agree that the ELEMENT and MIREC cohort studies are the most methodologically reliable studies to date on the impact of fluoride on neurodevelopment.

B.3.a ELEMENT Cohort Studies

91. The study participants in the ELEMENT cohort are exposed to "optimal" levels of fluoride through fluoridation of salt. The purpose of salt fluoridation is to replicate the fluoride doses that are produced through water fluoridation.

92. There is a reasonable *a priori* assumption that the daily exposures to fluoride in the ELEMENT cohort will generally be comparable with the exposures in water-fluoridated communities. The soundness of this *a priori* assumption is borne out by the data, as discussed below.

93. The first study of fluoride exposure and neurodevelopment in the ELEMENT cohort was published in 2017 ("Bashash 2017"). It found a significant linear dose-response relationship between prenatal fluoride exposure (as measured in the urine of the mother) and reduced childhood IQ.

100. Each 1.0 mg/L increase of fluoride in the mother's urine was associated with 6.3 less IQ points at 4 years of age, and 5 less IQ points at ages 6 to 12—effect sizes that are on par with the effects of lead.

101. In this first study of the ELEMENT cohort, no threshold was observed for the 4-year-old children, but there was some suggestion of a threshold of 0.8 mg/L in the 6-12 year old children.

102. The second study of the ELEMENT cohort ("Bashash 2018") examined the relationship between prenatal fluoride exposure and ADHD symptoms and found a significant linear dose-response relationship. Specifically, prenatal fluoride exposure was significantly associated with symptoms of

inattention among the children.

103. Both studies of the ELEMENT cohort extensively controlled for potential confounding factors, including birth weight, gestational age, maternal age, maternal education, maternal IQ, maternal smoking, socioeconomic status, and exposure to other neurotoxicants, including lead and mercury.

104. According to Dr. Joyce Donohue, the lead scientist on fluoride issues at EPA's Office of Water, the ELEMENT studies are well-conducted, and further justify a reassessment of fluoride safety standards to ensure that children are not being overexposed.

B.3.b MIREC Cohort Studies

105. The NIH has funded two studies of the MIREC cohort in Canada. The first of these studies was published in *JAMA Pediatrics* in August of 2019 ("Green 2019") and examined the relationship between prenatal fluoride exposure and childhood IQ.

106. As with the ELEMENT studies, Green 2019 controlled for a large number of potential confounders, including: maternal education, maternal age, quality of the child's home environment (HOME), gestational age, mother's race, city, maternal smoking, and exposure to other neurotoxicants, including lead, mercury, manganese, and arsenic.

107. Green 2019 examined 512 mother-child pairs living in communities with water fluoride levels at, or below, 0.7 mg/L and found that prenatal fluoride exposure (as measured in the mother's urine) was significantly associated with reduced IQ in boys.

108. Each 1 mg/L increase of fluoride in the mothers' urine was associated with 4 to 5 less IQ points among the boys, an effect size on par with lead.

109. Green 2019 also found significant associations between IQ (in both boys and girls), maternal fluoride intake (from water and other beverages), and water fluoride concentration.

110. The findings from the MIREC study are convergent with the findings from the ELEMENT cohort and support the *in utero* period being a susceptible period of life vis-à-vis fluoride toxicity.

111. Based on Green 2019's findings, the editor of *JAMA Pediatrics*, Dr. Dimitri Christiakis, stated that he would now recommend that pregnant women not drink water treated with fluoridation chemicals.

112. In November 2019, the second study of fluoride and neurodevelopmental effects in the MIREC cohort was published (Till 2019). Unlike the previous ELEMENT and MIREC studies, this study examined the impact of fluoridated water exposure during *infancy* among 398 children.

113. As with the other NIH-funded studies, Till 2019 controlled for a large number of potentially confounding factors, including child's sex and age, maternal education, maternal race, second-hand smoke, and Quality of the Child's Home Environment (HOME).

114. The Till 2019 study found that fluoride exposure during infancy was associated with a large decrease in non-verbal IQ. For each 0.5 mg/L increase in water fluoride concentration, formula-fed babies had a loss of 9.3 performance (non-verbal) IQ points.

115. Based on these findings, the authors of the Till 2019 study recommended that measures be taken to reduce fluoride exposure among infants.

B.4 NTP's Assessment of the Epidemiological Literature

116. As set forth in its draft Monograph, the NTP has concluded that "fluoride is presumed to be a cognitive neurodevelopmental hazard to humans."

117. The NTP explained that "the presumed hazard conclusion is supported by the low expectation that new studies would *decrease* the hazard conclusion."

118. According to the NTP, "the human body of evidence provides a consistent pattern of findings that high fluoride exposure is associated with decreased intelligence quotient (IQ) in children." The NTP identified 13 studies which it found to have low risk of bias, and "higher fluoride exposure was associated with at least one measure of decreased IQ in each of the 13 studies."

119. The NTP determined that the consistent association between fluoride and reduced IQ is

unlikely to be explained by inadequate control for potential confounders or errors in exposure measurement.

C. Neuroendocrine Effects

120. EPA's *Guidelines* require consideration of a chemical's ability to cause neurological effects via endocrine disruption (i.e., neuroendocrine effects), including disturbances of the thyroid gland.

121. EPA has recognized that "thyroid hormones are essential for normal brain development in humans and that hypothyroidism during fetal and early neonatal life may have profound adverse effects on the developing brain."

122. According to the *Guidelines*, "the development of the nervous system is intimately associated with the presence of circulating hormones such as thyroid hormone," and a thyroid disturbance during a specific developmental period may cause a "nervous system deficit, which could include cognitive dysfunction, altered neurological development, or visual deficits, [depending] on the severity of the thyroid disturbance and the specific developmental period when exposure to the chemical occurred."

123. In 2006, the NRC concluded that fluoride is an "endocrine disrupter" which may lower thyroid function.

124. The NRC reported that fluoride has been associated with lower thyroid function at estimated average intakes of 0.05-0.13 mg/kg/day in humans with adequate iodine intake, and at estimated average intakes as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency.

125. Pointing to data showing a "decreasing iodine intake by the U.S. population," the NRC called for research to examine fluoride's "possible role in the development of several diseases and mental states in the United States," including "thyroid disease."

126. According to national data from the CDC, more than 10% of women of child-bearing age in the US are iodine deficient.

127. Subsequent to the NRC report, a nationwide study from the UK (Peckham 2015) reported that artificially fluoridated water is associated with a significant increase in the prevalence of

hypothyroidism.

128. Additionally, a study from Canada (Malin 2018) reported a significant relationship between urinary fluoride and elevated TSH (thyroid stimulating hormone) among iodine-deficient adults in Canada, but not in the general population as a whole. Elevated TSH is indicative of a decrease in thyroid function.

129. Fluoride's known ability to disrupt the endocrine system, and its reported relationship with reduced thyroid function among adults with low-iodine intake, supports the conclusion that neurotoxicity is a hazard of developmental fluoride exposure.

D Mode of Action

130. EPA's *Guidelines* recognize that hazard identification is strengthened by, but not dependent upon, an identifiable mechanism by which the chemical can exert neurotoxic effects.

131. The National Academy of Sciences (NAS) has stated that "solid conclusions about causality can be drawn without mechanistic information, for example, when there is strong and consistent evidence from animal or epidemiology studies." The NAS added that "mechanistic frameworks today could probably be completed for only a few chemicals."

132. For most of the chemicals for which EPA has established reference doses pursuant to the *Guidelines*, the mode of action has not been known.

133. Several plausible mechanisms—both indirect and direct—have been identified that could help explain the neurotoxicity of fluoride.

134. Thyroid depression is a plausible indirect mechanism that could account for some of the neurotoxic effects reported in the literature.

135. A thyroid mechanism is particularly plausible as a cause of IQ loss among offspring born to women with suboptimal iodine intakes. In the United States, over 10% of women of child-bearing age are deficient in iodine.

136. In terms of direct mechanisms of fluoride neurotoxicity, there is some *in vitro*, *in vivo*, and epidemiological data suggesting that fluoride may cause disturbances in hippocampal mitochondrial

dynamics (marked by fission inhibition and fusion promotion). These disturbances play an important role in fluoride-induced cognitive loss.

137. The hippocampus is an important region in the brain for learning and memory, and many of the studies investigating the mechanisms of fluoride neurotoxicity have identified adverse effects in this region.

138. The existing animal research has identified many potential mechanisms, including oxidative stress, signaling disruption, and selective reductions in nicotinic receptors. Consensus is currently lacking as to which direct mechanism(s) are most important.

E Qualitative Dose Response

139. The *Guidelines* recognize that "determining a hazard often depends on whether a dose-response relationship is present," and thus "dose-response evaluation is a critical part of the qualitative characterization of a chemical's potential to produce neurotoxicity." Because "human studies covering a range of exposures are rarely available," the *Guidelines* state that the dose-response evaluation will typically be limited to animal data.

140. There is a substantial amount of dose-response data to inform the hazard assessment for fluoride neurotoxicity, from *both* animal *and* human data. While there are some inconsistencies, the data generally show that the incidence and/or severity of nervous system deficits increase as fluoride exposure increases.

141. In the human studies, a linear dose-response relationship has been identified in each of the three NIH-funded cohort studies that have investigated the effects of prenatal exposure. (Bashash 2017, Basahash 2018, Green 2019). With the possible exception of the IQ results in the 6-12 year olds, these three studies did not identify any apparent safe threshold.

142. The consistent finding of a linear-dose response relationship between fluoride and reduced IQ in the NIH-funded prospective cohort studies adds substantial support to neurotoxicity being a hazard of fluoride.

143. In animal studies, a prerequisite for dose-response analysis is that there be multiple treatment groups with different exposures to the test substance. Many of the animal studies on fluoride have used multiple treatment doses, and thus permit evaluation of dose response.

144. Of the 100+ studies that have been indexed in the National Library of Medicine's database since the NRC's 2006 review, 1 used four treatment doses, 17 used three treatment doses, and 16 used two treatment doses in addition to a control. Of these 34 studies, most show dose-response trends for one or more of the effects being investigated.

F. Pharmacokinetics

145. Under the *Guidelines*, consideration is given to the pharmacokinetics of the chemical with "particular importance" given to the pharmacokinetics of the blood-brain barrier.

146. EPA has recognized that "the developing brain is distinguished by the absence of a blood-brain barrier. The development of this barrier is a gradual process, beginning *in utero* and complete at approximately 6 months of age. Because the blood-brain barrier limits the passage of substances from blood to brain, in its absence, toxic agents can freely enter the developing brain."

147. The absence of an effective blood brain barrier renders the brain more vulnerable to the harm posed by neurotoxicants.

148. With respect to fluoride, the parties do not dispute that fluoride gets through the placenta, and that the fluoride a pregnant woman ingests has access to the fetus. Since the blood brain barrier is not yet developed during this time, the parties agree that fluoride gets into the fetal brain.

149. Studies of aborted human fetuses from areas of endemic fluorosis in China have reported substantial neuroanatomical and neurochemical damage to the brain.

150. After the blood brain barrier is finished forming at about 6 months of age, the blood brain barrier is able to reduce the uptake of fluoride into the brain, albeit not completely.

151. During the late stages of life, the permeability of the blood brain barrier begins to increase,

particularly among those with diseases such as Alzheimer's and Parkinson's.

152. The degeneration of the blood-brain barrier in the late stages of life provides a plausible basis for concern when considering the heightened body burden of fluoride during this period of life. Specifically:

- Studies have found that water fluoridation significantly increases the level of fluoride in bone, and that these levels increase with age.
- The fluoride that is taken into bone is not forever bound. When bone breakdown increases in the postmenopausal and elderly years, some of the fluoride stored in the tissue is released back into the bloodstream.
- Fluoride is principally excreted via the kidneys in urine. When kidney function declines, the rate of fluoride accumulation in the body increases.
- Kidney function (i.e., renal function) declines with age, and thus the kidneys during the late stages of life can be expected to be less efficient in clearing fluoride from the bloodstream.
- The breakdown of fluoride-rich bone coupled with the decrease in renal function in the late-stages of life will increase the amount of fluoride that is available to the elderly brain.

G. *In Vitro* Studies

153. EPA's *Guidelines* suggests that consideration be given to *in vitro* data (i.e., studies of cells in the test tube). While positive *in vitro* data are not sufficient, by themselves, to demonstrate a neurotoxic hazard in humans, the existence of such data helps enhance the reliability of *in vivo* data (i.e., studies of mammals).

154. Fluoride's ability to damage brain cells has been documented in *in vitro* experiments. While most of these studies have used high concentrations that are unlikely to be present in the human brain, several studies have examined environmentally realistic fluoride concentrations. For example, an *in vitro* study by Gao found that fluoride increased lipid peroxidation and reduced $\alpha 7$ nicotinic acetylcholine receptors in brain cells at concentrations that are commonly found in the blood of humans in fluoridated communities. Studies by Goschorska and colleagues have found evidence of inflammation at similar concentrations.

H. Validity of the Database

155. Under the *Guidelines*, the validity of the database should be evaluated by assessing the content validity, construct validity, concurrent validity, and predictive validity of the data.

156. *Content validity* addresses "whether the effects result from exposure." This factor weighs decisively in favor of a neurotoxicity hazard determination for fluoride:

- The NIH funded prospective birth cohort studies on fluoride have consistently associated prenatal exposure in humans with adverse neurodevelopmental effects.
- The *Guidelines* recognize that prospective cohort studies are the optimal form of epidemiological study for ascribing causality between chemical and disease.
- The NTP's 2019 systematic review concluded that the epidemiological studies are sufficiently compelling to classify fluoride as a presumed neurotoxicant in humans.
- The NRC's 2006 report concluded that neurotoxicity is a hazard of fluoride exposure in animals. A large number of studies published subsequent to NRC's report have corroborated this conclusion.
- Dr. Thayer, who served as the principal author of the NTP systematic review on fluoride's learning effects, agreed that the animal studies show that "at some level of exposure fluoride can damage the brain."

157. *Construct validity* addresses whether the neurologic effects that have been observed "are adverse or toxicologically significant." This factor is again decisively satisfied in the fluoride database:

- EPA has recognized that a loss of a *single* IQ point is associated with a loss in lifetime earnings.
- The NIH-funded studies have found 4 to 6-point drops in IQ for each 1 mg/L increase in maternal urinary fluoride, which is on par with the effects of lead.
- Recent data from Canada and the U.S. shows that more than 5% of pregnant women in fluoridated areas have urinary fluoride levels exceeding >2 mg/L.
- The NTP has described the epidemiological data on fluoride and IQ as showing a "relatively large magnitude of effect."
- The animal studies have consistently linked fluoride to learning and memory deficits, which EPA has used as the adverse effect upon which to establish reference doses for other suspected neurotoxicants.

158. *Concurrent Validity* addresses "whether there are correlative measures among behavioral, physiological, neurochemical, and morphological endpoints."

159. There is currently a lack of definitive research regarding correlative measures in fluoride neurotoxicity.

160. In animals, fluoride's cognitive deficits have been correlated in some studies with various neurochemical and neuroanatomical changes, which provides some support for concurrent validity.

161. In humans, cross-sectional studies have identified associations between fluoride, cognitive loss, increased TSH, and/or alterations in mitochondrial dynamics, which provides further support.

162. Overall, while there is some support for concurrent validity, this factor does not currently carry as much weight in the hazard assessment.

163. *Predictive validity* addresses "whether the effects are predictive of what will happen under various conditions." This factor weighs in favor of a hazard finding.

164. Neurotoxicity has been associated with fluoride exposure under many conditions, including experimental animals; occupationally-exposed workers; communities drinking naturally contaminated drinking water in China, India, Iran, and Mexico; and children born to pregnant women exposed to artificially fluoridated water and salt in both Canada and Mexico.

I. Hazard Conclusion

165. Under the *Guidelines*, the purpose of the hazard identification analysis is to determine if "sufficient evidence" exists to demonstrate that neurotoxicity is a hazard of the chemical. The existing database on fluoride provides a high degree of confidence that neurotoxicity is a hazard.

166. First, toxicological evidence was sufficient as of 2006 to permit the NRC to conclude that fluoride causes neuroanatomical and neurochemical effects in animals. Many additional animal studies have been published which further confirm this, and the NTP's 2019 report concluded that the animal studies support fluoride causing neurotoxic effects in humans.

167. Second, the *Guidelines* provide that a "single" well conducted study can constitute sufficient evidence for a hazard determination, and it is widely accepted that prospective cohort studies are the strongest study design for investigating the effects of environmental chemicals on human health. These types of studies are rarely available, but there are *six* available on fluoride. Of these six studies, the five that took individual measurements of fluoride each found significant associations between early-life exposure and adverse neurodevelopmental effects.

168. Third, the findings of the five prospective studies are consistent with, and strengthened by,

the following evidence:

- The increased vulnerability to neurotoxicants when the brain lacks an effective blood brain barrier;
- Pharmacokinetic data demonstrating placental transfer of fluoride to the fetus and the absence of a blood brain barrier *in utero*;
- Pathology studies of aborted fetuses from endemic fluorosis areas, which have reported substantial neuroanatomical and neurochemical damage;
- Animal studies reporting neuroanatomical, neurochemical, and behavioral alterations following prenatal exposure to fluoride;
- The findings of many cross-sectional studies associating fluoride with reduced IQ in children, including 9 which the NTP has described as "functionally prospective";
- Occupational studies reporting neurological effects from fluoride in the *mature* brain, which is more resistant to harm than the developing brain in the fetus and neonate;
- *In vitro* data showing fluoride can affect brain cells when present at environmentally relevant concentrations;
- The NRC's conclusion that fluoride is an "endocrine disruptor" which can lower thyroid function, particularly among individuals with low-iodine intake;
- The neuroendocrine research that has been published subsequent to the NRC report which further supports fluoride having an adverse effect on thyroid function among people with iodine deficiency;
- The well-established finding that thyroid disruption during pregnancy causes neurodevelopmental harm in the offspring; and

169. Taken together, the available evidence is sufficient to conclude that neurotoxicity is a hazard of fluoride exposure.

V. QUANTITATIVE DOSE RESPONSE ASSESSMENT

170. The second step in a risk assessment is a quantitative dose response assessment.

171. In a quantitative dose-response assessment, the dose-response relationship between the chemical and the outcome of interest is assessed in the available animal and/or human data.

172. Where available, EPA prefers to use human data for the dose-response analysis. In practice, however, EPA has used animal data in all of the risk assessments it has done under the *Guidelines*, and in all of the draft risk evaluations that it has issued under TSCA.

173. The purpose of the quantitative dose response assessment is to identify a "Point of Departure" for the derivation of a reference dose (RfD) or as the starting point for a Margin of Exposure

(MOE) analysis.

174. An RfD is the estimated dose that is likely to be without an appreciable risk of deleterious effects during a lifetime, including for susceptible populations.

175. The POD can be one of three different types of datapoints: a "Benchmark Dose Level" (BMDL), a "No Observed Adverse Effect Level" (NOAEL), or a "Lowest Observed Adverse Effect Level" (LOAEL).

176. Of the three types of PODs, EPA's preference is to use a BMDL, as it provides the most information about the slope of the dose-response curve.

177. The BMDL is the dose of a chemical that is associated with some defined level of effect known as the Benchmark Response (BMR). A BMR is generally chosen to represent the point at which the effect takes on some degree of biological significance.

178. After a POD is identified, EPA applies uncertainty factors to ensure that the reference dose protects against the expected range of sensitivity to the chemical across the population, and to account for data gaps in the literature.

A. BMDL for Fluoride-Induced IQ Loss in Humans

179. The NIH-funded ELEMENT and MIREC studies are well suited for the derivation of an BMDL for IQ loss because they are high-quality studies with exposures covering the range observed in the general population.

180. A loss of 1 IQ point is an appropriate BMR to use for a quantitative dose response assessment.

181. According to multiple EPA publications, including several EPA regulatory impact assessments, the loss of 1 IQ point is expected to cause a loss in lifetime earnings. EPA has recently estimated the loss to be up to $18,686 per person.

182. A 1-to-2 IQ point reduction at the population level was recognized as an adverse effect by the U.S. EPA Clean Air Scientific Advisory Committee, which emphasized that "an IQ loss on the order of one to two IQ points [should] be prevented in all but a small percentile of the population."

183. The European Food Safety Authority selected the loss of 1 IQ point as the BMR for its dose response analysis for lead.

184. EPA's retained experts in this case (Drs. Ellen Chang and Joyce Tsuji from Exponent) selected the loss of 1 IQ point as the BMR for their own quantitative dose response analysis for a prior matter.

185. Analysis of the maternal urinary fluoride data from the ELEMENT cohort using a BMR of 1 IQ point results in a BMDL of 0.1 mg/L for IQ loss by age 4.

186. Analysis of the maternal urinary fluoride data from the MIREC cohort using the same BMR results in a BMDL of 0.21 mg/L for IQ loss by age 3 to 4.

187. Analysis of the maternal fluoride intake data (from beverages) in the MIREC cohort results in a BMDL of 0.15 mg/day for IQ loss by age 3 to 4.

188. Based on these results, the BMDL for maternal urinary fluoride is in the range of 0.1 to 0.21 mg/L. The POD is thus in the range of 0.1 to 0.21 mg/L. As will be discussed below, the risk estimate does not depend on what point in this range is selected, and thus for simplicity purposes the POD will be identified as **≤0.2 mg/L.**

B. NOAEL/LOAELs for Fluoride-Induced Learning/Memory Impairments in Animals

189. Since suitable data is available to derive a BMDL for IQ loss in humans, it is not *necessary* to derive a POD from animal data. However, a separate derivation of a POD from animal data helps to inform the confidence to be given to the risk assessment.

190. The following considerations justify use of the learning/memory studies in animals to

establish a POD for fluoride neurotoxicity:

- EPA has used impairment in learning and memory in rodents as the adverse effect upon which to base the RfD for other chemicals, thus this is an accepted endpoint to use in deriving an RfD;
- A substantial number of the animal studies on fluoride have used 2 or 3 treatment groups, and EPA has found this to be sufficient for dose-response assessment, including animal studies with as few as 10 rats per group.
- EPA has used animal research to establish the POD for each of the neurotoxicity risk assessments that it has thus far conducted under the *Guidelines*.

191. In the National Library of Medicine's database, there are a total of 37 rodent studies which have investigated fluoride's impact on learning and memory since the NRC's 2006 report. All but 3 of these studies found adverse effects in the fluoride-treated rodents, including 16 of the 17 that investigated prenatal fluoride exposures.

192. Based on pharmacokinetic considerations and the findings from the human prospective studies, the *in utero* period is likely a sensitive life stage for fluoride neurotoxicity. It is appropriate, therefore, to derive a POD from the animal studies that have investigated *in utero* exposures. Further, in order for the data to be suitable for dose-response assessment, the studies should have at least 2 treatment groups in addition to the control.

193. There are a total of 10 animal studies in the National Library of Medicine's database that investigated i*n utero* exposures to multiple doses of fluoride, ranging from 4.5 mg/L to 45 mg/L. Of these 10 studies, 9 reported learning and/or memory impairments in the fluoride-treated rats with visually evident dose-response trends.

194. While each of these 10 ten studies has one or methodological limitations, the consistency in the dose-response trends across nine separate studies adds confidence that the relationship between fluoride and the neurological impairments is causal.

195. Depending on how protective of public health EPA's risk managers choose to be, the available 10 studies offer a range of LOAELs and NOAELs that could be used as the POD. Within this range of possible PODs, EPA's retained toxicologist, Joyce Tsuji, has stated that a NOAEL of 20 mg/L—

the *least* protective POD that can be selected—would be an appropriate POD to use.

196. Since the 20 mg/L NOAEL is the least protective POD that can be selected from the data, if a risk assessment using this POD identifies a risk from fluoridation chemicals, then all other PODs would necessarily show a risk as well.

197. For purposes of simplicity, the 20 mg/L NOAEL is used as the POD for this assessment. When adjusted for bodyweight, it is expressed as a dosage of **3.3 mg/kg/day.**

D. Uncertainty Factors

198. Once a POD is identified, EPA does an assessment to determine what "uncertainty factors" should be applied.

D.1 General Principles and Practices

199. Uncertainty factors are applied to account for expected variations in susceptibility among humans (i.e., *intra*species variability), expected differences in susceptibility between animals and humans (i.e., *inter*species variability), and, where applicable, differences in the length of exposure between the study and human conditions (i.e., subchronic to chronic), research gaps in the overall database (i.e., database deficiency), and converting from a LOAEL to a NOAEL.

200. These uncertainty factors are "typically multiples of 10," although each can be reduced to a factor of 3 if warranted by available chemical-specific information.

201. *Intraspecies Variability (UF_H)*: EPA recognizes that susceptibility to toxic substances is not uniform across the human population, and that because of differences in *toxicokinetics* and/or *toxicodynamics*, some subsets of the population will be more vulnerable to harm than others.

202. *Toxicokinetics* refers to the "processes which determine the extent and duration of exposure of the target organ or site of toxicity to the active chemical species," while *toxicodynamics* refers to the

"processes involved in the translation of such exposure of the target organ or site of action into the generation of a toxic effect." Put more simply, toxicokinetics governs how much of the chemical gets to the target site (i.e., access), while toxicodynamics governs how much of the chemical is necessary at the target site to cause the adverse effect (i.e., sensitivity).

203. If there are no chemical-specific data on toxicokinetics and toxicodynamics, EPA uses a default uncertainty factor of 10 for intraspecies variability. This default factor of 10 is "considered to be appropriate in the absence of convincing data to the contrary" and is comprised of two co-equal factors of 3, one for toxicokinetics and one for toxicodynamics. Consistent with this, EPA has used a UF_H 10 in each of the nine risk assessments where it has established reference values pursuant to the *Guidelines*.

204. *Interspecies Variability (UF_A)*: EPA recognizes that susceptibility to toxic substances differs across species. As with intraspecies variability, interspecies variability is rooted in principles of both toxicokinetics and toxicodynamics. With respect to the kinetics component, EPA has developed a hierarchical framework of approaches that are geared towards ascertaining the "human equivalent dose" (HED) of a dose given to animals.

205. EPA's "optimal" approach for determining the HED is to use a *physiologically based toxicokinetic model (PBTK).* A PBTK is an empirically-based, chemical-specific model that allows EPA to calculate the HED of a given dose of a given chemical of a given route (i.e., oral, dermal, or inhalation) in a given species.

206. Where a PBTK model is not available, the "intermediate" approach is to use *chemical-specific information* that, while falling short of a full PBTK model, provides some reliable guidance.

207. Where there is no reliable chemical-specific information on kinetics, EPA uses a *default* allometric scaling method.

208. Allometric scaling relates to "scaling of physiological rates or quantities to relative growth and size (mass or volume) of one animal species relative to another species."

209. Body weight scaling to the 3/4 power is EPA's default method for allometric scaling (hereafter referred to as the $BW^{3/4}$ Method). Under the $BW^{3/4}$ Method, the HED is 14% of the dose given to mice, and 24% of the dose given to rats.

210. The $BW^{3/4}$ Method "predominantly addresses factors involved in estimating toxicokinetics, as well as some toxicodynamic factors." EPA thus maintains a default UF of 3 to account for uncertainty with toxicodynamics and residual uncertainty with toxicokinetics.

211. Under the $BW^{3/4}$ Method, the Human Equivalent Dose of the animal POD (3.3 mg/kg/day) is **0.79 mg/kg/day.** This is expressed as POD_{HED}, and is the dosage to which uncertainty factors are applied.

D.2 Application of Uncertainty Factors to the Human POD for Fluoride

212. As a practical matter, there is no need to determine what uncertainty factor(s) should be applied to the human POD of <0.2 mg/L in pregnant women. This is because human exposure (as discussed below) in fluoridated areas exceeds this POD, and thus a risk is evident before applying a single uncertainty factor.

D.3 Application of Uncertainty Factors to the Animal POD for Fluoride

213. EPA's risk assessment expert, Dr. Tsuji, agrees that uncertainty factors should be applied to the fluoride POD. She offered no opinion, however, as to what the size of the factors should be.

214. Plaintiffs' risk assessment expert, Dr. Kathleen Thiessen, has applied the uncertainty factors consistent with EPA's standard practice, and derived an uncertainty factor of 10 for intraspecies (human-to-human) variability and an uncertainty factor of 3 for interspecies (animal-to-human) variability. The composite uncertainty factor thus equals 30.

215. A composite uncertainty factor of 30 is lower than the composite uncertainty factor that

EPA has used in each of its risk assessments under the *Guidelines*. In EPA's risk assessments, the composite uncertainty factor has ranged from 100 to 3,000.

216. Applying the uncertainty factors to the animal POD (0.79 mg/kg/day) produces a reference dose of **0.03 mg/kg/day**.

E The Reference Doses Derived from Human and Animal Data

217. Based on the above calculations, the resulting reference doses are **≤0.2 mg/L** (maternal urinary fluoride content in humans), and **0.03 mg/kg/day** (learning/memory impairments in humans).

218. Despite being based on the *least protective* POD from the animal data, the 0.03 mg/kg/day reference dose for neurotoxicity is still *lower* than EPA's current reference dose for severe dental fluorosis (0.08 mg/kg/day).

219. The fact that the RfD for neurotoxicity is lower than the RfD for severe dental fluorosis is an indication that the former is a more sensitive effect of fluoride exposure. This conclusion is supported by the epidemiological literature, including studies which have found associations between fluoride and IQ in children without—and at doses not believed to cause—severe fluorosis.

VI. EXPOSURE ASSESSMENT

A. Statement of Purpose, Scope, Level of Detail, and Approach

220. The *Guidelines* state that the Exposure Assessment should provide a statement of the purpose, scope, level of detail, and approach used to assess the exposure.

221. In the 2016 Amendments to TSCA, Congress made clear that the unreasonable risk assessment must consider and protect susceptible populations. Based on this statutory mandate, it is appropriate to focus the Exposure Assessment on susceptible populations.

222. Focusing on the exposures of susceptible populations is specifically identified in the

Guidelines as being an appropriate focus of the Exposure Assessment. This assessment thus does so.

223. The fetus, infant, and elderly have each been identified as a likely susceptible population vis-à-vis fluoride neurotoxicity. These populations thus comprise the focus of the Exposure Assessment.

224. The Exposure Assessment is intended to generate sufficient detail to permit a direct comparison with the reference values.

225. For the fetus, the Exposure Assessment focuses on published maternal urinary fluoride concentration. This focus is appropriate for two reasons: (1) urinary fluoride content is a good indicator of total fluoride exposure, and (2) the prospective cohort studies have analyzed IQ as a function of maternal urinary fluoride content. An exposure assessment that focuses on maternal urinary fluoride content thus allows for a direct comparison with the toxicity data.

226. In addition, for all age groups including the fetus, the Exposure Assessment considers EPA's own water intake data (as reviewed by the NRC) to determine total daily fluoride intake from fluoridated water (0.7 mg/L).

227. The focus on total daily intake of fluoride from fluoridated water is appropriate because Plaintiffs' Citizen Petition is focused on one condition of use: the addition of fluoridation chemicals to drinking water.

228. It is also appropriate to rely on EPA's water intake data because there is no reason to believe that water intake has materially changed in the United States since 2000, which is when EPA published the data. In fact, in 2010, the EPA used this same data to estimate fluoride exposure in the U.S.

B. Maternal Urinary Fluoride Concentrations

229. Early studies from the United States found that that the concentration of fluoride in urine mirrors the concentration of fluoride in drinking water. Based on this early data, a person drinking water with 1 mg/L of fluoride will be expected to have about 1 mg/L fluoride in their urine.

230. The strong influence of water-fluoride concentration on urine-fluoride concentration reflects the fact that water is generally the largest source of fluoride in a person's diet, particularly in communities with fluoridation programs.

231. Maternal urinary fluoride concentrations (MUF) were measured in over 1,000 pregnant women from the MIREC cohort in Canada. This results were published in 2018 in the journal *Environmental Health Perspectives* ("Till 2018").

232. The Till 2018 study found that water fluoridation was the major predictor of urine-fluoride levels, with *creatinine*-adjusted MUF concentrations of **0.87 mg/L** and 0.46 mg/L in fluoridated (0.6 ppm) and non-fluoridated (0.12 ppm) communities, a difference of 0.4 mg/L.

233. Five percent of the women in fluoridated areas in the Till 2018 study (i.e., the "95th percentile") had *creatinine*-adjusted MUF values exceeding 2 mg/L, which is about 1 mg/L more fluoride than the 95th percentile women in non-fluoridated areas.

234. In addition to adjusting for creatinine, the Till 2018 study also adjusted for *specific gravity*. The *specific-gravity* adjusted MUF values were **0.71 mg/L** for the fluoridated group, and 0.41 mg/L in the non-fluoridated group.

235. Dr. Angeles Martinez-Mier is a recognized expert in the field of urine-fluoride analysis, and is the scientist who measured the fluoride in the Till 2018 study, as well as in all other MIREC and ELEMENT cohort studies.

236. Dr. Martinez-Mier has recently completed a study along with researchers form the University of California San Francisco (UCSF) that measured MUF in a cohort of 50 pregnant women in California.

237. This new study, which has been submitted and accepted for publication, found an average *specific-gravity*-adjusted MUF o**f 0.72 mg/L** among the women living in fluoridated areas and 0.46 mg/L in women living in non-fluoridated areas.

238. The MUF concentrations reported in the California study are very similar to the MUF concentrations from the Canadian study (i.e., 0.72 mg/L in fluoridated areas of California vs. 0.71 mg/L in fluoridated areas of Canada).

239. There are no other contemporary studies of urinary fluoride concentrations in the United States. The CDC tested fluoride in the urine of children in its 2015-2016 National Health and Nutrition Examination Survey (NHANES), but the data has not yet been released.

240. Based on the available data, the average MUF in fluoridated areas in North America appears to be ~0.7 mg/L (when adjusted for specific gravity), and ~0.9 mg/L (when adjusted for creatinine).

C. Total Daily Fluoride Intake from Water

241. The EPA has recognized that drinking water is generally the most significant source of fluoride in a person's diet in fluoridated communities.

242. EPA has extensive data on water consumption in the United States. (EPA 2000). This data permits calculations of total fluoride intake from drinking water for various age groups.

243. The EPA commissioned the National Research Council (NRC) to review the adequacy of EPA's regulatory standards for fluoride, which included a comprehensive exposure assessment for the USA.

244. In its 2006 report, the NRC used EPA's water consumption data to estimate fluoride intake from drinking water. Later, in 2010, the EPA published its own estimates of fluoride intake from this same drinking water consumption data. EPA's estimates were consistent with NRC's estimates, although the two organizations presented the data somewhat differently.

245. In NRC's exposure assessment, the NRC estimated fluoride intake from fluoridated water (0.7 mg/L) among people in the 90th percentile, 95th percentile, and 99th percentile of water intake. In EPA's exposure assessment, the EPA estimated fluoride intake among people in the 90th percentile.

246. In NRC's exposure assessment, the NRC provided exposure estimates for many different age groups, including infants less than 6 months old. The EPA, by contrast, did not provide exposure estimates for infants less than 6 months old, and did not provide as detailed a breakdown for the adult age groups.

247. Of all age groups, the NRC found that infants less than 6 months-old consume the most fluoride by bodyweight in the population, followed by infants 6 months or older.

248. For infants less than six months, the NRC estimated that fluoride intake from fluoridated water at the 90th, 95th, and 99th percentiles is 0.118, 0.143, and 0.168 mg/kg/day, respectively.

249. For infants older than six months, the NRC estimated that fluoride intake from fluoridated water at the 90th, 95th, and 99th percentiles is 0.081, 0.089, and 0.119 mg/kg/day, respectively.

250. For young adults of child-bearing age (ages 20-24), the NRC estimated that fluoride intake from fluoridated water at the 90th, 95th, and 99th percentiles were 0.022, 0.027, and 0.056 mg/kg/day, respectively.

251. For older adults of child-bearing age (age > 25 years), the NRC estimated that fluoride intake from fluoridated water at the 90th, 95th, and 99th percentiles were 0.022, 0.028, and 0.046 mg/kg/day, respectively.

252. For elderly adults (ages $\geq$ 65 years), the NRC estimated that fluoride intake from fluoridated water at the 90th, 95th, and 99th percentiles were 0.022, 0.026, and 0.037 mg/kg/day, respectively.

253. In total, NRC estimated that over 5% of the population consumes more than 0.03 mg/kg/day of fluoride from water with the 95th percentile dose registering at **0.031 mg/kg/day**.

VII. RISK CHARACTERIZATION

A. General Considerations About Risk

254. Risk characterization involves a comparison of hazard values with exposure levels to

qualitatively gauge the potential for risk.

255. EPA does not require that human exposure levels exceed a known adverse effect level to make an unreasonable risk determination under TSCA.

256. In the draft risk evaluations that EPA has thus far released under the amended TSCA, EPA's unreasonable risk determinations have all involved conditions of use where human exposures were below the known adverse effect levels.

B. Margin of Exposure (MOE)

B.1 The Basic Construct

257. The Margin-of-Exposure (MOE) approach is an appropriate method to use to characterize the neurotoxic risks of fluoridation chemicals because (1) the EPA generally uses the MOE approach to characterize *non-cancer* risk under TSCA, and (2) the *Guidelines* recommend the MOE approach to characterize *neurotoxic* risk.

258. Under the MOE approach, a "Calculated MOE" (otherwise known as the "Actual MOE") is derived by comparing (dividing) the POD by the human exposure level. This Calculated MOE is then compared against a "Benchmark MOE" (otherwise known as the "Target MOE") which is the product of all relevant uncertainty factors.

259. If the Calculated MOE is less than the Benchmark MOE, the "basic construct" of the MOE method is that an "unacceptable risk" (aka "risk of concern") exists.

260. The MOE and RfD methods for characterizing risk "are fundamentally equivalent," and, thus, "for a given risk and given exposure of a [chemical], if exposure to a [chemical] were found to be acceptable under an [RfD] analysis it would also pasas under the MOE approach, and vice-versa."

B.2 MOE Applied to the Human POD

261. Application of the MOE approach to the human POD demonstrates an unacceptable risk.

262. When the human POD (0.2 mg/L MUF) is divided by the average MUF in fluoridated areas (0.7 to 0.87 mg/L), the Calculated MOE is on the order of 0.2 to 0.3.

263. Even if *no uncertainty factors are used* for the Benchmark MOE (i.e., Benchmark MOE = 1), the Calculated MOE is lower than the Benchmark MOE because the Calculated MOE is less than 1. The human data thus shows an unacceptable risk when assessed under the MOE method.

B.3 MOE Applied to the Animal POD

264. Application of the MOE approach to the animal-derived POD also demonstrates an unacceptable risk, despite the fact that the POD is the least protective POD that could be selected.

265. First, the Benchmark MOE is 30, as this is the product of the two uncertainty factors discussed earlier: i.e., intraspecies UF of 10 and interspecies UF of 3.

266. Second, the Calculated MOE for infants under 6 months of age is 5.6. This is derived by dividing the POD of 0.79 mg/kg/day by infant exposure of 0.146 mg/kg/day.

267. The Calculated MOE for infants (5.6) is less than the Benchmark MOE (30), and thus an unacceptable risk is indicated.

268. Unreasonable risks are also indicated for other age groups and segments of the population, including between 1 and 5% of adults of child-bearing age and the elderly.

VIII. RISK DETERMINATION

269. If a risk is identified using the MOE method, EPA may consider other risk-related factors prior to making an unreasonable risk determination under TSCA.

270. Other risk-related factors that EPA has identified as relevant to the risk determination are

the population exposed (including any potentially exposed or susceptible subpopulations); the severity of the hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties.

A. The Population Exposed

271. In its TSCA risk evaluations, EPA has recognized that "the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and the extent of exposure to the substance." The number of people exposed to a chemical under the condition of use is thus a relevant factor in an unreasonable risk determination.

272. EPA also considers whether the population exposed is the general public or occupationally-exposed workers, as there are mechanisms available to protect workers from chemical hazards (e.g., personal protective equipment).

273. In its draft risk evaluations under the amended TSCA, EPA has found unreasonable risks for conditions of use involving *thousands* of occupationally-exposed workers.

274. The extent of exposure to fluoridation chemicals is orders of magnitude greater than the chemicals EPA has found to pose unreasonable risks.

275. Approximately 200 *million* people from the general population live in communities where fluoridation chemicals are added to drinking water.

276. Exposure to fluoridation chemicals is not limited to people who live in areas where these chemicals are added to the water. As EPA has recognized, "Cooking and preparing foods with water that contains fluoride increases the fluoride content of the food as served. This is true for home-prepared and commercial foods." People living in non-fluoridated areas are thus exposed to fluoridation chemicals anytime they consume a processed beverage or food (e.g., sodas, juices, alcoholic beverages, etc) made with fluoridated water.

277. Because of the widespread extent of human exposure to fluoridation chemicals, even a small

risk of harm can result in millions of people being harmed (e.g., if fluoridation chemicals caused neurotoxic injury in only 1% of consumers, this would represent over 2 *million* people).

B. Susceptible Subpopulations

278. In addition to considering the number of people exposed, EPA considers the potential for susceptible subpopulations to be exposed.

279. Under TSCA, a susceptible subpopulation is defined as "a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, *may* be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly." 15 U.S.C. § 2602(12).

280. EPA has recognized that susceptibility to a chemical may be "intrinsic" (biological, e.g., life stage) or "extrinsic" (acquired, e.g., lifestyle).

281. In EPA's neurotoxicity risk assessments, "a population subgroup is susceptible if exposure occurs during a period of sensitivity." Life stage is thus an important intrinsic factor for identifying susceptible subpopulations in neurotoxicity risk assessments.

282. Pregnant women are a susceptible subpopulation to fluoridation chemicals due to the susceptibility of the fetus. The fetus is susceptible because (1) fluoride passes through the placenta, (2) there is no blood brain barrier to prevent the uptake of fluoride into the brain, and (3) the rapidly developing brain is more vulnerable to the effect of neurotoxicants. The susceptibility of the fetal brain to fluoride is further supported by:

- prospective cohort studies that have consistently found associations between prenatal fluoride exposure and neurodevelopmental harm;
- pathology studies that have found neuoroanatomical and neurochemical harm in aborted fetuses from areas of endemic fluorosis; and
- animal studies that have found neuroanatomical, neurochemical, and behavioral alterations, including cognitive deficits, following prenatal exposure.

283. Over 2.5 million pregnant women are estimated to live in fluoridated areas.

284. Infancy is another life stage that is susceptible to the neurotoxic effects of fluoride. While breast-fed babies are protected from fluoride (due to its absence in breast milk), bottle-fed babies have *both* an intrinsic *and* extrinsic susceptibility. Bottle-fed infants have an intrinsic susceptibility because they are a *life stage* marked by an incomplete blood brain barrier and rapidly developing nervous system; they have an extrinsic susceptibility because they have a *life style* (i.e., formula-feeding) that results in having the highest fluoride dose, by bodyweight, of all age groups in the population if fluoridated water is is used to reconstitute the formula.

285. Importantly, none of the existing animal studies on fluoride and cognition have assessed the effect of formula-feeding during the early postnatal period. Unlike bottle-fed human infants, rats and mice receive their entire caloric intake during the nursing period from their mother's milk, which has very low levels of fluoride. The available animal studies are thus likely to understate the effect of early-life exposure to fluoride in bottle-fed infants.

286. Approximately 1 million *exclusively formula-fed* infants are estimated to live in fluoridated areas.

287. The elderly are another population that are susceptible due to life stage. The EPA has recognized that the elderly are "at particular risk because of the limited ability of the nervous system to regenerate or compensate to neurotoxic insult." In addition, due to declining kidney function, and release of accumulated fluoride from bone, there is a greater body burden of fluoride during the elderly years. This increased level of circulating fluoride will have greater access to the brain due to age-related increases in the permeability of the blood brain barrier. The susceptibility of the elderly is further supported by (1) animal studies finding brain-changes after long-term fluoride exposure that parallel the changes seen in humans with dementia, and (2) a recent epidemiological study from Scotland which found a significant association between dementia risk and the presence of fluoride in drinking water.

288. Approximately 50 million elderly individuals are estimated to live in fluoridated areas of the U.S.

289. Life stage is not the only intrinsic factor that increases susceptibility to fluoridation chemicals. The EPA has also recognized that kidney disease is an intrinsic factor that increases susceptibility to fluoride by increasing the build-up of fluoride in the body, and that fluoride toxicity is enhanced in the presence of nutrient deficiencies, including calcium and iodine.

290. The EPA has also recognized that genetics is an intrinsic factor that may increase a person's susceptibility to fluoride toxicity. Although the EPA has not specifically addressed what role genetics may play with respect to fluoride neurotoxicity, two recent epidemiological studies suggest that fluoride's impact on IQ may be magnified in the presence of genetic differences related to dopamine receptors (e.g., COMT gene polymorphisms).

291. The intrinsic factors that increase susceptibility to fluoride can co-exist in the same individual, further increasing the risk. For example, a pregnant mother may have an iodine deficiency; an infant may have a COMT gene polymorphism; and an elderly individual may have kidney disease and a nutrient deficiency.

292. Due to the widespread scope of water fluoridation in the U.S., large numbers of people with intrinsic and/or extrinsic factors that increase the risk of fluoride toxicity are being exposed.

C. Severity of the Hazard

293. The EPA has recognized that even small reductions in population IQ from chemical exposures is a serious health matter that warrants regulatory action to prevent.

294. Based on a BMD analysis of the ELEMENT and MIREC cohort data, an increase of 0.1 to 0.2 mg/L fluoride in a pregnant mother's urine is associated with a 1 point drop in the IQ of the offspring.

295. The average MUF in pregnant women living in fluoridated areas is in the range of 0.7 to

0.87 mg/L, with up to 5% of women having more than 2 mg/L. These concentrations substantially exceed the concentration associated with IQ loss.

296. The addition of fluoridation chemicals to drinking water increases MUF by approximately 0.4 mg/L, which is a concentration associated with an approximate 2-point drop in the offspring's IQ.

297. Economists have devised methods to calculate the societal gains from preventing IQ losses, as higher IQs will, on average, result in higher lifetime incomes. In terms of 2006-dollars, economists have estimated the value of 1 IQ point to be about $18,000.

298. The EPA has recognized that a 1-point drop in IQ results in a loss of lifetime earnings. At a general discount rate of 3%, EPA has estimated that the loss of 1 IQ point reduces lifetime earnings by $18,686.

299. Each year, there are approximately 2.5 million pregnant women living in fluoridated areas.

300. The large number of pregnant women living in fluoridated areas, coupled with the high concentrations of MUF documented in these areas, presents the potential of substantial population loss of IQ points.

301. According to unrebutted calculations by Dr. Philippe Grandjean, the addition of fluoridation chemicals to water results in an approximate loss of 4.5 to 25 million IQ points among children 0 to 5 years of age.

302. The loss of IQ points associated with fluoridation chemicals is in the range of what has been calculated for known major causes of IQ loss, including preterm births (i.e., 34 million lost IQ points among 0 to 5-year-old children) and lead exposure (23 million lost IQ points among 0 to 5-year-old children).

303. A population-wide loss of IQ on this scale is expected to produce a loss in lifetime earnings on the scale of hundreds of billions of dollars for each cohort of 0-to-5 year old children.

D. Reversibility of the Hazard

304. Damage to the developing brain can result in permanent harm.

305. While the reversibility of fluoride-induced IQ loss has not been specifically addressed in the literature to date, the epidemiological evidence on fluoride and IQ is consistent with the effect being permanent.

306. The Bashash 2017 study measured the impact of prenatal fluoride on IQ at age 4 and ages 6 to 12. Similar reductions in IQ were observed in both age groups, suggesting that the effect of prenatal fluoride exposure on childhood IQ does not disappear over time.

307. Several studies of older populations living in endemic fluorosis areas have found increased rates of cognitive impairment, as well as neurological symptoms such as headaches.

308. With respect to the elderly brain, the EPA has acknowledged that it is "at particular risk because of the *limited ability of the nervous system to regenerate* or compensate to neurotoxic insult."

E. Uncertainties

E.1 General Considerations:

309. In the ideal world, all risk assessments would be based on a very strong knowledge base (i.e., reliable and complete data on the nature and extent of contamination, fate and transport processes, the magnitude and frequency of human and ecological exposure, and the inherent toxicity of all of the chemicals). However, in real life, information is usually limited on one or more of these key data needed for risk assessment calculations. This means that risk assessors often have to make estimates and use judgment when performing risk calculations, and consequently all risk estimates are uncertain to some degree.

310. Uncertainties are not uncommon in risk assessment; they are the norm. The National Research Council has stated that uncertainty is "the dominant analytical difficulty" in risk assessment.

311. Every study has its limitations, including prospective cohort studies.

312. For a limitation to be meaningful, it should be able to plausibly explain the reported association between a chemical and an effect.

E.2 Uncertainties in the Fluoride Database

313. Various limitations exist in the current research base on fluoride neurotoxicity. None of these limitations, however, can plausibly explain the consistent relationship between fluoride and cognitive deficits that have been observed in both animal and epidemiological studies.

E.2.a Imprecision in Exposure Estimates

314. The methods used to measure prenatal fluoride exposure in the ELEMENT and MIREC studies will introduce some imprecision into the exposure estimates. For example, the urinary fluoride measurements were based on spot samples, which primarily reflect short-term exposures that may not be representative of a mother's exposure during pregnancy. This limitation is lessened, but not eliminated, by the use of multiple urine samples during pregnancy.

315. The imprecision in the prenatal exposure methods from the ELEMENT and MIREC cohorts are unlikely to explain the reported associations between prenatal fluoride and adverse neurodevelopmental findings. The imprecision is an example of what epidemiologists call "nondifferential error." Rather than leading to spurious or inflated associations, nondifferential errors tend to bias the results towards the null. Thus, rather than making the studies more likely to find an association, exposure imprecision makes the studies *less likely to find it.*

316. The NTP's 2019 systematic review concluded that exposure error is not an important source of bias in the available data on fluoride neurotoxicity.

E.2.b Failure to Control for All Potential Confounders

317. EPA's retained epidemiologist, Dr. Ellen Chang, has opined that the consistent statistical association between fluoride and reduced IQ may be the result of inadequate controls of confounding factors.

318. To be a confounding factor, the variable (e.g., parental education, socioeconomics, etc) must be associated with the exposure (in this case, fluoride) and the effect (in this case, neurotoxicity).

319. In her expert report, Dr. Chang fails to explain which potential confounding factor(s) could explain the consistent association between fluoride and reduced IQ across multiple populations and study designs.

320. The NTP Monograph concluded that inadequate control for confounding factors is unlikely to explain the association between fluoride and IQ reduction.

E.2.c <u>Generalizability of ELEMENT and MIREC studies to the United States</u>

321. Questions have been raised about the generalizability of the ELEMENT and MIREC cohort findings to populations in the United States.

322. EPA routinely relies upon data on chemical toxicity from other countries to estimate risks from those same chemicals in the United States. For example, the EPA relied on data on methylmercury and neurotoxicity from a cohort in Faroe Islands to establish the reference dose for that chemical.

323. In the specific context of fluoride neurotoxicity, EPA and other federal agencies have cited and relied upon a study of IQ in fluoridated areas of New Zealand as supporting the safety of fluoridated water in the US with no analysis to assess the "generalizability" of these findings.

324. Would the EPA and NIH invest millions of dollars in studies that are not relevant to populations in the U.S.? Whatever the answer to this question is, the scientists who are conducting the ELEMENT and MIREC studies agree that the studies are relevant to populations living in fluoridated areas of the U.S.

325. Dr. Howard Hu, the principal investigator of the ELEMENT studies, has stated that the findings of his studies "are consistent with and support the conclusion that fluoride is a developmental neurotoxicant at levels of exposure seen in the general population in artificially fluoridated communities."

326. Dr. Bruce Lanphear, the co-principal investigator of the MIEEC studies, has stated that the Canadian findings are applicable to the United States, and that—based on the results—he would recommend that pregnant women not drink fluoridated water. Dr. Lanphear's opinion is seconded by the editor of *JAMA Pediatrics*, which published the MIREC prenatal study.

327. In order to conclude that the ELEMENT and MIREC studies are not generalizable to fluoridated areas of the United States one or both of the following must be true: (1) people in the United States are biologically more resistant to the toxic effects of fluoride than Canadians or Mexicans, (2) the levels of fluoride associated with harm in the Canadian and Mexican are materially higher than the levels of exposure in the U.S. fluoridated areas.

328. The EPA has identified no data, or biologic rationale, to suggest that Americans are biologically more resistant to fluoride's effects than Canadians or Mexicans. If the ELEMENT and MIREC cohort findings are not generalizable to the US, therefore, it must be the result of material differences in exposure.

329. EPA has extensive data in its possession on fluoride exposures in the United States. The Agency, however, has not presented any data, nor identified any reason, to suggest that U.S. residents in water-fluoridated areas are exposed to materially less fluoride than their counterparts in water-fluoridated areas of Canada and salt-fluoridated areas of Mexico.

330. The available published data support the generalizability of the ELEMENT and MIREC findings to the United States, as will now be discussed.

Generalizability of the Canadian data to the U.S.

331. Urinary fluoride levels are a "good indicator of total daily fluoride intake," and are generally

expected to reflect the concentration of fluoride in water.

332. Canada and the United States add fluoride to water at the same approximate concentration, i.e., generally 0.6 mg/L in Canada; and generally 0.7 mg/L in the U.S.

333. As noted earlier, the urine fluoride concentrations from the MIREC study are very similar to the concentrations recently reported from a cohort in California (i.e., 0.71 mg/L in Canada vs. 0.72 mg/L).

334. Ideally, there would be nationwide data available for urine fluoride levels in the U.S., as such data would allow for more definitive comparison of fluoride exposures in Canada and the U.S. No such national data is available. As EPA has recognized, however, the existence of data gaps does not excuse the need for a risk assessment, nor preclude a finding of risk.

335. The similarity in water fluoride levels between Canada and the U.S., and the similarity in urine fluoride levels in the available datasets, provide a reasonable basis to infer that fluoride exposures in the water-fluoridated areas of the two countries will be generally comparable. Since EPA has failed to identify a reason to meaningfully question this inference, the analysis need not go any further.

Generalizability of the Mexican data to the U.S.

336. The study participants in the ELEMENT cohort are exposed to so-called "optimal" levels of fluoride through fluoridation of table salt.

337. The purpose of salt fluoridation is to replicate the fluoride doses that are produced through water fluoridation. It is a reasonable *a priori* assumption, therefore, that the daily exposures to fluoride in the ELEMENT cohort will be generally comparable with exposures in water-fluoridated communities. The soundness of this *a priori* assumption is borne out by the data.

338. As with the MIREC study, the ELEMENT study measured the fluoride concentration in the urine of the mothers and did so using the same laboratory (University of Indiana) and scientist (Dr. Martinez-Mier).

339. Dr. Martinez-Mier measured urine-fluoride in the ELEMENT cohort by adjusting for *creatinine*, rather than specific gravity. This resulted in an average concentration of **0.90 mg/L** in the 299 mothers described in 2017, and **0.85 mg/L** in the 213 mothers described in the subsequent study. These average concentrations are effectively the same as what Dr. Martinez-Mier found when she used the creatinine method for the MIREC cohort. As documented in the 2018 article, the creatinine-adjusted urine-fluoride concentration in the MIREC cohort was **0.87 mg/L.**

340. While use of the creatinine-adjustment method in the ELEMENT studies precludes direct comparison with the urine-fluoride data from the recent Californian study, there is an important comparison point between these studies which further confirms the generalizability of the ELEMENT findings to the U.S. Specifically, in both the ELEMENT and California cohorts, Dr. Martinez-Mier measured fluoride concentrations in the blood of the pregnant women, and the average results were essentially identical between the two populations: 0.022 mg/L in the ELEMENT cohort and 0.021 in the California study.

341. The data generated by the MIREC, ELEMENT, and California studies are consistent in showing similar internal fluoride concentrations across the populations.

342. EPA points out that it is difficult to quantify fluoride intake (i.e., external dose) on the basis of urinary fluoride concentrations (i.e., internal, absorbed dose). By extension, EPA contends that one cannot use urinary fluoride data from Canada, Mexico and the U.S. to compare total fluoride intake across these populations. But, even if true, Dr. Hu has appropriately explained that it is the internal, absorbed dose (which is reflected by the urine fluoride content) that is more important to predicting toxicity, not external exposure. Thus, urine fluoride is the more appropriate metric to use when generalizing the results of the ELEMENT and MIREC studies to the U.S.

E.2.d <u>Lack of Definitive Proof of Causation at 0.7 mg/L</u>

343. EPA's retained epidemiologist, Dr. Ellen Chang from Exponent, has concluded that the

epidemiological evidence is not yet sufficient to establish fluoride at 0.7 mg/L as a "known" cause of neurotoxicity.

344. Dr. Chang has reached similar conclusions regarding other chemical-related health concerns using similar methods as she has applied in this case. Dr. Chang is careful to point out, however, that her conclusion of "insufficient evidence" of being a "known" cause of an effect is not inconsistent with the chemical being a "presumed" cause under the standards used by the NTP.

345. EPA has conceded that it "does not require that human exposure levels exceed a known adverse effect level to make an unreasonable risk determination under TSCA." EPA bases its unreasonable risk determinations on whether human exposures are unacceptably close to the estimated adverse effect levels.

346. The material question for this risk determination, therefore, is not whether there is conclusive proof of causation at 0.7 mg/L, but whether 0.7 mg/L is unacceptably close to the danger level. Neither Dr. Chang, nor Dr. Tsuji, attempted to answer this question.

347. According to the NTP's draft monograph, the evidence is sufficiently clear to reliably presume that 1.5 mg/L fluoride causes neurotoxic effects, including IQ loss.

348. Based on NTP's conclusion, the margin between the *concentration* of fluoride that is presumed to *cause* IQ loss (i.e., an adverse effect level) is only two times greater than the *concentration* of fluoride added to water. For purposes of risk assessment, this is an unreasonably narrow margin because it is EPA's longstanding risk assessment policy to apply an intraspecies uncertainty factor of 10 to account for differences in susceptibility across the human population, unless there is convincing chemical-specific data that supports a lower adjustment.

349. Moreover, even if no uncertainty factors were applied, EPA water consumption data demonstrates that some individuals living in areas with 0.7 mg/L fluoride will ingest more fluoride from water than individuals living in areas with 1.5 mg/L.

E.3 Absence of Systematic Review

350. EPA contends that Plaintiffs' expert conclusions on risk are not credible because they are not the product of a formal systematic review. This contention is unpersuasive for the following reasons:

351. Up until the past 5 to 10 years, EPA did not use a systematic review protocol for its risk assessments. To find, therefore, that a risk assessment is not credible if it does not use a systematic review would call into question the credibility of most of EPA's own risk assessments, which are the scientific basis of numerous environmental regulations in this country.

352. EPA's experts on fluoridation's benefits in this case (Dr. Charlotte Lewis and Dr. Gary Slade) did not conduct systematic reviews, but instead performed narrative reviews of the scientific literature using a weight of the evidence analysis. The Court presumes that EPA would not offer an expert opinion in federal court unless the Agency deemed the opinion to be scientifically credible.

353. EPA's experts, Dr. Chang and Dr. Tsuji, conducted systematic reviews of both the epidemiological and animal literature for this case, and did not identify any studies that were omitted by Plaintiffs' experts which would materially alter the conclusions.

354. Plaintiffs' epidemiologist, Dr. Grandjean, derived his BMD estimates from the ELEMENT and MIREC studies, which EPA and its experts both agree are the most methodologically reliable studies on fluoride neurotoxicity.

355. According to the Deputy Director of EPA's Office of Pollution Prevention and Toxics, Dr. Tala Henry, a risk assessment conducted pursuant to the *Guidelines* is "effectively" a systematic review.

356. Plaintiffs' risk assessment, Dr. Kathleen Thiessen, conducted a risk assessment pursuant to the *Guidelines*.

F. Benefits

[As set forth in Plaintiffs' Motion in Limine *No. 1, Plaintiffs contend that benefits are a "nonrisk factor" that the statute prohibits from considering as part of the unreasonable risk determination. To the extent, however, that the Court disagrees, Plaintiffs have set forth here some of the facts that the evidence will establish.]*

357. Fluoridation chemicals are added to water for the purpose of preventing tooth decay (i.e., caries).

358. Tooth decay rates in the United States substantially decreased in the second half of the twentieth century. This "caries decline" is commonly attributed to the introduction of water fluoridation. However, similar (and often greater) caries declines occurred throughout Europe during the same time period, despite the latter's rejection of fluoridation.

359. When fluoridation first began in the 1940s, the public health community believed that fluoride's predominant benefits came from *ingestion* prior to the eruption of teeth.

360. Today, the CDC recognizes that fluoride's predominant benefit comes from *topical* contact with the teeth after eruption, not from swallowing it.

361. As recognized by the CDC, fluoridation chemicals provide no known dental benefits during the *in utero* and *neonatal* stages of life (i.e, the stages of life prior to tooth eruption). These life stages are the same life stages that appear to be at greatest risk of fluoride neurotoxicity. For these susceptible populations, therefore, there is *no known benefit, only risk.*

362. The EPA and National Academy of Sciences (NAS) accept that fluoride is not an essential nutrient. There is thus no physiological *need* for *any age group* to *swallow* fluoride.

363. Swallowing fluoride is inevitable when it is added to the drinking water.

364. The Iowa Fluoride Study (IFS) is the only prospective cohort study to investigate the relationship between total daily fluoride *ingestion* during childhood and the development of caries. The IFS study was funded by the NIH.

365. The IFS data shows that total daily fluoride ingestion from birth through six years of age causes dental fluorosis but does not protect against caries.

366. Randomized Controlled Trials (RCTs) are the gold standard study design for determining the benefits and safety of health care interventions. There are no RCTs on water fluoridation.

367. Blinding of examiners is an important study method, the absence of which has been found to spuriously inflate the benefit of health care interventions. There have been very few blinded studies on water fluoridation.

368. The absence of randomization procedures and blinding in fluoridation studies can plausibly explain a substantial portion of the reported associations with reduced caries.

369. The Cochrane Collaboration is a leading international authority regarding systematic reviews of health care interventions.

370. In 2015, the Cochrane Collaboration published a systematic review on the effectiveness of water fluoridation in preventing caries. The review concluded that:

> - While the available studies do indicate a dental health benefit, the data come predominantly from low-quality studies conducted prior to the widespread use of fluoride toothpaste.
> - There is very little contemporary evidence, meeting the review's inclusion criteria, that has evaluated the effectiveness of water fluoridation for the prevention of caries.
> - There is insufficient information to determine the effect on caries levels of stopping water fluoridation programs.
> - There is insufficient evidence to determine whether water fluoridation results in a change in disparities in caries levels across socioeconomic groups.
> - There is no evidence meeting the review's inclusion criteria to demonstrate the effectiveness of water fluoridation for preventing caries in adults.
> - There is a significant association between dental fluorosis (of aesthetic concern or all levels of dental fluorosis) and fluoride level.

IX. STANDING

371. Plaintiff Food & Water Watch (FWW) is a nonprofit membership organization that champions healthy food and clean water for all.

372. A “core” part of FWW’s mission is “the belief that clean, safe water for drinking and

recreational uses is a fundamental right that should be afforded to all people." FWW thus advocates for more government responsibility in protecting drinking water resources, and engages in legal efforts to oppose regulatory action/inaction that threatens the safety of drinking water.

373. Some of FWW's 70,000 members "expend substantial sums of money and endure substantial inconvenience in order to protect themselves and their families from the risks of neurological harm posed by fluoridation chemicals in food and water."

374. The concern about neurological risks expressed by some FWW members is based, in part, on neurological ailments they, or their children, have suffered from drinking fluoridated water.

375. Julie Simms is one of the FWW members that has suffered neurological ailments from fluoridation chemicals. As described in her declaration, Ms. Simms had suffered from daily headaches and frequent debilitating migraines for the better part of 20 years until, at a friend's suggestion, she stopped drinking fluoridated water.

376. In 2013, at the advice of a friend, Ms. Simms stopped drinking fluoridated water. After three days of drinking low-fluoride water, Ms. Simms experienced a notable improvement in the symptoms of her daily headaches, and within 3 weeks, they had had completely cleared. Ms. Simms also experienced an improvement in both the frequency and symptomology of her migraines.

377. Ms. Simms' recovery following her cessation of exposure to fluoridated water is discussed in her medical records. Her doctor, Dr. Lisa Davison, agreed that fluoride was a likely trigger of her headaches.

378. Ms. Simms has maintained a strict regimen since 2013 to limit her exposure to fluoride in both drinking water and processed beverages. It has now been about 6 years since she began this regimen, and her daily headaches have not returned.

379. The medications listed in Dr. Davison's April 2016 medical notes confirm that she is no longer taking medications for this once intractable problem.

380. According to the National Research Council, "[t]here are numerous reports of mental and physiological changes after exposure to fluoride from various routes (air, food, and water) and for various time periods."

381. The NRC notes that several of the case reports can be characterized as "experimental studies," since they involved "individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under 'blind' conditions. In most cases, the symptoms disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated."

382. The NRC's summary of the literature provides some support for Ms. Simms's concerns that fluoridated water was a cause or contributing factor to her headaches. This is particularly so when considering that previously unexplained improvements in Ms. Simms's symptoms during the 1990s appear to correlate with the periods of time in which she was residing in non-fluoridated areas. As with the case reports described by the NRC, Ms. Simms underwent withdrawal from her source of fluoride exposure under blind conditions (in which the symptoms improved), and had subsequent re-exposures under blind conditions (in which the symptoms worsened). As explained by the NRC, this adds confidence to the causal nature of the relationship.

383. Subsequent to the NRC's report, an epidemiological study found a significant association between elevated fluoride in drinking water and the occurrence of headaches. Fluoride has also been linked to headaches in several case reports, including in some of the reports cited by the NRC.

384. Avoiding fluoridation chemicals has been a taxing endeavor for Ms. Simms, as it has required her to spend "considerable sums of money" and has also interfered with her ability to enjoy things that others may take for granted, like drinking water from her sink, and travelling to other places without having to worry about whether the food or water will make her sick.

385. Plaintiff Audrey Adams is another FWW member who has been impacted by the neurological effects of fluoridation chemicals. Ms. Adams's autistic son, Plaintiff Kyle Adams, has

experienced various adverse symptoms, including headaches, when exposed to fluoridated water. Mrs. Adams has been advised by both of Kyle's treating doctors to avoid exposing Kyle to fluoride, including in water.

386. Mrs. Adams has spent considerable sums of money to minimize Kyle's exposure to fluoridation chemicals contained in the tap water in their home, and other communities in their area.

387. Plaintiff Kristin Lavelle is a health professional at San Francisco General Hospital/San Francisco Department of Public Health who first became concerned about the risks of fluoridation chemicals after reading a review by an EPA scientist explaining his concerns about the health effects of fluoridation chemicals.

388. One of Ms. Lavelle's primary health concerns with fluoride exposure is the potential risk of dementia, as she has seen first hand the devastating effects of Alzheimer's, as her grandfather suffered from it at the end of his life, and her aunt and father-in-law are both currently suffering from it as well.

389. Ms. Lavelle's concern about the dementia risk was heightened upon reading the NRC's 2006 review, as it reported that the brain changes seen in fluoride-treated animals "parallel the changes seen in humans with dementia" and called for studies to investigate fluoride's relationship to dementia in humans.

390. Ms. Lavelle was also concerned to read in the NRC report that the half-life of fluoride in human bone is approximately 20 years, and that the fluoride stored in bone begins to be released back into our bloodstream at increasing rates after menopause.

391. According to Ms. Lavelle, the "increased circulation of fluoride in our blood later in life concerns me in light of the NRC's concerns about fluoride's potential link with dementia, and the studies linking fluoride to cognitive decline in late-life years."

392. Based on these, and other health concerns, Ms. Lavelle has spent considerable sums of money to protect herself and her family from fluoridation chemicals, including purchasing water filters and

bottled water. However, Ms. Lavelle recognizes that she cannot fully eliminate her exposure to fluoridated water because "many processed beverages and foods are made with" it, yet there are no labels to indicate the fluoride content on any given product.

393. Plaintiff Brenda Staudenmaier is a water treatment professional who has taken steps to minimize her family's exposure to fluoridation chemicals due to the health concerns reported in the scientific literature.

394. Due to limited financial resources, Ms. Staudenmaier is not able to fully eliminate her exposure, and continues to consume processed beverages and foods. As a result, urinary fluoride tests show that Ms. Staudenmaier's urinary fluoride levels are sometimes as high as 1 mg/L.

395. Ms. Staudenmaier will continue spending money to minimize her exposure to fluoridation chemicals until fluoridation chemicals are removed from the water.

396. Jessica Trader is a member of Food & Water Watch who lives in San Francisco, which fluoridates its water.

397. Ms. Trader was diagnosed with dental fluorosis, which is a disorder of tooth enamel caused by too much fluoride. This condition has caused visible dark staining on Ms. Trader's front teeth.

398. The staining of Ms. Trader's front teeth has caused her social anxiety and embarrassment, as she fears that people will find her unattractive, or neglectful of her hygiene.

399. Ms. Trader's diagnosis of fluorosis has caused her concern about what additional fluoride exposures may do her health. Ms. Trader thus spends money purchasing spring water, and has purchased a professional water filtration system at her business, to minimize her exposure to the fluoridation chemicals that are added to San Francisco's water supply.

X. LEGISLATIVE HISTORY

400. When the Toxic Substances Control Act (TSCA) was enacted in 1976, Congress described

it as "protective legislation" whose "overriding purpose" is "to provide protection of health and the environment through authorities which are designed to prevent harm."

401. Congress stated that "factual certainty respecting the existence of an unreasonable risk of a particular harm may not be possible and the bill does not require it." Congress recognized that "uncertainty is particularly likely to occur when dealing with the long term or chronic effects of a substance or mixture."

402. According to the House Report, the demonstration of risk "must be based not only on consideration of facts but also on consideration of scientific theories, projections of trends from currently available data, modeling using reasonable assumptions, and extrapolations from limited data." Consistent with this, Congress envisioned regulatory action being taken under TSCA "even though there are uncertainties as to the threshold levels of causation."

PROPOSED CONCLUSIONS OF LAW

XI. STANDING

A. Zone of Interests

403. By allowing "any person" to bring a Section 21 citizen petition, Congress granted standing to the outer limits of Article III. *See Friends of the Earth, Inc. v. Gaston Copper Recycling Corp.*, 204 F.3d 149, 155 (4th Cir. 2000). Thus, as with citizen suits under the Clean Water Act, if a Section 21 plaintiff under TWCA "meets the constitutional requirements for standing, then he *ipso facto* satisfies the statutory threshold as well." *Id.*

B. Injury in Fact

404. An injury-in-fact for purposes of Article III "need not be capable of sustaining a valid cause of action under applicable tort law." *Denney v. Deutsche Bank AG*, 443 F.3d 253, 264–65 (2d Cir. 2006). This is especially so where, as here, the statute is designed to *prevent* harm *before* it occurs. *Baur v.*

Veneman, 352 F.3d 625, 633 (2nd Cir. 2003) ("[W]here the very purpose of the regulatory statute is risk minimization, it should be presumed that plaintiffs 'should be allowed to bring suit to prevent the sorts of injuries that the regulatory scheme was designed to prevent ... to ensure that the agencies adhere to the will of Congress." (citation omitted)). An injury-in-fact in Section 21 suits, therefore, may be established by evidence of a reasonable concern that the challenged policy puts the plaintiff at increased *risk* of harm. *Central Delta Water Agency v. United States*, 306 F.3d 938, 949 (9th Cir. 2002). As evident by the Ninth Circuit's decision in *Hall v. Norton*, 266 F.3d 969, 976 (9th Cir. 2001), an injury-in-fact does not require expert testimony to corroborate the plaintiff's individual concerns.

405. The standing declarants Julie Simms and Kyle Adams have at least a reasonable basis for thinking their health may be jeopardized by fluoridation chemicals. The ongoing economic injury they have sustained to minimize their exposure to fluoridation chemicals is thus a cognizable injury under *Monsanto Co. v. Geertson Seed Farms*, 561 U.S. 139, 153-154 (2010).

406. In the case of Ms. Simms, she suffered from daily headaches for the better part of 20 years until she stopped drinking fluoridated water, at which point she experienced a notable improvement with three days and a complete recovery within 3 weeks. In addition, the National Research Council has identified credible case reports in the medical literature of some individuals having similar sensitivities to fluoride as Ms. Simms appears to have, and a recent epidemiological study found a significant correlation between fluoride in water and headaches in adults. Based on her improvement, Ms. Simms's doctor agreed that fluoride was a likely trigger of her symptoms.

407. While Ms. Simms may not have clear medical proof of harm under the standards required in personal injury actions, she does have reasonable grounds for concern. For purposes of standing, this is enough.

408. A similar conclusion applies to Mr. Adams, whose two doctors have identified him as having a fluoride sensitivity in which headaches are one of the symptoms of exposure. The fact that Mr.

Adams's doctors have expressed concern about the impact of fluoride on his health makes his concern, as a lay person, a reasonable one.

409. All of the individual standing declarants, including Ms. Lavelle and Ms. Staudenmaier, have an actual or imminent injury-in-fact under the precedent set forth in *Natural Resources Defense Council v. United States Envtl. Prot. Agency*, 735 F.3d 873, 878-79 (9th Cir. 2013) (hereafter, "*NRDC*"). Here, as in *NRDC*, a risk of harm to Plaintiffs is indicated by application of EPA's "Margin of Exposure" methodology. Further, as in *NRDC*, there is no effective way for Plaintiffs to avoid exposure to the chemical at issue, because countless processed foods and beverages are made with fluoridated drinking water, but there are no labels to indicate the fluoride content of either. Thus, as with the plaintiffs in *NRDC*, there is a "credible threat" that Plaintiffs will be exposed to chemicals that pose a risk under a Margin of Exposure analysis. Under *NRDC*, this is sufficient for standing.

410. As in *Baur v. Veneman*, 352 F.3d 625, 637 (2nd Cir. 2003), there are "two critical factors that weigh in favor of concluding that standing exists in this case."

411. First, "government studies and statements confirm" several of Plaintiffs' key allegations regarding the neurotoxic risks posed by fluoride ingestion, and the alleged risk of harm arises from an established government policy. With respect to the first factor, (A) the National Research Council's report, which was conducted at the request of EPA, concluded that neurotoxicity is a hazard of fluoride in animals, and that there is a basis for concern that fluoride could be a cause dementia in humans; (B) the National Toxicology Program issued a draft systematic review in October 2019 wherein NTP announced its conclusion that fluoride is a presumed neurotoxicant in human beings; and (C) the National Institutes of Health have been funding studies to examine the neurotoxic effects of low-level fluoride exposure in North American populations.

412. Second, it is undisputed that EPA has the authority under TSCA to prohibit or restrict the addition of fluoridation chemicals to drinking water, and thus Plaintiffs' risk arises directly out of EPA's

failure to exercise its authority. *See Lujan v. Defs. of Wildlife*, 504 U.S. 555, 561–62 (1992) (stating that the challenged policy for purposes of standing can be either government "action" and "inaction").

413. Plaintiffs have suffered an injury-in-fact under *New York Pub. Interest Research Grp. v. Whitman*, 321 F.3d 316, 325–26 (2d Cir. 2003). There, plaintiffs suffered economic injury trying to protect themselves from the potential health effects of air pollution. Despite the fact that there was "uncertainty" as to whether plaintiffs were being exposed, let alone harmed, by the air pollutants, the court held that uncertainty about the potential for harm does not negate standing, as people may reasonably seek to protect themselves even where the risk is uncertain. *Id.* A similar reasoning applies here as well. In other words, it need not be proven that fluoridation chemicals increase the Plaintiffs' risk of harm; the fact that there is credible uncertainty as to the potential for fluoridation to cause neurological harm, including dementia, is sufficient to establish injury-in-fact for Article III.

414. Plaintiffs have suffered an injury-in-fact based on the loss of enjoyment of their environment and their property under the precedents of *Friends of the Earth, Inc. v. Laidlaw Envtl. Servs. (TOC), Inc.*, 528 U.S. 167, 181-84 (2000), *Covington v. Jefferson County*, 358 F.3d 626, 641 (9th Cir. 2004), and *Gaston*, 204 F.3d 149, 155 (4th Cir. 2000). In these cases, the plaintiffs suffered an injury-in fact based on their concerns about the potential (yet unproven) effects of chemical contaminants in nearby waterways and adjacent properties which caused them, *inter alia*, to stop fishing or swimming. Here, the Plaintiffs express similar concerns, albeit here the chemicals are directly entering their homes via their tap water, and are causing Plaintiffs to avoid drinking, or bathing in, the water in their own homes. As explained by the Fourth Circuit in *Gaston*, no federal circuit has "required additional scientific proof where there was a direct nexus between the claimant and the area of environmental impairment." *Gaston*, 204 F.3d at 159. The Court will thus not require such additional proof here; the Plaintiffs therefore have an injury-in-fact under the precedents of *Friends of the Earth*, *Covington*, and *Gaston*.

415. Finally, it is no consequence that the injury-in-fact that Plaintiffs suffered is shared by many

people in the population. The Supreme Court has "already made it clear that standing is not to be denied simply because many people suffer the same injury." U*nited States v. Students Challenging Regulatory Agency Procedures (SCRAP)*, 412 U.S. 669, 687 (1973). Indeed, "[t]o deny standing to persons who are in fact injured simply because many others are also injured, would mean that the most injurious and widespread Government actions could be questioned by nobody. *Id.* at 688.

C. Causation

416. Causation is established for purposes of standing because it is undisputed that EPA has the authority under TSCA to prohibit or limit the addition of fluoridation chemicals to drinking water. Thus, Plaintiffs exposure to fluoridation chemicals in drinking water (and the many processed beverages and foods made therefrom) is the direct result of EPA's *inaction*. *See Lujan v. Defs. of Wildlife*, 504 U.S. 555, 561–62 (1992) (stating that the challenged policy for purposes of standing can be either government "action" and "inaction").

D. Redressability

417. Redressability is established because, if the Court finds in Plaintiffs' favor, the Court must order EPA to initiate a rulemaking proceeding to eliminate the unreasonable risk posed by fluoridation chemicals in drinking water. While there is no guarantee that EPA's rulemaking proceeding will result in the outcome that Plaintiffs desire, this does not negate the redressability prong for standing, as evident by the Tenth Circuit's decision in *Catron County Bd. Of Com'rs, New Mexico v. United States Fish & Wildlife Service*, 75 F.3d 1429, 1433 (10th Cir. 1996).

XII. UNREASONABLE RISK

418. Plaintiffs satisfy their burden of providing an unreasonable risk under Section 21 of TSCA if they can prove by a preponderance of the evidence that an unreasonable risk exists for a single susceptible

subpopulation. It is not necessary for Plaintiffs to prove a risk for the entire population.

419. The quantum of proof necessary to demonstrate an unreasonable risk under TSCA is informed by the statute's "overriding purpose" of preventing harm before it occurs. In order to effectuate this purpose, a demonstration of unreasonable risk does not require conclusive proof of actual harm.[1]

420. A court's *de novo* determination of unreasonable *risk* under Section 21 is appropriately guided (although not mandatorily so) by the methods and principles of *risk* assessment, including NRC/EPA's four-step paradigm of hazard assessment, dose-response assessment, exposure assessment, and risk characterization.

421. In addition to being guided by methods and principles of risk assessment, a court's *de novo* determination of unreasonable risk under Section 21 is appropriately guided (although not mandatorily so) by the risk-related factors that EPA itself considers in making risk determinations under Section 6(b), including: number of people exposed; types of populations exposed (e.g., occupational vs. general public, susceptible subpopulations, etc.); severity of the hazard; reversibility of the hazard, and uncertainties.

422. Although EPA has imposed a formal systematic review requirement on its risk evaluations under Section 6(b), this requirement does not bind a court in a *de novo* Section 21 action. While a court may appropriately consider the existence of a systematic review as a factor affecting the weight to be afforded to any given expert opinion, a plaintiffs' entitlement to relief does not require that such a review be conducted.

[1] House Report at 32 ("[F]actual certainty respecting the existence of an unreasonable risk of a particular harm may not be possible and the bill does not require it."); *Ethyl Corp. v. U.S. E.P.A.*, 541 F.2d 1, 12 & 25 (D.C. 1976) (en banc) (rejecting contention that proof of a "significant risk" under the Clean Air Act requires "factual proof of actual harm" and explaining that "awaiting certainty will often allow for only reactive, not preventive, regulation"); John S. Applegate, *The Perils of Unreasonable Risk: Information, Regulatory Policy, and Toxic Substances Control*, 91 COLUM. L. REV. 261, 273 (1991) (describing TSCA's unreasonable risk standard as "a regulation of risk instead of actual harm"); see also Ethyl Corp., 541 F.2d 1, 12 (D.C. 1976) (en banc) (rejecting contention that proof of a "significant risk" requires "factual proof of actual harm"); *id.* at 273 ("Risk is an expression of uncertainty; it is easier to prove than actual harm. Regulation based on risk permits regulatory action based on *ex ante* collective danger rather than *ex post* individual injury, and also operates preventatively to avert injury to the public as a whole.").

423. Even if a systematic review *were* required for a court to make a *de novo* unreasonable risk determination under Section 21, that requirement has been satisfied in this case. First, Plaintiffs' risk assessment expert conducted a risk assessment pursuant to the *Guidelines for Neurotoxicity Risk Assessment*, which EPA's own expert has admitted is "effectively" the equivalent of a systematic review. Second, EPA's experts have conducted systematic reviews of both the human and animal literature, as has the National Toxicology Program. The Court's determination will thus be fully informed by the findings of systematic reviews. Third, EPA's experts have testified that their systematic reviews failed to identify any studies that materially challenge the results of Plaintiffs' experts' conclusions. Fourth, all parties agree that the ELEMENT and MIREC cohort studies are the best available studies on fluoride neurotoxicity, and these are the studies upon which Plaintiffs' epidemiologist, Dr. Philippe Grandjean, based his estimates of risk.

424. The determination of unreasonable risk under TSCA *must* be made "without consideration of costs or other nonrisk factors." Based on the plain language, structure, and purpose of TSCA, nonrisk factors include a chemical's benefits. Accordingly, since the caries-prevention properties of fluoridation chemicals are clearly a form of benefit, they are a "nonrisk factor" that cannot be considered as part of a court's determination of unreasonable risk under TSCA.

425. Plaintiffs have proved by a preponderance of the evidence that (1) neurotoxicity is a hazard of fluoride exposure, (2) there is a risk of this hazard occurring from the addition of fluoridation chemicals to drinking water, and (3) this risk is an unreasonable one when judged according to the relevant risk-related considerations. Accordingly, Plaintiffs have met their burden of proving an unreasonable risk under the Act.

December 19, 2019

Respectfully submitted,

/s/ Michael Connett
MICHAEL CONNETT
Attorney for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was served by Notice of Electronic Filing this 19th day of December, 2019, upon all ECF registered counsel of record using the Court's CM/ECF system.

/s/ Michael Connett
MICHAEL CONNETT